1 TITLE PAGE

PROTOCOL

TITLE:	A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia
PROTOCOL NUMBER:	ACE-CL-309
STUDY DRUG:	Acalabrutinib (ACP-196)
IND NUMBER:	118717
EUDRACT NUMBER:	2015-004454-17
SPONSOR MEDICAL MONITOR:	PPD Phone: PPD Email: PPD
SPONSOR:	Acerta Pharma, BV Kloosterstraat 9 5349 AB Oss The Netherlands
ORIGINAL PROTOCOL DATE:	Version 0.0 – 24 March 2016
AMENDMENT 1 DATE:	Version 1.0 – 04 August 2016
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AMENDMENT 2.1 DATE:	Version 2.1 – 13 October 2016
AMENDMENT 3.0 DATE:	Version 3.0 – 11 May 2017
AMENDMENT 4.0 DATE:	Version 4.0 – 29 June 2017
AMENDMENT 5.0 DATE:	Version 5.0 – 17 November 2017
AMENDMENT 6.0 DATE:	Version 6.0 – 03 June 2020
AMENDMENT 7.0 DATE:	Version 7.0 – 17 May 2021
AMENDMENT 8.0 DATE:	Version 8.0 – 26 May 2021

PROTOCOL APPROVAL PAGE
Version 8.0

I have carefully read Protocol ACE-CL-309 entitled “A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator’s Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory 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 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 8.0

This protocol is being amended to include the following changes:

- No further data will be collected for post-treatment disease follow-up or survival follow-up after the final data cutoff.

Summary of Changes from Amendment 7.0 to Amendment 8.0

Description of Change	Sections
Clarified that no further data will collected after the final data cutoff for post-treatment disease follow-up or survival follow-up.	Section 11.4 Section 11.5

2 SYNOPSIS

Name of Sponsor/Company:
Acerta Pharma BV

Name of Investigational Product:
Acalabrutinib (ACP-196)

Name of Active Ingredient:
Acalabrutinib

Title of Study:
A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia

Study period: Approximately 4 years, until final data cutoff (DCO); approximately >5 years, until last subject last visit (LSLV) (total of >9 years)	**Phase of development:** 3

Objectives:

Primary:

- To evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with idelalisib/rituximab or bendamustine/rituximab (Arm B) based on Independent Review Committee (IRC) assessment of progression-free survival (PFS) per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria (Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012) hereafter referred to as IWCLL 2008 criteria in subjects with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL).

Secondary:

To evaluate Arm A compared with Arm B in terms of:

- Investigator (INV)-assessed PFS per IWCLL 2008 criteria.
- INV- and IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria.
- Overall survival (OS).
- Patient-reported outcomes (PROs) by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) (will no longer be collected as of Amendment 6.0).
- INV- and IRC-assessed duration of response (DOR).
- Time to next treatment (TTNT).

Safety:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).

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Methodology:

This randomized, global, multicenter, open-label, Phase 3 study will evaluate the efficacy and safety of acalabrutinib monotherapy versus Investigator's choice of either idelalisib/rituximab or bendamustine/rituximab in subjects with R/R CLL.

Approximately 306 eligible subjects will be randomized in a 1:1 ratio into 2 arms (n = 153 each) to receive either:

Arm A: Acalabrutinib 100 mg orally (PO) twice per day (BID) administered until an unacceptable drug-related toxicity occurs or until disease progression.

Arm B: Investigator's choice of:

- Idelalisib 150 mg PO BID administered in combination with ≤ 8 doses of intravenous (IV) rituximab (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 IV every 2 weeks for 4 infusions, then every 4 weeks for an additional 3 infusions) until disease progression or unacceptable toxicity.
- Bendamustine 70 mg/m^2 IV (Day 1 and 2 of each cycle) in combination with rituximab IV (375 mg/m^2/500 mg/m^2) on Day 1 of each cycle for up to 6 cycles.

Subjects will be randomized based on the following stratification factors:

Presence of chromosome deletion 17p13.1 (17p del)
Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2)
Number of prior therapies (1, 2, or 3 versus ≥ 4)

Dose modification provisions for acalabrutinib, idelalisib, and bendamustine are provided in the study protocol. No dose modifications are allowed for rituximab. Each treatment cycle will consist of 28 days (4 weeks).

Assessment of response and progression will be conducted in accordance with the IWCLL 2008 criteria (Hallek 2008), with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will not be considered progressive disease (Appendix 10). 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 until confirmation of disease progression or death, consent withdrawal, or loss to follow-up. Subjects from Arm B who have confirmed disease progression may be eligible before the final DCO to receive crossover treatment single-agent acalabrutinib at 100 mg orally BID at Investigator discretion until disease progression or unacceptable toxicity.

A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression, and should be scheduled within 7 days of his or her last dose of all study drugs, if possible. In addition to the TT visit, all subjects who discontinue study drug(s) will have a safety follow-up (SFU) visit 30 (+ 7) days after the last dose of all study drugs, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. All subjects who discontinue treatment due to an intolerable AE or any reason other than disease progression, death, lost to follow-up or consent withdrawn will be followed on study for disease progression or death.

Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

Refer to Appendix 1 to Appendix 4 for a comprehensive list of study assessments and their timing. The study schema is provided in Figure 7-1.

Number of subjects (planned): 306

Diagnosis and main criteria for inclusion:

Subjects with CLL who have relapsed after ≥ 1 prior treatment regimen.

Inclusion criteria:

1. Men and women ≥ 18 years of age.
2. ECOG performance status of 0 to 2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008):
    a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, or CD23) and CD5.
    b. Prolymphocytes may comprise ≤ 55% of blood lymphocytes.
    c. Presence of ≥ 5 x 10^9 B lymphocytes/L (5000/μL) in the peripheral blood (at any point since initial diagnosis).
4. Must have documented CD20-positive CLL.
5. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment:
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/μL).
    b. Massive (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 (ECOG performance score 2; inability to work or perform usual activities).
    iii. Fevers higher than 100.5°F or 38.0°C for ≥ 2 weeks before screening without evidence of infection.
    iv. Night sweats for > 1 month before screening without evidence of infection.

6. Meet the following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥ 750 cells/µL (0.75 x 10^9/L), or ≥ 500 cells/µL (0.50 x 10^9/L) in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.
    b. Platelet count ≥ 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. If an Investigator has chosen bendamustine/rituximab as the Arm B treatment, platelets must be ≥ 75,000 cells/µL (75 x 10^9/L).
    c. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.0 x upper limit of normal (ULN).
    d. Total bilirubin ≤ 1.5 x ULN.
    e. Estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].
7. Must have received ≥ 1 prior systemic therapies for CLL. Note: Single-agent steroids or localized radiation are not considered a prior line of therapy. If a single-agent anti-CD20 antibody was previously administered, subjects must have received ≥ 2 doses.

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, 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Highly effective forms of contraception are defined in Section 9.2.5.
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 idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Highly effective forms of contraception are defined in Section 9.2.5.
10. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
11. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules without difficulty.
12. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

Exclusion criteria:

1. Known central nervous system (CNS) lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone or equivalent).
4. Prior exposure to a BCL-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., Bruton tyrosine kinase [BTK] inhibitors or phosphoinositide-3 kinase [PI3K] inhibitors). Prior bendamustine is allowed if Investigator's choice for treatment in Arm B is idelalisib with rituximab. Bendamustine retreatment is allowed if the prior response to bendamustine lasted > 24 months.
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
6. Corticosteroid use > 20 mg daily prednisone equivalent within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. For example, subjects requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.
7. Prior radio- or toxin-conjugated antibody therapy.
8. Prior allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose of study drug(s) or presence of graft-vs-host disease or receiving treatment for graft-vs-host disease.

9. Major surgical procedure within 30 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
10. History of prior malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 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 nonmelanomatous skin cancer.
    c. Adequately treated carcinoma in situ without current evidence of disease.
11. Significant cardiovascular disease such as uncontrolled or untreated symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec (calculated using Fridericia's formula: $QT/RR^{0.33}$) at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
12. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
13. Received a live virus vaccination within 28 days of first dose of study drug.
14. Known history of infection with human immunodeficiency virus (HIV) or any uncontrolled active systemic infection (e.g., bacterial, viral, or fungal). For study sites in Germany: active infection with human immunodeficiency virus (seropositivity for HIV-1 or HIV-2 antibodies, and if positive, reactivity against the HIV-specific p24 antigen).
15. Active CMV infection (active viremia as evidenced by positive polymerase chain reaction [PCR] result for CMV DNA).
16. Serologic status reflecting active hepatitis B or C infection.
    a. Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative PCR result before randomization. Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded.
    b. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR positive will be excluded.
17. Ongoing, drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
18. History of or ongoing drug-induced pneumonitis.
19. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.

20. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
21. History of bleeding diathesis (e.g., hemophilia, von Willebrand disease).
22. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
24. Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer.
25. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
26. Breast feeding or pregnant.
27. Concurrent participation in another therapeutic clinical trial.
28. Prothrombin time/international normalized ratio (INR) or activated partial thromboplastin time (aPTT; in the absence of a Lupus anticoagulant) > 2.0 x ULN. Exception: Subjects receiving warfarin are excluded, however, those receiving other anticoagulant therapy who have a higher INR/aPTT may be permitted to enroll to this study after discussion with the medical monitor.
29. History of confirmed progressive multifocal leukoencephalopathy (PML)

Investigational product, dosage and mode of administration:

Acalabrutinib:

Acalabrutinib is provided as hard gelatin capsules for oral administration. Acalabrutinib 100 mg will be administered orally BID. It is recommended that acalabrutinib be taken as close to the scheduled time as possible (preferably within ± 1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time, with a return to the normal schedule with the following dose.

Duration of treatment:

For subjects receiving acalabrutinib: Acalabrutinib will be administered until disease progression or unacceptable toxicity.

For subjects receiving idelalisib/rituximab: Idelalisib will be administered until disease progression or unacceptable toxicity. Rituximab will be administered for a maximum of 8 infusions administered in the first 6 cycles.

For subjects receiving bendamustine/rituximab: This regimen will be administered for a maximum of 6 cycles.

After the final data cutoff (DCO), the following applies to subjects who are still on treatment and deriving clinical benefit:

- In a given country, when acalabrutinib or idelalisib are commercially available and reasonably accessible, subjects will be transitioned off study, and treatment will continue outside of the study protocol, per local laws and regulations

- Where idelalisib is not commercially available and reasonably accessible, subjects who are receiving idelalisib may be transitioned to receive commercial acalabrutinib at the discretion of the investigator.
- Where acalabrutinib is not commercially available and reasonably accessible, subjects may be re-consented to continue within this study to receive acalabrutinib in line with standards of care.

Reference therapy, dosage and mode of administration:

Idelalisib:

Commercially available idelalisib will be provided as film-coated tablets (150 and 100 mg) for oral administration per the instructions in the locally approved labelling (e.g., see United States prescribing information) and per institutional standards.

Idelalisib 150 mg will be administered orally BID.

Bendamustine:

Commercially available bendamustine 70 mg/m^2 will be administered as an IV infusion on Days 1 and 2 of a 28-day cycle according to the instructions in locally approved labelling (e.g., see United States prescribing information) and institutional standards. Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full six cycles to be received, wherever possible. A maximum of 6 cycles can be administered. See further instructions for data entry in such cases in the eCRF guidelines.

Rituximab:

Commercially available rituximab will be supplied for IV administration according to the instructions in the locally approved labelling (e.g., see United States prescribing information) and per institutional standards; premedication is required.

When administered with idelalisib, the rituximab regimen will be 375 mg/m^2 IV on Day 1 of the first cycle, followed by 500 mg/m^2 IV every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions.

When administered with bendamustine, the rituximab regimen will be 375 mg/m^2 IV on Day 1 of the first cycle and 500 mg/m^2 IV on Day 1 of Cycles 2 to 6.

Criteria for Evaluation:

Primary Endpoint:

The primary endpoint of the study is PFS (defined as the time from randomization until disease progression or death from any cause) as assessed by the IRC per IWCLL 2008 criteria.

Secondary Endpoints:

- INV-assessed PFS per IWCLL 2008 criteria.
- INV-assessed ORR (defined as the proportion of patients who achieve a best response of complete remission [CR], complete remission with incomplete bone

marrow recovery [CRi], nodular partial remission [nPR], or partial remission [PR]) per IWCLL 2008 criteria.

- IRC-assessed ORR per IWCLL 2008 criteria.
- OS (defined as the time from randomization to the date of death due to any cause).
- PROs as measured by change in scores from baseline to each assessment in the FACIT-Fatigue (will no longer be collected as of Amendment 6.0).
- INV- and IRC-assessed DOR (defined as the time from the first documentation of objective response to the earlier time of disease progression [assessed by the IRC per IWCLL 2008 criteria] or death from any cause).
- TTNT (defined as the time from randomization to institution of nonprotocol-specified treatment for CLL. For crossover patients, TTNT should be defined as time from initial treatment of acalabrutinib to institution of nonprotocol-specified treatment for CLL).

Safety Endpoints:

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

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Safety Plan:

The safety of this study will be monitored by an independent Data Monitoring Committee (DMC). The DMC will meet and review the safety data periodically and the results of the interim analysis and provide recommendations according to the DMC charter.

The first safety data review will be performed by the DMC after 50 subjects have been randomized and had the opportunity to receive 8 weeks of study treatment. After the first review meeting, the DMC will meet approximately every 6 months and as needed when required by the Sponsor or the DMC. This analysis will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs.

The medical monitor will review this information on an ongoing basis until the first safety data review is conducted by the DMC.

Concomitant Therapy and Clinical Practice:

Permitted Concomitant Therapy:

Standard supportive care medications are permitted; this includes premedication for rituximab infusion as per rituximab prescribing information. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines (Smith 2015) or per institutional guidelines.

Subjects with a risk factor for tumor lysis syndrome (TLS) should be considered for hydration and uric acid-lowering agent and more frequent monitoring of appropriate laboratory tests. Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

For subjects at risk for pneumonitis: In selected subjects (e.g., those with a history of recurrent pneumonias), anti-infectious prevention should be considered.

For subjects at risk for infections: Bacterial/viral/fungal prophylaxis is allowed per institutional standards.

Prohibited Concomitant Therapy:

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited. 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. Corticosteroids may be administered for longer than 2 weeks to treat idelalisib-related adverse events (e.g., pneumonitis and colitis). High-dose corticosteroids used to treat the underlying CLL are not allowed on study during or prior to discontinuation of study treatment. 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 rituximab infusion-related reactions are permitted.

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

Required Concomitant Medications:
Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP) and CMV (ZYDELIG SmPC and United States prescribing information). Prophylaxis for PJP in accordance with local guidelines and institutional standards should therefore be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia. CMV testing will be required for subjects receiving idelalisib or bendamustine treatment while on study (see Section 11.1.27).

Acalabrutinib and Concomitant Therapy:
The effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole, or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. The decision to treat with proton-pump inhibitors during the study is at the Investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

Concomitant administration of drugs that are strong inhibitors/inducers of CYP3A is not recommended (see Section 9.1.3 for more detailed information).

Statistical Methods:

All efficacy analyses will be performed using the intent-to-treat (ITT) population, unless otherwise specified.

Primary Efficacy Analysis:

CCI [redacted] 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 status, ECOG status, and number of prior therapies). The hazard ratio (HR) and its 95% confidence interval (CI) will be computed from a stratified Cox regression model.

Secondary Endpoints and Analysis:
ORR will be assessed for Arms A versus B using a Cochran-Mantel-Haenszel test stratified by the randomization strata.

The following 3 secondary outcomes will be assessed for Arms A vs B in a manner similar to the method used for PFS:

- OS
- DOR
- TTNT

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 (refer to Section 12.8).

Interim Analysis:

CCI [redacted] The stopping rules are based on the primary efficacy endpoint of PFS using Lan-DeMets alpha-spending function with the O'Brien-Fleming boundary. CCI [redacted]

Sample Size:

Under the model assumptions, the study is expected to enroll approximately 306 subjects with 1:1 randomization ratio. CCI [redacted]

A median PFS of 19.4 and 15.2 months has been reported for idelalisib plus rituximab and bendamustine plus rituximab, respectively, in patients with R/R CLL (Fischer 2011). CCI [redacted]

For a full description of statistical analysis methods, please refer to Section 12.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4-1. Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
11q del	chromosome deletion 11q22.3
17p del	chromosome deletion 17p13.1
ACP-196	acalabrutinib
AE(s)	adverse event(s)
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
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BID	twice per day
BR	bendamustine with rituximab
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
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
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

Abbreviation or Specialist Term	Explanation
CYP	cytochrome P450
DCO	data cutoff
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	
EDC	electronic data capture (system)
CCI	
ESMO	European Society for Medical Oncology
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gi/L	giga/liter; $x10^9$/liter
G-CSF	Granulocyte colony-stimulating factor
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IGHV	immunoglobulin heavy-chain variable
IND	Investigational New Drug
INV	Investigator
INR	international normalized ratio
ITP	idiopathic thrombocytopenic purpura

Abbreviation or Specialist Term	Explanation
IRB	institutional review board
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous
IVIG	intravenous immunoglobulins
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IXRS	interactive voice/web response system
JCV	John Cunningham virus
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease (defined as the proportion of subjects with <1 CLL cell in 10^4 leukocytes)
MRI	magnetic resonance imaging
CCI	
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PI3K	phosphoinositide-3 kinase
PJP	*Pneumocystis jirovecii* pneumonia
PLCγ	phospholipase C gamma
PLT	platelet count
PO	per os (by mouth, orally)
PR	partial remission (response)
PML	Progressive multifocal leukoencephalopathy
PRL	partial remission (response) with lymphocytosis

Abbreviation or Specialist Term	Explanation
PRO(s)	patient-reported outcome(s)
PS	performance status
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once per day (dosing)
CCI	
QM	every month
QTc	corrected QT interval
R/R	relapsed/refractory
RSI	Reference Safety Information
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SFU	safety follow-up
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic leukemia
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
TT	treatment termination
TTNT	time to next treatment
ULN	upper limit of normal

5 INTRODUCTION

5.1 Chronic Lymphocytic Leukemia

CLL is a malignancy of B cells that predominantly affects the older population. The diagnosis of CLL is established using peripheral blood and immunophenotyping and requires a minimum of 5 x 10^9 monoclonal B cells that co-express CD5 and CD19, CD20 or CD23. 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). Staging is predominantly by Rai (Rai 1975) or Binet (Binet 1981) both of which distinguish prognostic groups and define patients that should be considered for treatment versus those who should be managed with a watch and wait approach. While patients with early disease have not been shown to have a survival advantage with early treatment, many patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. International guidelines (IWCLL 2008) that outline indications for treatment have been established (Hallek 2008) and are widely used for determining when to initiate CLL treatment.

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, has shown the benefit of the addition of rituximab to fludarabine and cyclophosphamide (FCR) in PFS and OS in patients with previously untreated CLL (Hallek 2010). Bendamustine in combination with rituximab (BR) has also been studied in frontline CLL and was found to be less toxic but also less efficacious than FCR (Eichhorst 2013).

Patients who have high risk cytogenetics such as deletions in the long arm of chromosome 11 [11q del)] or in the short arm of chromosome 17 [17p del], have inferior outcomes and may

prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens (Hallek 2010, Hillmen 2007). In addition, elderly patients and those with comorbidities are often unable to tolerate combination chemoimmunotherapy regimens, or experience inferior clinical outcomes when treated with these regimens.

Currently, CLL remains an incurable disease with relapse inevitable and most patients requiring multiple lines of therapy. Therapeutic choice after relapse requires the evaluation of the intensity of the previous therapies, the duration of response to those therapies, and patient comorbidities. Allogeneic stem cell transplant was the treatment of choice for potentially long lasting remissions for those who could tolerate the toxicities. In the last decade targeted therapies against B cell markers/antigens or against components of the B cell receptor such as BTK or PI3Kδ have demonstrated efficacy with less toxicity (Wiestner 2015). However, newer therapies with less toxicity and stronger and more durable responses are still needed for the treatment of R/R CLL.

5.2 BTK Inhibition for the Treatment of CLL

BTK inhibition is an established therapeutic intervention for the treatment of CLL. Ibrutinib (IMBRUVICA®), a first-generation BTK inhibitor, has demonstrated efficacy in patients with R/R CLL based on data from single-arm Phase 2 studies (PCYC 1102/1103) and the randomized Phase 3 study (RESONATE) (IMBRUVICA prescribing information). In the RESONATE study, which had a median follow-up of 9.4 months, ibrutinib demonstrated improvement over ofatumumab in PFS (HR = 0.22), OS (HR = 0.43) and ORR (42.6% versus 4.1% by independent assessment and 69.7% versus 21.4% by Investigator assessment).

5.3 Acalabrutinib

CCI [redacted] For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

Acalabrutinib is an investigational product. Acalabrutinib (Calquence) has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy, for CLL, and for small lymphocytic lymphoma.

5.3.1 Mechanism of Action

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

5.3.2 Safety Pharmacology

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

5.3.3 Drug-drug Interaction Potential

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

Please refer to Section 9.1.3 for guidance on drugs that may cause drug-drug interactions.

5.4 Clinical Experience – Acalabrutinib

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

5.5 Idelalisib in Combination with Rituximab

Idelalisib is an inhibitor of PI3Kδ, which is hyperactivated in B-cell malignancies and plays a vital role in the B-cell receptor pathway. Idelalisib in combination with rituximab was approved for the treatment of R/R CLL based on a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of idelalisib in combination with rituximab (N = 110) versus rituximab plus placebo (N = 110) (Furman 2014). This study enrolled patients were unable to undergo chemotherapy due to comorbid conditions (i.e., decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses). This study showed significantly improved PFS (HR = 0.15, $p < 0.001$), ORR (81% vs 13%, $p < 0.001$) and OS at

12 months (92% vs 80%, HR = 0.28; p = 0.02) in favor of idelalisib in combination with rituximab. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2016) recommend idelalisib therapy as second-line therapy, ahead of chemoimmunotherapy, in R/R CLL. The European Society for Medical Oncology (ESMO) guidelines (Eichhorst 2015) specifically recommend idelalisib/rituximab for patients in the relapsed setting if TP53 deletion/mutation is present, or if relapsed occurred within 24 to 36 months of chemoimmunotherapy, or if the disease did not respond to first-line therapy.

Therapy with idelalisib is better tolerated than traditional chemoimmunotherapy, but is also associated with clinically important safety risks, including hepatotoxicity, severe diarrhea or colitis, pneumonitis, severe cutaneous reactions, and intestinal perforation.

5.6 Bendamustine in Combination with Rituximab

Evidence of the efficacy of bendamustine in combination with rituximab in R/R CLL was provided by a multicenter Phase 2 trial of this regimen conducted by the German Chronic Lymphocytic Group (Fischer 2011). This single-arm, open-label study enrolled 78 patients, including 22 patients with fludarabine-refractory disease and 14 patients with 17p del. The ORR was 59% (95% CI: 47.3%, 70%) and with a median follow-up of 24 months the median PFS was 14.7 months. Notable activity was seen in patients with fludarabine-refractory disease but not in patients with 17p del. As mentioned previously, NCCN guidelines recommend chemoimmunotherapy, including bendamustine/rituximab as third-line treatment for R/R CLL but does not recommend it for patients with 17p del. ESMO guidelines also do not recommend bendamustine/rituximab for patients with 17p del or TP53 mutation. They do, however, recommend repeating first-line chemoimmunotherapy (including bendamustine/rituximab) if relapse or progression occurred at least 24 to 36 months after initial chemoimmunotherapy. Hematologic toxicity and severe infections are the greatest safety risks associated with this regimen; as a result, this regimen is also mostly recommended for younger patients without significant comorbidities.

5.7 Benefit/Risk

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/SLL or Richter's syndrome. In the Phase 1/2 study of acalabrutinib in subjects with

R/R CLL/SLL (ACE-CL-001), no dose-limiting toxicities (DLTs) were identified at dosages of ≤ 400 mg once per day (QD) or 100 to 200 mg BID. 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. In summary, the preliminary data suggest that acalabrutinib is well tolerated and has robust activity as a single agent. Based on available data, the risk/benefit for acalabrutinib is likely to be favorable compared with idelalisib/rituximab and bendamustine/rituximab for the treatment of patients with R/R CLL. For more detailed and updated information on the benefit/risk profile of acalabrutinib, please refer to the Acalabrutinib Investigator Brochure.

6 TRIAL OBJECTIVES AND PURPOSE

6.1 Primary Objective

To evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with idelalisib/rituximab or bendamustine/rituximab (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria in subjects with R/R CLL.

6.2 Secondary Objectives

To evaluate Arm A compared with Arm B in terms of:

- INV-assessed PFS per IWCLL 2008 criteria.
- INV- and IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria (defined as the proportion of patients who achieve a best response of CR, CRi, nPR, or PR).
- OS.
- PROs by FACIT Fatigue (will no longer be collected as of Amendment 6.0).
- INV- and IRC-assessed DOR (defined as the time from the first documentation of objective response to the earlier time of disease progression [assessed by the IRC per IWCLL 2008 criteria] or death from any cause).
- Time to next treatment (TTNT) (defined as the time from randomization to institution of non-protocol specified treatment for CLL. For crossover patients, TTNT should be defined as time from initial treatment of acalabrutinib to institution of nonprotocol-specified treatment for CLL).
-

6.3 Safety Objective

Incidence and severity of AEs and SAEs.

6.4 CCI

CCI

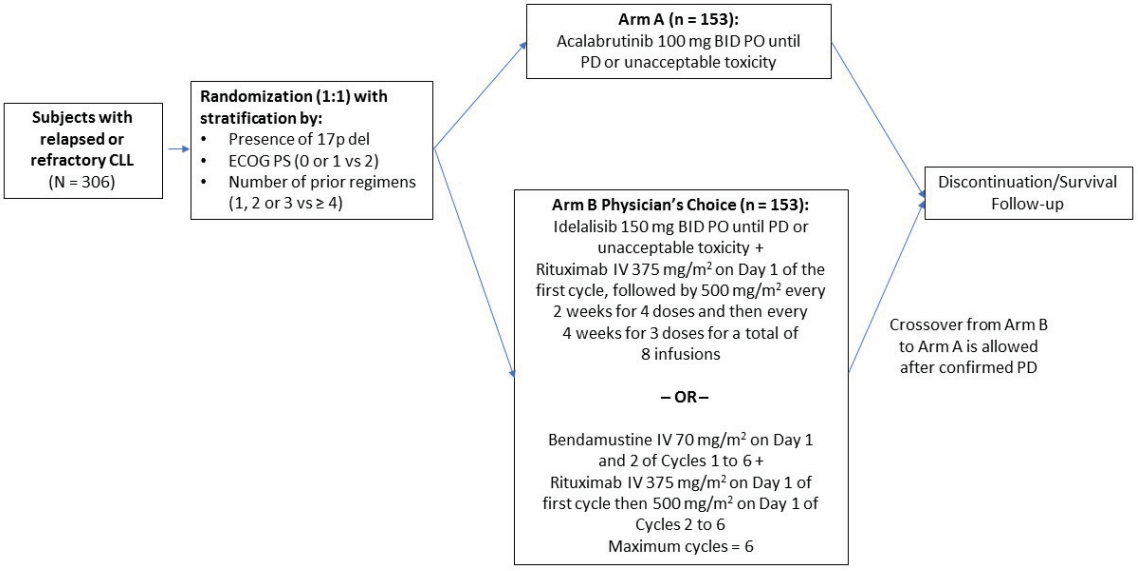
[redacted]

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This randomized, global (approximately 150 sites), multicenter, open-label, Phase 3 study will evaluate the efficacy and safety of acalabrutinib monotherapy versus idelalisib/rituximab or bendamustine/rituximab in subjects with R/R CLL.

Figure 7-1. Study Schema



Abbreviations: BID = twice per day; CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; PD = progressive disease; PO = oral.
Note: Prior to the final data cutoff, subjects who cross over from Arm B to Arm A must meet all eligibility requirements for the main study period.

Each treatment cycle will consist of 28 days (4 weeks).

Approximately 306 eligible subjects will be randomized in a 1:1 ratio into 2 arms (n = 153 each) to receive either:

Arm A: Acalabrutinib 100 mg PO BID until an unacceptable drug-related toxicity occurs or until disease progression.

Arm B: Before randomization Investigator's choice of:

- Idelalisib 150 mg PO BID administered until disease progression or unacceptable toxicity in combination with ≤ 8 IV infusions of rituximab.
- Bendamustine 70 mg/m^2 IV (Day 1 and 2 of each cycle) in combination with rituximab IV (375 mg/m^2/500 mg/m^2) on Day 1 of each cycle for up to 6 cycles.

Subjects will be randomized based on the following stratification factors:

- Presence of 17p del

- ECOG performance status (0 or 1 versus 2)
- Number of prior therapies (1, 2 or 3 versus ≥ 4)

Note: At Investigator discretion, subjects randomized to Arm B who have confirmed disease progression may be eligible to receive crossover treatment with single-agent acalabrutinib at 100 mg PO BID until disease progression or unacceptable toxicity.

Crossover:

Eligible subjects may cross over from Arm B to acalabrutinib monotherapy upon confirmed disease progression before the final DCO. Eligibility for crossover includes meeting all eligibility criteria for the main study period. Screening for eligibility and trial assessments during crossover are described in Appendix 4 and should occur within 30 days of disease progression. Subjects may not receive any new systemic therapy between confirmation of disease progression and the initiation of crossover therapy with acalabrutinib.

The following documentation will be reviewed before enrollment to the crossover arm by the medical monitor:

Radiology reports from computed tomography (CT)/magnetic resonance imaging (MRI); CT/MRI from disease progression can be used for the new tumor imaging baseline against which to assess tumor response on crossover treatment if obtained within 30 days prior to crossover dosing Cycle 1 Day 1.

See also Section 11.1.23 for a more detailed description of crossover-related procedures and authorization process.

Crossover procedures:

For all treatment arms (Arms A, B, and crossover), radiologic tumor assessment will be done at screening, 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 bendamustine-treated subjects, the second radiologic tumor assessment will occur at the next 12-week interval (± 14 days) regardless of whether the subject is on study drug. Safety evaluations will consist of assessments of AEs, physical exams, and safety laboratory panels. Assessment of response and progression will be conducted in accordance with the IWCLL 2008 criteria for CLL

(Hallek 2008), with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will not be considered progressive disease (Cheson 2012, see Appendix 10). The Investigator will evaluate sites of disease by radiologic imaging (primary); physical examination or other procedures as necessary; review of hematology and serum chemistry results; and disease-related symptoms. The same methods of assessment used to assess disease at baseline should be used throughout the study. A central laboratory will perform all hematology testing for the primary endpoint analysis.

In the setting of suspected CR on the basis of physical exam, laboratory findings (including hematologic profile with ALC, ANC, platelet count, and Hgb) and radiologic tumor assessment meeting all IWCLL response criteria for CR (Appendix 10), bone marrow analysis (a bone marrow aspirate/biopsy and sample of peripheral blood to be obtained between 8-12 weeks from the end of treatment or, if study treatment has been discontinued at the time of suspected CR, of the radiographic imaging of suspected CR) will be required to confirm CR pathologically and to assess minimal residual disease (MRD).

A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression, and should be scheduled within 7 days of his or her last dose of all study drugs, if possible. In addition to the TT visit, all subjects who discontinue all study drugs will have a safety follow-up visit (SFU) visit 30 days (+ 7 days) after the last dose of all study drugs. If subjects discontinued treatment due to unacceptable toxicity or any reason other than disease progression, death, loss to follow-up or consent withdrawal, subjects will continue to be followed for disease progression or death.

Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Refer to Appendix 1 to Appendix 4 for the full list of assessments required during this period.

Once the Investigator has confirmed that a subject has progressive disease, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional

malignancy occurrence, and subject survival status will be recorded. Subjects will be followed for survival until death, loss to follow-up, consent withdrawal, or study closure, whichever occurs first. Survival status must be assessed, and the date of death must be documented for each subject randomized, regardless of whether the subject received treatment.

The primary efficacy analysis will be based on assessment from an IRC. As part of the IRC review, radiologic 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 DMC procedures will be provided in a separate charter. The DMC will review the safety data periodically and provide recommendations according to the charter.

One interim analysis is planned for the study, when approximately 79 PFS events (two-thirds of the primary event goal) have been observed, to assess early efficacy of Arm A versus Arm B with respect to the primary efficacy endpoint, PFS (see Section 12.3).

Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for a comprehensive list of study assessments and their timing.

7.2 Number of Subjects

Approximately 306 eligible subjects will be randomized in a 1:1 ratio into 2 arms (n = 153 each) to receive treatment in either Arm A or Arm B.

7.3 Estimated Study Duration

The end of the study is defined as the date of the last visit of the last subject in the study (LSLV).

After the final data cutoff (DCO), the following applies to subjects who are still on treatment and deriving clinical benefit:

- In a given country, when acalabrutinib or idelalisib are commercially available and reasonably accessible, subjects will be transitioned off study, and treatment will continue outside of the study protocol, per local laws and regulations.

- Where idelalisib is not commercially available and reasonably accessible, subjects who are receiving idelalisib may be transitioned to receive commercial acalabrutinib at the discretion of the investigator.
- Where acalabrutinib is not commercially available and reasonably accessible, subjects may be re-consented to continue within this study to receive acalabrutinib in line with standards of care.

After the DCO, all subjects' medical procedures and assessments will continue to be documented in the subject's medical records, but only SAEs will be reported using a paper form. Of the data collected at the study site after the final DCO, only SAEs will be reported.

7.4 Treatment Assignment

This study will use an interactive voice/web response system (IXRS) 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.

Randomization will be performed stratified by the following factors:

- Presence of 17p del
- ECOG performance status (0 or 1 versus 2)
- Number of prior therapies (1, 2, or 3 versus ≥ 4)

7.5 Criteria for Study Termination

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.
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

8 SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Subject Inclusion Criteria

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

1. Men and women ≥ 18 years of age.
2. ECOG performance status of 0 to 2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008):
    a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, or CD23) and CD5.
    b. Prolymphocytes may comprise ≤ 55% of blood lymphocytes.
    c. Presence of ≥ 5 x 10^9 B lymphocytes/L (5000/μL) in the peripheral blood (at any point since initial diagnosis).
4. Must have documented CD20-positive CLL.
5. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment:
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/μL).
    b. Massive (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 (ECOG performance score 2; inability to work or perform usual activities).
        iii. Fevers higher than 100.5°F or 38.0°C for ≥ 2 weeks before screening without evidence of infection.

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

6. 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. If an Investigator has chosen bendamustine/rituximab as the Arm B treatment, platelets must be ≥ 75,000 cells/μL (75 x 10^9/L).
    c. Serum AST and ALT ≤ 2.0 x ULN.
    d. Total bilirubin ≤ 1.5 x ULN.
    e. Estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].
7. Must have received ≥ 1 prior systemic therapies for CLL. Note: Single-agent steroids or localized radiation are not considered a prior line of therapy. If a single-agent anti-CD20 antibody was previously administered, subjects must have received ≥ 2 doses.
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, 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Highly effective forms of contraception are defined in Section 9.2.5.
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 idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Highly effective forms of contraception are defined in Section 9.2.5.
10. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
11. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules without difficulty.
12. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

8.2 Subject Exclusion Criteria

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

1. Known CNS lymphoma or leukemia.

2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled AIHA or ITP defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone or equivalent).
4. Prior exposure to a BCL-2 inhibitor (e.g., venetoclax/ABT-199) or a BCR inhibitor (e.g., BTK inhibitors or PI3K inhibitors). Prior bendamustine is allowed if Investigator's choice for treatment in Arm B is idelalisib with rituximab. Bendamustine retreatment is allowed if the prior response to bendamustine lasted > 24 months.
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
6. Corticosteroid use > 20 mg daily prednisone equivalent within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. For example, subjects requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.
7. Prior radio- or toxin-conjugated antibody therapy.
8. Prior allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose of study drug(s) or presence of graft-vs-host disease or receiving treatment for graft-vs-host disease.
9. Major surgical procedure within 30 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
10. History of prior malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 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 nonmelanomatous skin cancer.
    c. Adequately treated carcinoma in situ without current evidence of disease.
11. Significant cardiovascular disease such as uncontrolled or untreated 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 (calculated using Fridericia's formula: $QT/RR^{0.33}$) at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
12. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
13. Received a live virus vaccination within 28 days of first dose of study drug.
14. Known history of infection with HIV or any uncontrolled active systemic infection (e.g., bacterial, viral, or fungal). For study sites in Germany: active infection with human

immunodeficiency virus (seropositivity for HIV-1 or HIV-2 antibodies, and if positive, reactivity against the HIV-specific p24 antigen).

15. Active CMV infection (active viremia as evidenced by positive polymerase chain reaction [PCR] result for CMV DNA).
16. Serologic status reflecting active hepatitis B or C infection.
    a. Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before randomization. Those who are HbsAg-positive or hepatitis B PCR positive will be excluded.
    b. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR positive will be excluded.
17. Ongoing, drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
18. History of or ongoing drug-induced pneumonitis.
19. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.
20. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
21. History of bleeding diathesis (e.g., hemophilia, von Willebrand disease).
22. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
24. Requires treatment with a strong CYP3A inhibitor/inducer.
25. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
26. Breast feeding or pregnant.
27. Concurrent participation in another therapeutic clinical trial.
28. Prothrombin time/INR or aPTT (in the absence of a Lupus anticoagulant) > 2.0 x ULN. Exception: Subjects receiving warfarin are excluded, however, those receiving other anticoagulant therapy who have a higher INR/aPTT may be permitted to enroll to this study after discussion with the medical monitor.
29. History of confirmed progressive multifocal leukoencephalopathy (PML)

8.3 Withdrawal of Subjects from Treatment or Assessment

8.3.1 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 study
- Decision by Sponsor to terminate the study
- Subject lost to follow-up
- Death
- Other

8.3.2 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 case report form (CRF) and in the source documents. Subjects who withdraw consent should still be encouraged to complete the SFU 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 TREATMENT OF SUBJECTS

9.1 Concomitant Medications

9.1.1 Permitted Concomitant Medications

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

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

For subjects at risk for pneumonitis: In selected subjects (e.g., those with a history of recurrent pneumonias), anti-infectious prevention should be considered.

Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning before study drug administration may be warranted. Such support may also offer the benefit of reducing the risk for other bacterial infections (Stern 2014). Prophylaxis with intravenous immunoglobulin (IVIG) may be appropriate in subjects with low immunoglobulin levels (Raanani 2009). Local practices or guidelines regarding infection prophylaxis may be followed.

For subjects at risk for infections: Bacterial/viral/fungal prophylaxis is allowed per institutional standards.

9.1.2 Prohibited or Restricted 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. Corticosteroids may be administered for longer than 2 weeks to treat idelalisib-related AEs (e.g., pneumonitis and colitis). 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 rituximab infusion-related reactions are permitted.

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

9.1.3 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, concomitant administration of acalabrutinib with a strong CYP3A inhibitor increased exposure of acalabrutinib by approximately 5-fold (refer to the Investigator Brochure for additional details). Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 5) with acalabrutinib should be avoided when possible. If a subject requires short-term treatment with a strong CYP3A inhibitor while on study (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. If a subject requires a moderate CYP3A inhibitor while on study, decrease the acalabrutinib dose to 100 mg QD. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer has the potential to decrease acalabrutinib exposure and could reduce efficacy. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong CYP3A inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer. For additional information on drugs with potential drug-drug interactions, refer to the Acalabrutinib Investigator Brochure.

If subjects receiving idelalisib are taking concomitant strong CYP3A inhibitors, monitor for signs of idelalisib toxicity. Coadministration of strong CYP3A inducers or CYP3A substrates with idelalisib should be avoided.

Based on these considerations, subjects who require therapy with the drugs listed in Appendix 5 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug.

9.1.4 Guidelines for the Use of Drugs that Affect Gastric pH

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

acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the Investigator's discretion, with an understanding of balancing the potential benefit to the subject's gastrointestinal condition against a potential risk of decreased exposure to acalabrutinib.

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

9.1.5 Required Concomitant Medications

Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as PJP and CMV (ZYDELIG SmPC and ZYDELIG prescribing information). Prophylaxis for PJP in accordance with local guidelines and institutional standards should therefore be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia.

9.2 Risks Associated with Study Treatment

9.2.1 Acalabrutinib

Refer to Section 10.3.3 for specific dose modification and discontinuation guidelines.

Risks Associated with Acalabrutinib

The following summarizes the experience with acalabrutinib in hematological cancer studies. For more detailed information on TEAEs, please refer to the Acalabrutinib Investigator Brochure. Full details regarding the clinical safety of acalabrutinib are presented in Sections 5 and 6 of the Acalabrutinib Investigator's Brochure.

Hemorrhage

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

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

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

Infections

Serious infections, including fatal events, have been reported in subjects treated with acalabrutinib. Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to the sections below for additional information and monitoring guidance for viral hepatitis and additional information and management guidance for signs and symptoms of PML.

Hepatitis B Reactivation

Cases of hepatitis B virus (HBV) reactivation have been reported in subjects treated with acalabrutinib, with one case resulting in liver failure and death. Please refer to Section 11.1.11 for monitoring of HBV and management of subjects with HBV reactivation, including subjects who are routinely receiving IVIG for CLL management.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported in subjects 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 JC virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in subjects treated with acalabrutinib. Monitor blood counts as specified in the Schedule of Assessments and as medically appropriate. Please refer to Section 10.3 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.

Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in subjects treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for patients to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Please refer to Section 11.8.3 for second primary malignancy reporting guidance.

Atrial Fibrillation

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

Reference Safety Information

See the Reference Safety Information (RSI) in the Acalabrutinib Investigator Brochure for assessment of expectedness of serious adverse reactions.

9.2.2 Idelalisib

For complete information, refer to the United States Prescribing Information or local label, which serves as RSI for idelalisib for this global study. Please refer to Section 10.3.4 for specific dose modification and discontinuation guidelines.

Contraindications

History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.

Risks Associated with Idelalisib

- Monitor hepatic function prior to and during treatment, and in the event of transaminase elevation, interrupt, reduce or discontinue idelalisib.
- Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue idelalisib.
- Monitor for pulmonary symptoms and bilateral interstitial infiltrates associated with pneumonitis. Interrupt or discontinue idelalisib.
- Monitor for signs and symptoms of infection. Interrupt idelalisib if infection is suspected.
    - Interrupt idelalisib in subjects with suspected PJP infection of any grade, and discontinue idelalisib if PJP infection of any grade is confirmed.
- Monitor subjects with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection. For subjects with evidence of CMV infection of any grade or viremia (PCR above the lower limit of quantitation or positive antigen test), hold idelalisib until the infection has resolved. If treatment with idelalisib is resumed, monitor subjects (by PCR or antigen test) for CMV reactivation at least monthly and consider administering pre-emptive CMV therapy.
- Subjects should be monitored for respiratory signs and symptoms throughout treatment. Subjects should be advised to report new respiratory symptoms promptly.
- Discontinue idelalisib if intestinal perforation is suspected.
- If Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, interrupt idelalisib until the etiology of the reaction has been determined. If SJS or TEN is confirmed, discontinue idelalisib.
- Monitor subjects for the development of severe cutaneous reactions and discontinue idelalisib.

- Monitor subjects for serious allergic reactions, including anaphylaxis, and discontinue idelalisib.
- Monitor blood counts at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in subjects while ANC is less than 1.0 Gi/L.
- May cause fetal harm (see Section 9.2.5 for guidelines on contraception).

Drug-drug Interactions

Avoid coadministration of strong CYP3A inducers (Appendix 5) with idelalisib. Idelalisib is a strong CYP3A inhibitor. If subjects are taking concomitant strong CYP3A inhibitors (Appendix 5), monitor for signs of idelalisib toxicity. Follow dose modifications for adverse reactions.

9.2.3 Bendamustine

For complete information, refer to the United States Prescribing Information/label which, will serve as RSI for bendamustine for this global study. Please refer to Section 10.3.5 for specific dose modification and discontinuation guidelines.

Contraindications

History of a hypersensitivity reaction to bendamustine. Reactions included anaphylaxis and anaphylactoid reactions.

Risks Associated with Bendamustine

- Myelosuppression: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death.
- Infections: Monitor for fever and other signs of infection or reactivation of infections and treat promptly.
- Subjects should be monitored for respiratory signs and symptoms throughout treatment. Subjects should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine should be considered if there are signs of (opportunistic) infections. Anaphylaxis and infusion reactions: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue bendamustine. Premedicate in subsequent cycles for milder reactions.
- TLS: Acute renal failure and death; anticipate and use supportive measures.

- Skin reactions: Discontinue for severe skin reactions. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes.
- Other malignancies: Pre-malignant and malignant diseases have been reported.
- Extravasation injury: Assure good venous access and monitor infusion site during and after administration.
- May cause fetal harm (see Section 9.2.5 for guidelines on contraception).

Drug-drug Interactions

Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine.

9.2.4 Rituximab

For complete information, refer to the United States label for the RSI for rituximab for this study. Also refer to Section 10.3.6 in this protocol for specific dose modification and discontinuation guidelines.

Contraindications

None.

Warnings and Precautions

- Fatal infusion reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor subjects and discontinue rituximab infusion for severe reactions
- Severe, including fatal, mucocutaneous reactions can occur in subjects receiving rituximab.
- HBV reactivation can occur in patients treated with rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Monitor subjects for HBV reactivation during and after treatment with rituximab. Discontinue rituximab and concomitant medications in the event of HBV reactivation.
- Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur in subjects receiving rituximab.

- TLS: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function.
- Infections: Withhold rituximab and institute appropriate anti-infective therapy.
- Cardiac arrhythmias and angina: Discontinue infusions in case of serious or life-threatening events.
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms.
- Live virus vaccines: Do not administer live virus vaccines prior to or during rituximab.
- Cytopenias: Monitor blood counts at regular intervals.

Drug-drug Interactions

Renal toxicity may result when rituximab is used in combination with cisplatin.

9.2.5 Reproductive Toxicity

Definition of women of non-reproductive potential:

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

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

OR

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

OR

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

Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and 2 days after the last dose of acalabrutinib, 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, 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 idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Men must also agree to refrain from donating sperm during the study and for 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer. Examples of highly effective methods of contraception are defined below.

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

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

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

†Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and postovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method 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.

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

There are no adequate and well-controlled studies of rituximab in pregnant women. Based on findings in animals, idelalisib may cause fetal harm when administered to a pregnant woman. Bendamustine can cause fetal harm when administered to pregnant women.

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. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the Investigator if they, or their partners, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue study drug(s) immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 11.8.5.

9.3 Treatment Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other acalabrutinib/idelalisib treatments will be taken at home. Subjects will receive a drug diary to record that each dose was taken and to record reasons for any missed doses.

Subject compliance with acalabrutinib/idelalisib will be assessed at each study visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next

visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 10.4. Returned capsules must not be redispensed to another subject.

9.4 Enrollment and Randomization Procedures

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

- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be randomized into the study.
- To confirm eligibility, the study center will fax/email a completed Enrollment Confirmation Form to the Sponsor or designee. The enrollment date will be the date that the Sponsor confirms eligibility for randomization.
- The Sponsor, or designee, will aim to fax/email a completed Enrollment Confirmation Form to the study center within 48 hours of receipt.

This study will use an IXRS for randomization. As subjects qualify for randomization, designated study center personnel will contact the IXRS, which will assign a treatment arm to each eligible subject.

Treatment must begin within the screening window (Section 11). It is recommended to begin treatment as soon as possible after randomization.

9.5 Restrictions

Dietary Restrictions

Acalabrutinib should be taken with water and may be taken with or without food. Because acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against using herbal remedies or dietary supplements that contain potent CYP3A inhibitors or CYP3A inducers (in particular, St John's wort, which is a potent CYP3A inducer).

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

10 STUDY DRUG MATERIALS AND MANAGEMENT

10.1 Identification of Investigational Medicinal Product

The following regimens are being evaluated on this study:

ARM	REGIMEN
A: Acalabrutinib	Acalabrutinib 100 mg PO BID
B: Idelalisib/Rituximab	Idelalisib 150 mg PO BID + rituximab 375 mg/m^2 IV on Day 1 of the first cycle, followed by 500 mg/m^2 IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions.
B: Bendamustine/Rituximab	Bendamustine: 70 mg/m^2 IV on Days 1 and 2 of a 28-day cycle for a maximum of 6 cycles + rituximab 375 mg/m^2 IV on Day 1 of the first cycle and 500 mg/m^2 IV on Day 1 of Cycles 2 to 6.

Abbreviations: BID = twice per day; IV = intravenous; PO = orally.

10.1.1 Acalabrutinib

Acalabrutinib is provided as hard gelatin capsules for oral administration. The capsules are packaged in opaque high-density polyethylene 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. CCI [redacted]

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

10.1.2 Idelalisib

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

Commercially available idelalisib will be provided as film coated tablets (100 and 150 mg) for oral administration per the instructions in the locally approved labelling (e.g., see United States prescribing information) and per institutional standards.

10.1.3 Bendamustine

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

Commercially available bendamustine will be supplied for IV administration according to the instructions in the locally approved labelling (e.g., see United States prescribing information) and per institutional standards.

10.1.4 Rituximab

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

Commercially available rituximab will be supplied for IV administration according to the instructions in the locally approved labelling (e.g., see United States prescribing information) and per institutional standards.

10.2 Study Drug Preparation and Administration

10.2.1 Acalabrutinib

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

Acalabrutinib is intended to be administered orally 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 (preferably within ± 1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been

> 3 hours, the dose should not be taken and the subject should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

10.2.2 Idelalisib

Idelalisib 150 mg will be orally administered BID until disease progression or unacceptable toxicity. Idelalisib may be taken with or without food; tablets should be swallowed whole. Idelalisib will be stored and administered according to the instructions in locally approved labelling and institutional standards. The United States Prescribing Information for idelalisib will serve as the RSI for this global study, to facilitate determination of expectedness or unexpectedness of adverse events possibly associated with idelalisib.

10.2.3 Bendamustine

Bendamustine 70 mg/m^2 will be administered as an IV infusion on Days 1 and 2 of a 28-day cycle. Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full six cycles to be received, wherever possible. See further instructions for data entry in such cases in the eCRF guidelines. A maximum of 6 cycles of bendamustine are allowed. Bendamustine will be reconstituted, administered and stored according to the instructions in locally approved labelling and institutional standards. Consult the medical monitor for guidance if the local or institutional standards for bendamustine dosing differ from the protocol. In any case, the protocol defined total dose per cycle should be administered regardless of local or institutional variation in the dosing schedule. The United States Prescribing Information for bendamustine will serve as the RSI for this global study, to facilitate determination of expectedness or unexpectedness of adverse events possibly associated with bendamustine.

10.2.4 Rituximab

When administered with idelalisib, the rituximab regimen will be 375 mg/m^2 on Day 1 of the first cycle, followed by 500 mg/m^2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions.

When administered with bendamustine, the rituximab regimen will be 375 mg/m^2 on Day 1 of the first cycle and 500 mg/m^2 on Day 1 of Cycles 2 to 6.

Rituximab will be reconstituted, administered and stored according to the instructions in locally approved labelling and institutional standards. Rituximab should be administered as an IV infusion through a dedicated line under the close supervision of an experienced physician. Rituximab infusions should not be administered as an IV push or bolus. Premedication is required before each infusion (Section 10.3.7). The United States Prescribing Information for rituximab will serve as RSI for this global study, to facilitate determination of expectedness or unexpectedness of adverse events possibly associated with rituximab.

10.3 Dose Delays and Modifications

10.3.1 Safety Criteria for Adjustment or Stopping Doses

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 both hematologic and non-hematologic toxicities will be based on the grading scale in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

10.3.2 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. Refer to Section 11.1.25 for more information on assessing disease progression under these circumstances. 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.

Surgery

Susceptibility to bleeding has been observed with acalabrutinib use. As a precaution, it is suggested per protocol that acalabrutinib be withheld for 3 days before and 3 days after any major surgical procedure (see Section 9.2.1 Hemorrhage).

10.3.3 Guidelines for Dose Modification and Discontinuation for Acalabrutinib

The actions in Table 10-1 should be followed for the following toxicities (according to CTCAE criteria version 4.03) (see Section 11.7.4 for guidelines on the grading of toxicities):

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

Table 10-1. Drug Modification Actions for Acalabrutinib

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

Abbreviation: PO = orally; 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 PO BID for this protocol.

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

10.3.4 Guidelines for Dose Modification and Discontinuation for Idelalisib

Idelalisib dose reductions are described below (Table 10-2). For severe or life-threatening toxicities related to idelalisib, withhold drug until toxicity is resolved. If resuming idelalisib after interruption for severe or life-threatening toxicities, reduce the dose to 100 mg PO BID. Recurrence of severe or life-threatening idelalisib-related toxicity upon rechallenge should result in permanent discontinuation of idelalisib. If idelalisib is discontinued, subjects can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Study drug (idelalisib) may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment (idelalisib) should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

Table 10-2. Dose Modifications for Toxicities Due to Idelalisib

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue idelalisib in subjects with any severity of symptomatic pneumonitis		
ALT/AST	**> 3 to 5 x ULN**	**> 5 to 20 x ULN**	**> 20 x ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤ 1 x ULN.	Withhold idelalisib. Monitor at least weekly until ALT/AST are ≤ 1 x ULN, then may resume idelalisib at 100 mg PO BID.	Discontinue idelalisib permanently.
Bilirubin	**> 1.5 to 3 x ULN**	**> 3 to 10 x ULN**	**> 10 x ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤ 1 x ULN.	Withhold idelalisib. Monitor at least weekly until bilirubin is ≤ 1 x ULN, then may resume idelalisib at 100 mg PO BID.	Discontinue idelalisib permanently
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain idelalisib dose. Monitor at least weekly until resolved.	Withhold idelalisib. Monitor at least weekly until resolved, then may resume idelalisib at 100 mg PO BID.	Discontinue idelalisib permanently

Table 10-2. Dose Modifications for Toxicities Due to Idelalisib

Neutropenia	**ANC 1.0 to < 1.5 Gi/L**	**ANC 0.5 to < 1.0 Gi/L**	**ANC < 0.5 Gi/L**
	Maintain idelalisib dose.	Maintain idelalisib dose. Monitor ANC at least weekly.	Interrupt idelalisib. Monitor ANC at least weekly until ANC ≥ 0.5 Gi/L, then may resume idelalisib at 100 mg PO BID.
Thrombocytopenia	**Platelets 50 to < 75 Gi/L**	**Platelets 25 to < 50 Gi/L**	**Platelets < 25 Gi/L**
	Maintain idelalisib dose	Maintain idelalisib dose. Monitor platelet counts at least weekly.	Interrupt idelalisib. Monitor platelet counts at least weekly, may resume idelalisib at 100 mg PO BID when platelets ≥ 25 Gi/L.
Infections	**Grade 3 or higher sepsis or pneumonia**		
	Interrupt idelalisib until infection has resolved		
	Evidence of CMV infection or viremia		
	Withhold idelalisib in subjects with evidence of CMV infection of any grade or viremia (PCR above the lower limit of quantitation or positive antigen test). Idelalisib may be restarted once subject has PCR below the lower limit of quantitation; as per Investigator discretion. If idelalisib is resumed, monitor (by PCR or antigen test) for CMV reactivation at least monthly.		
	Evidence of PJP infection		
	Withhold idelalisib in subjects with suspected PJP infection of any grade. Permanently discontinue idelalisib in subjects with active or confirmed PJP infection.		

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; Gi/L = giga/liter; PO = orally; ULN = upper limit of normal.
*Moderate diarrhea: Increase of 4 to 6 stools per day over baseline; severe diarrhea: Increase of ≥7 stools per day over baseline.

10.3.5 Guidelines for Dose Modification and Discontinuation for Bendamustine

Bendamustine administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant Grade ≥ 2 nonhematologic toxicity. Once nonhematologic toxicity has recovered to Grade ≤ 1 and/or the blood counts have improved (ANC ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L), bendamustine can be reinitiated at the discretion of the treating

physician. In addition, dose reduction may be warranted (see the US Prescribing Information for bendamustine). If bendamustine is discontinued, subjects can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Dose modifications for hematologic toxicity: for Grade ≥ 3 toxicity, reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle; if Grade ≥ 3 toxicity recurs, reduce the dose to 25 mg/m^2 IV on Days 1 and 2 of each cycle.

Dose modifications for nonhematologic toxicity: for clinically significant Grade ≥ 3 toxicity, reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

Subjects should be monitored for respiratory signs and symptoms throughout treatment. Subjects should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine should be considered if there are signs of (opportunistic) infections.

Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full six cycles to be received, wherever possible. See further instructions for data entry in such cases in the eCRF guidelines. Locally and/or regionally approved minor schedule variations in administration of bendamustine + rituximab may be accommodated, provided the doses of both bendamustine and rituximab remain the same as specified in the protocol, and the total doses per cycle remain the same as per protocol, with modifications for toxicity as provided above.

In the event of dosing delays due to toxicity, when possible, dosing of both bendamustine and rituximab should be held, and readministered together once toxicity has resolved to grade 1 or better (or to study baseline). In such cases, the cycle schedule will be shifted accordingly (see instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

Study drug (bendamustine) may be held a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment (bendamustine) should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by Medical Monitor.

10.3.6 Guidelines for Dose Modification and Discontinuation for Rituximab

No dose modification is allowed for rituximab. If rituximab is discontinued, subjects can continue to receive idelalisib or bendamustine as outlined in this protocol. If bendamustine or idelalisib are discontinued, subjects can continue to receive rituximab up to the maximum number of infusions allowed on this protocol. The initial dose of rituximab may be divided for administration, per local or institutional standards.

10.3.7 Premedication Requirements (Rituximab)

Premedicate before each rituximab infusion with acetaminophen and an antihistamine in accordance with prescribing information or institutional standards.

10.4 Study Drug Accountability

Acalabrutinib, rituximab, bendamustine, and idelalisib must be kept in a locked limited access cabinet or space, under appropriate storage conditions. 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.

11 STUDY ACTIVITIES AND ASSESSMENTS

The Schedule of Assessments are provided in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. See Appendix 13 for management of study procedures during pandemic. 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. Screening clinical and laboratory evaluations may be repeated as medically appropriate and to support eligibility, if completed during the 30-day screening window. Throughout the study clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such unscheduled

assessments will be captured in the protocol-specific database as appropriate. This study will primarily use central laboratory testing for laboratory evaluations. Samples from sites' local laboratories will be used if central testing is unavailable.

11.1 Description of Procedures

11.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the IRB or IEC, confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information, if required by local regulations.

11.1.2 Medical History

Collect and record the subject's complete history including concurrent medical signs and symptoms, alcohol use and, if a smoker, cigarette use. Disease history, including the date of initial diagnosis, Rai and Binet staging within 30 days of first dose with study drug, documentation of refractory disease, prior anticancer treatments with best responses and progression-free interval to these treatments, and history of autoimmune CLL complications and their treatment will also be recorded based upon available documents and subject history.

11.1.3 Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criteria (Sections 8.1 and 8.2). Blood samples for hematology and serum chemistry collected at screening will be evaluated by a central laboratory to confirm eligibility. With the exception of fluorescence in situ hybridization (FISH), if central laboratory results submitted during the screening period are unable to be analyzed (e.g., specimen clotted or hemolysis) to support eligibility, the medical monitor may review local laboratory results and approve the subject for randomization based on these lab values on a case-by-case basis provided another sample is redrawn and submitted before treatment. The following de-identified documentation is requested before randomization:

- Copies of a pathology report confirming diagnosis of CLL.
- Radiology reports from screening CT/MRI.
- Copies of bone marrow aspirate and biopsy report.
- Copies of FISH.

Treatment must begin within the screening window (first dose of study drug should be administered within 30 days of signing consent) unless otherwise indicated. Subjects can be re-screened which requires signing the ICF again and repeating screening procedures, with the exception of the bone marrow biopsy and aspirate and CT/MRI scan, if still within 30 days of the first dose. Subjects that re-screen must be re-entered in IXRS and will receive a new Subject ID.

11.1.4 ECOG Performance Status

The ECOG performance index is provided in Appendix 6.

11.1.5 Physical Examination, Vital Signs, Height & Weight, CCI

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

CCI

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

11.1.6 Electrocardiogram (ECG)

An ECG will be performed at screening. Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs.

11.1.7 Patient Reported Outcomes (PRO)

As of Amendment 6.0, the [redacted] instruments (i.e., FACIT-Fatigue, [redacted] will no longer be administered in this study. Through Amendment 5.0, the subject was to complete the questionnaires detailed below before any other study procedures at required visits.

FACIT-Fatigue

The FACIT-Fatigue questionnaire is an instrument for use as a measure of fatigue-related quality of life in subjects with cancer and other chronic diseases (http://www.facit.org). The 13-item FACIT-Fatigue Scale measures each item on a 5-point Likert scale. The FACIT-Fatigue Scale has been validated in the general population (Cella 2002) as well as in subjects with cancer or rheumatoid arthritis. Refer to Appendix 7 for more information.

[redacted]

CCI

11.1.8 Concomitant Medications and Therapy

Document all concomitant medications and procedures from 30 days before the start of study drug administration until 30 days after the last dose of study drug or the start of a new anticancer treatment (whichever comes first).

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

11.1.9 AEs

The accepted regulatory definition for an AE is provided in Section 11.7.1. Refer to Section 11.8.1 for the AE reporting period. Important additional requirements for reporting SAEs are explained in Section 11.8.7.

11.1.10 Serum/Urine Pregnancy Test

Serum pregnancy testing, per the Schedule of Assessments (Appendix 1 to Appendix 4), will be required only for women of childbearing potential. More frequent pregnancy testing (either urine or serum) than delineated in the Schedule of Assessments may be done if required by local regulatory authorities.

11.1.11 Hepatitis B and C Testing and Monitoring

Hepatitis virus serology testing at screening must include HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. Testing will be done by local or central laboratory. Subjects with seropositivity for HBsAg at screening may not be enrolled in the study (see Exclusion 16). Subjects who are HBsAg negative but anti-HBc positive at screening may be enrolled provided they have a negative quantitative PCR for HBV DNA (undetectable viral load) at screening. Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and every month during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV 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.

For sites in countries or regions with high endemic levels of HBV infection where prophylactic treatment with antiviral agents during treatment with immunosuppressive therapies may be the local or regional standard of care, such antiviral prophylaxis may be permitted on study, providing the antiviral agent is not a strong inducer or inhibitor of CYP3A. Subjects who receive antiviral prophylaxis for HBV on study should still comply with the requirement for serial monitoring for HBV reactivation by quantitative PCR for HBV DNA at the frequency prescribed above (and in the Schedule of Assessments).

For subjects with CLL whose disease management includes periodic administration of IVIG, the IVIG may cause false positive hepatitis B serologic tests. Subjects receiving routine IVIG who have anti-HBc antibody or surface antigen positivity without evidence of active viremia (e.g., negative hepatitis B DNA by quantitative PCR at screening) may still participate in the study, but should have monitoring for potential HBV reactivation, as follows. 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 in these subjects 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 by quantitative PCR for HCV RNA during screening. Such subjects may be enrolled provided the quantitative PCR is negative (undetectable viral load). No further monitoring for HCV RNA during treatment is necessary if initial PCR results are negative.

Refer to Section 9.2.1 and Appendix 1 to Appendix 4 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or who have a known history of HBV or HCV.

11.1.12 HIV Testing (for Study Sites in Germany)

A peripheral blood sample (required) will be drawn and sent at screening to a central vendor to be tested for seropositivity for HIV-1 antibody, HIV-2 antibody, and if positive, reactivity for the HIV-specific p24 antigen. Subjects with active infection with HIV-1 or HIV-2 may not enroll in the study (Exclusion Criterion #14).

11.1.13 Cytogenetics and FISH Panel

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

evaluation will also be drawn at Cycle 7, and when a subject has disease progression or at the TT or SFU visits.

11.1.14 CCI

CCI

11.1.15 Hematology

Hematology will be evaluated by a central laboratory and will include a complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. 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.

11.1.16 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

11.1.17 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

11.1.18 Serum Immunoglobulin and β_2-microglobulin

Sample(s) will be sent to a central laboratory for quantitative immunoglobulin (IgG, IgM, and IgA) levels and serum β_2-microglobulin.

11.1.19 T/B/Natural Killer (NK)/monocyte Cell Count

Whole blood samples will be analyzed for absolute T/B/NK cell counts (CD3, CD19, CD4, CD8, CD14, CD16/56) using a standard cell marker panel.

11.1.20 CCI

CCI

11.1.21 CCI

CCI

11.1.22 Computed Tomography or Magnetic Resonance Imaging Scans

Radiologic 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 radiologic 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.

Pretreatment radiologic tumor assessment must be obtained within 30 days before the first dose and standard of care tumor assessments may be used, provided they comply with the radiologic requirements as outlined in the radiology manual. Radiologic tumor assessment will also be performed 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 bendamustine-treated subjects, the second radiologic tumor assessment will occur at the next 12-week interval (± 14 days) regardless of whether the subject is on study drug. CT or MRI scans can be performed ≤ 7 days before response evaluation. CT or MRI scans will be performed until disease progression is confirmed, regardless of whether the subject remains on treatment. In the event disease progression is suspected due to physical examination or laboratory test, a CT or MRI scan must be performed to confirm disease progression. If the sole measurable lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion that has not been previously irradiated.

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. Target lymph nodes should not be selected from previously irradiated areas. 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. The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

A central imaging service will be used to provide independent radiologic assessments for the purposes of the primary endpoint. Only confirmation of disease progression by the Sponsor will be reported back to the site.

If the subject's physical examination findings, laboratory evaluations (with hematology profile including absolute lymphocyte count, ANC, platelet count, and Hgb), and radiographic

evaluations suggest that CR has been achieved in all response parameters, a bone marrow aspirate and biopsy must be obtained to confirm the CR and to evaluate minimal residual disease (MRD). The bone marrow aspirate and biopsy must be done within 8-12 weeks of the CT/MRI imaging that supported the assessment of CR. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done at a central laboratory for confirmation of Richter's transformation. Biopsy of the affected site is diagnostic and sufficient for confirmation. If per local standard of care or at Investigator discretion an ancillary whole-body PET-CT scan (not required for study) is performed, the results of this scan should be captured in the electronic data capture (EDC) system as an unscheduled visit.

11.1.23 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. The Schedule of Assessments for Arm A (acalabrutinib monotherapy), Arm B (separate schedules for idelalisib + rituximab or bendamustine + rituximab), and crossover subjects are found in Appendix 1 to Appendix 4, for screening, treatment, post-treatment disease follow-up, and long-term survival phases.

11.1.24 Assessments to Determine Eligibility for Crossover

Assessments to determine eligibility for crossover before the final DCO include the following:

1. Subjects who develop Sponsor-confirmed progressive disease on either of the Arm B Investigator choice treatments will be eligible to cross over to acalabrutinib monotherapy upon development of Sponsor-confirmed disease progression according to IWCLL 2008 criteria for CLL; this eligibility for crossover is not time-limited relative to discontinuation of active treatment and extends into the post-treatment follow-up period, including subjects who may have discontinued study treatment for reasons other than disease progression.
2. Arm B subjects who discontinue study treatment (either by completing course of treatment, or by premature discontinuation related to toxicity or other reason) remain eligible for crossover to acalabrutinib monotherapy. Such subjects will enter the post-treatment follow-up period and continue to be actively monitored according to the Schedule of Assessments for their randomized treatment arm with every 3-month study

visits, physical exam, labs, collection of adverse events, and radiologic tumor imaging scans at the protocol-required frequency; it is important that these scheduled assessments not be missed.

Following the Sponsor communication to study site confirming progressive disease, the site may request authorization for crossover of Arm B subjects, contingent on review of the following requirements:

- Eligibility for crossover includes (after Sponsor-assessed disease progression has been confirmed) meeting all eligibility criteria for the main study, including ECOG performance status and the laboratory parameters as outlined in the inclusion criteria. Screening for eligibility and trial assessments during crossover are described in Appendix 4 and should occur within 30 days of disease progression. Subjects who previously tested anti-HBc negative at initial screening for the main study period and are approved for Crossover Screening will undergo hepatitis serology and HBV DNA PCR testing. If these patients are discovered to be anti-HBc positive but HBV PCR negative (required to meet eligibility) at Crossover Screening, they will undergo monthly HBV PCR monitoring for reactivation (as required for the main study period).
  Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during Crossover Screening and every month during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitoring should continue until 12 months after the last dose of study drug. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.
- While subjects who have been randomized to any of the study treatment arms who discontinue study treatment for reasons other than disease progression (e.g., have not yet progressed) may receive alternative (non-protocol specified) anticancer treatments without restriction during the post-treatment follow up period as clinically indicated per Investigator discretion [such treatments and clinical indication for treatment must be entered into the EDC], subjects may not receive any new systemic therapy in the interval between Sponsor confirmation of disease progression and the initiation of crossover therapy with acalabrutinib.

- The following documentation will be reviewed before enrollment to the crossover arm by the medical monitor:
  - Radiology reports from computed tomography (CT)/magnetic resonance imaging (MRI); CT/MRI from disease progression can be used for the new tumor imaging baseline against which to assess tumor response on crossover treatment if within 30 days of crossover dosing Cycle 1 Day 1.
- Crossover treatment should be initiated within a window of 30 days after the crossover approval is granted.
- Once crossover treatment is initiated, the Schedule of Assessments (Appendix 4) will be followed; this is closely similar to that of subjects who were originally randomized to Arm A acalabrutinib monotherapy.
- Safety and efficacy data for subjects who cross over to acalabrutinib monotherapy will be analyzed as a stand-alone group, independent of Arm B or Arm A.

See also Section 7.1, Overall Study Design, for details on crossover procedures.

11.1.25 Overall Response Evaluations

Overall response assessments will be based upon evaluation of physical exams, recording of symptoms, radiologic evaluations, and hematologic evaluations per the Schedule of Assessments. (Note: CBC with differential, including ALC, must be done within 7 days, and bone marrow aspirate/biopsy [when applicable] must be done within 8-12 weeks of suspected CR, of the contemporaneous radiologic evaluation supporting CR, when all IWCLL response criteria for CR/CRi have been met in a subject with no disease-related symptoms, see Appendix 10). Subjects who have signs and symptoms of disease progression outside of the scheduled study visits and assessments 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 should be confirmed by a central laboratory (samples from local laboratories can be used if central testing is unavailable). Any suspected case of disease progression should be confirmed with a CT scan if one was not obtained and should be reported to the Sponsor or designee. Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. In addition, when clinically appropriate, based on Investigator-perceived risk-benefit assessment, a subject may continue treatment and remain under close observation until progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease.

11.1.26 Bone Marrow Aspirate and Biopsy

For Eligibility

A unilateral bone marrow aspirate and biopsy will be collected 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 confirmation of eligibility, and may be stored for future Acerta CLL-directed research.

Bone Marrow Aspirate and Biopsy for Confirmation of CR/CRi and Minimal Residual Disease (MRD)/Response Evaluation (additional details are provided in Appendix 10).

In the setting of suspected CR, when the subject's physical examination findings, laboratory evaluations (including hematology profile with ALC, ANC, platelet count, and Hgb), and radiographic findings indicate that all IWCLL response parameters for CR have been achieved (Appendix 10), a bone marrow aspirate and biopsy and peripheral blood sample must be obtained to confirm the CR/CRi pathologically and to evaluate MRD. According to IWCLL response criteria, CR/CRi requires all of the supporting clinical assessments (see Appendix 10), a tabular summary of IWCLL Response Assessment Criteria, per Hallek 2008 and updated for persistent lymphocytosis per Cheson 2012) be assessed at least two months following completion of therapy (for purposes of this study protocol, within 8-12 weeks of suspected CR). The proper timing of bone marrow sampling, therefore, will differ according to the duration of treatments in Arm A and Arm B, as outlined in the following sub-section. A single determination of MRD will be made in this study, during the time window noted above for confirmation of CR. Per IWCLL guidance, a marrow aspirate sample (as opposed to peripheral blood sample) will be used for determination of MRD at this time point.

In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to confirm, and to exclude alternate etiologies such as autoimmune and drug-related cytopenias. A bone marrow aspirate and biopsy may also be obtained, if indicated, for confirmation of progressive disease by Richter's transformation.

Timing of Bone Marrow Aspirate and Biopsy in Setting of Suspected CR, According to Treatment Arm.

Arm A: Acalabrutinib monotherapy, or Crossover treatment to acalabrutinib monotherapy:

For subjects randomized to Arm A acalabrutinib monotherapy, which is administered continuously until the time of disease progression: if the subject's physical examination findings, laboratory evaluations (including hematology profile with ALC, ANC, platelet count, and Hgb), and radiographic evaluations suggest that all IWCLL response assessment criteria for CR have been achieved, a bone marrow biopsy/aspirate and peripheral blood sample to confirm pathology and evaluate MRD should be obtained between 8-12 weeks from the time of supportive clinical assessments, including CT/MRI imaging of suggested CR.

Arm B: Idelalisib/Rituximab:

For subjects randomized to Arm B treatment with idelalisib plus rituximab, with idelalisib administered continuously until the time of disease progression while the rituximab is administered for a maximum of 8 infusions: if the subject's physical examination findings, laboratory evaluations (including hematology profile with ALC, ANC, platelet count and Hgb), and radiographic evaluations suggest that all IWCLL response criteria for CR have been achieved prior to the completion of the 8 cycles of rituximab treatment, a bone marrow biopsy/aspirate and peripheral blood sample to confirm pathology and evaluate MRD should be obtained between 8-12 weeks after the completion of rituximab treatment. For subjects who continue on idelalisib monotherapy once rituximab treatment has been completed, and have not yet developed progressive disease, 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 should be obtained between 8-12 weeks from the time of supportive clinical assessments.

Arm B: Bendamustine/Rituximab:

For subjects on bendamustine plus rituximab, which are both of finite duration and limited to 6 cycles of treatment: if the subject's physical examination findings, laboratory evaluations (including hematology profile with ALC, ANC, platelet count and Hgb), and radiographic evaluations suggest that a CR has been achieved prior to completion of treatment, a confirmatory bone marrow biopsy/aspirate and peripheral blood sample to confirm pathology and to evaluate MRD should be obtained no earlier than between 8-12 weeks after the completion of treatment. 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/aspirated and peripheral blood sample to confirm pathology and evaluate MRD should be obtained no earlier than between 8-12 weeks from the time of supportive clinical assessments.

11.1.27 Cytomegalovirus Testing

CMV testing at screening (and crossover screening) must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at screening. Subjects assigned to Arm B must have monthly CMV DNA PCR testing while on treatment. Monthly monitoring for CMV should continue by CMV DNA PCR testing for previously treated Arm B

subjects until 12 months after the last dose of idelalisib or bendamustine, including the crossover period. The screening CMV serologies will be advisory only, to guide Investigators in assessing risk of new infection or reactivation of CMV while on study.

11.2 TT and SFU Visits

Until final DCO, a TT visit is required for safety assessments for any subjects who permanently discontinue treatment for any reason (except for death, lost to follow up, or withdrawal of consent), including disease progression. The TT 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 study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit.

Until final DCO, 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 1 to Appendix 4 for the assessments required for the TT and SFU visits.

11.3 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.

After the final DCO, all data collected at the study site, per standard of care, will be recorded in the subject's medical records. Only SAEs will be reported.

11.4 Post-treatment Disease Follow-up

Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should

occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Refer to Appendix 1 to Appendix 4 for the full list of assessments required during this period.

After the final DCO, no further data will be collected for post-treatment disease follow-up.

11.5 Survival Follow-up

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

After the final DCO, no further data will be collected for survival follow-up.

11.6 Missed Evaluations

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

11.7 Adverse Events and Serious Adverse Events

11.7.1 Definition of Adverse Events

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

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL that were not present before the AE reporting period (see Section 11.8.1).
- Pre-existing medical conditions (other than the condition being studied) judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

- Abnormal laboratory values considered clinically significant by the Investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

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

- **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.

11.7.2 Serious Adverse Event

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

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

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening (i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Requires or prolongs inpatient 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).
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- Is considered a significant medical event by the Investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

After the final DCO, all data collected at the study site, per standard of care, will be recorded in the subject’s medical records. Only SAEs will be reported.

11.7.3 Adverse Events of Special Interest

The following events are adverse events of special interest and must be reported to the Sponsor expeditiously (see Section 11.8.7 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

11.7.4 Severity

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

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

11.8 Documenting and Reporting of AEs and SAEs

The Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs must be reported using the SAE report form or clinical database.

11.8.1 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 the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

11.8.2 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.

Disease progression itself is not considered an AE unless it is considered to be drug-related by the Investigator; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

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

See Appendix 11 for more detail on assessing causality.

11.8.3 Second Primary Malignancies

Adverse events 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 (IP) under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

11.8.4 Hy's Law

Cases in which a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Refer to Appendix 12 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

11.8.5 Pregnancy

The Investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to the Study Representative. Any pregnancy-associated SAE must be reported using the SAE report form according to the usual timelines and directions for SAE reporting (Section 11.8.1).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib, 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine or 12 months after last dose of rituximab (whichever is longer) will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous

miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

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

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

11.8.6 Overdose

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

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

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

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

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

All SAEs and AESIs must be reported within 24 hours of discovery. Initial SAE/AESI reports and follow-up information will be reported using the protocol-specific EDC system, according to the instructions provided in the Investigator site file. If electronic SAE reporting is not available,

paper SAE forms must be emailed or faxed to the Study Representative. The Study representative may request follow-up and other additional information from the Investigator (e.g., hospital admission/discharge notes and laboratory results).

After the final DCO, all AEs, SAEs, irrespective of attribution of causality, and periodic laboratory results will be collected and recorded in the subject's medical records. Only the SAEs will be reported to the sponsor using a paper form.

Whenever possible, AEs/SAEs should be reported by diagnosis term, not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the 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 the Study Representative as outlined above.

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of 'related' may be used for expedited reporting purposes) and the SAE is not listed in the current Acalabrutinib Investigator Brochure (i.e., an unexpected event). In this case, the Study Representative 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.

11.8.8 Type and Duration of Follow-up of Subjects after AEs

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

12 STATISTICS

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.

IRC

There will be an IRC which will conduct response evaluations in accordance with its charter.

DMC

The DMC will review the safety data periodically and the results of the interim analysis and provide recommendations according to the DMC charter.

The first safety data review will be performed by the DMC after approximately 50 subjects have been randomized and had the opportunity to be treated for approximately 8 weeks. After the first review meeting, the DMC will meet and review data approximately every 6 months and as needed when required by the Sponsor or the DMC. This analysis will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs. The medical monitor will review this information on an ongoing basis until the first safety data review is conducted by the DMC.

12.1 Randomization

This study will use an IXRS for randomization. Approximately 306 eligible subjects will be randomized in a 1:1 ratio into 2 arms (n = 153 each) to receive either acalabrutinib 100 mg BID (Arm A) or idelalisib/rituximab or bendamustine/rituximab (Arm B).

Subjects will be randomized based on the following stratification factors:

- Presence of 17p del
- ECOG performance status (0 or 1 versus 2)
- Number of prior regimens (1, 2, or 3 versus ≥ 4)

12.2 Determination of Sample Size

The study is expected to enroll approximately 306 subjects with 1:1 randomization ratio.

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

12.3 Interim Analysis

One interim analysis will be conducted to assess early efficacy of Arm A versus Arm B with respect to the primary efficacy endpoint, IRC-assessed PFS using Lan and DeMets with O'Brien-Fleming boundaries (Lan 1983, O'Brien 1979). CCI [redacted] The nominal alpha levels for the interim and final analyses will be determined based the actual number of PFS events observed at the time of the analyses.

If the criterion for early efficacy is met at the time of the interim analysis, the DMC may recommend stopping the study in accordance with the terms of the DMC charter.

If the primary endpoint achieves statistical significance, then selected secondary endpoints will be tested in a manner that will preserve the overall Type I error rate at the 2-sided significance level of 0.05. The SAP will describe the methodology for multiplicity adjustment.

12.4 Final Analysis

The final analysis will occur when the primary endpoint is mature, i.e., CCI [redacted]

12.5 Analysis Populations

ITT Population

The ITT population is defined as all randomized subjects. All efficacy analysis will be performed in the ITT population and will be analyzed as randomized unless specified otherwise. In addition, the ITT population will be used to summarize demographics, as well as baseline and disease characteristics.

Safety Population

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

Note: safety and efficacy data for subjects who crossover to acalabrutinib monotherapy will be analyzed as a stand-alone group, independent of Arm B or Arm A.

Additional details will be presented in the statistical analysis plan (SAP).

CCI [redacted]

12.6 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.

12.7 Efficacy Analyses

12.7.1 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 not meeting these criteria and alive by the analysis DCO date will be censored and the detailed censoring rules will be specified in the SAP.

A stratified log-rank test will be used for the primary comparison of PFS. Additionally, a stratified Cox regression model will be used to provide the estimated PFS HR and 2-sided 95% CIs for acalabrutinib relative to Investigator's choice. Kaplan-Meier (KM) curves will be presented for each treatment arm. Median PFS and its 95% CI, as well as landmark PFS and associated 95% CI at selected times, will be provided.

The SAP will describe the sensitivity analyses to be performed.

12.7.2 Secondary Endpoints and Methods

Conditional on the positive result of primary endpoint, select key secondary endpoints will be tested. The SAP will describe Type I error control for the secondary outcomes.

INV-assessed PFS

INV-assessed PFS is defined as time from randomization until disease progression (assessed by the Investigator per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Analysis methods for INV-assessed PFS will be similar to those described for PFS as assessed by the IRC per IWCLL 2008 criteria.

INV-assessed ORR

INV-assessed ORR is defined as the proportion of subjects who achieve a CR, CRi, nPR, or PR over the course of the study per Investigator assessment. Subjects who do not have any postbaseline response assessment will be considered to be nonresponders.

ORR will be compared between treatment arms using the Cochran-Mantel-Haenszel chi-square test, adjusted for randomization stratification factors.

IRC-assessed ORR

IRC-assessed ORR will be summarized and analyzed similarly to INV-assessed ORR.

OS

OS is defined as the time from date of randomization until date of death due to any cause. Subjects who have not died by the analysis DCO date will be censored at the last date known to be alive before the cutoff date. Subjects known to be alive or dead after the DCO date will be censored at the DCO date. The analysis methods for OS will be similar to those described for PFS.

PRO Measures

The FACIT-Fatigue PRO endpoint was analyzed through Amendment 5.0 only. FACIT-Fatigue will be collected as scheduled in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. The baseline score is defined as the last score collected on or before first dose of study drug. Total score and change from baseline in total score at each postbaseline assessment time point will be assessed.

INV- and IRC-assessed DOR

DOR is defined as the time from the first documentation of objective response to the earlier time of disease progression (assessed by the Investigator or IRC per IWCLL 2008 criteria) or death from any cause. The same censoring rules and analysis methods will be applied as described for PFS.

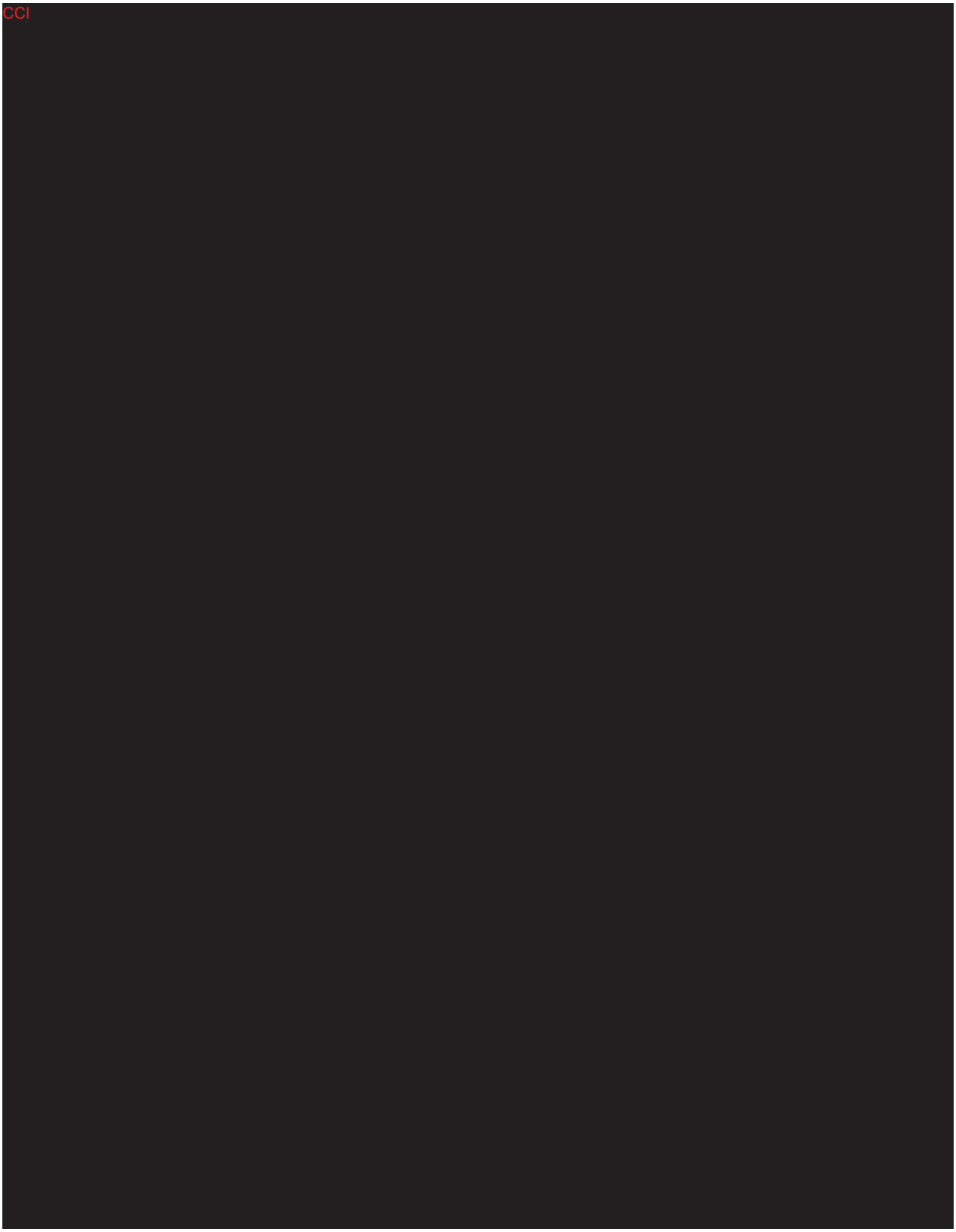
Time to Next Treatment

TTNT is defined as the time from randomization to institution of nonprotocol-specified treatment for CLL. The analysis methods for TTNT will be similar to those described for PFS. For crossover patients, TTNT should be defined as time from initial treatment of acalabrutinib to institution of nonprotocol-specified treatment for CLL.

12.7.3 CCI

CCI

CCI



12.8 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.

Adverse Events

AEs will be graded by the Investigator according to the National Cancer Institute (NCI) CTCAE v4.03 for nonhematologic and hematologic 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).

Treatment-Emergent Adverse Events

All TEAEs will be summarized by treatment arm. AE incidence rates will also be summarized by severity and relationship to study drug. In addition, TEAEs 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 B is 9 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 modification; serious TEAEs; and TEAEs resulting in death will be summarized by treatment arm.

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

Clinical Laboratory Tests

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 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 worsened are counted in the numerator of percentage calculation while the denominator is all subjects in each treatment arm.

Analysis of Lymphocytosis:

For all subjects with baseline and any postbaseline ALC measurements, summaries of ALC at peak will be provided by treatment arm.

Treatment-related 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 5000/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 postbaseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

Analysis of Serum Immunoglobulins

Serum immunoglobulins (IgA, IgG and IgM) are collected as scheduled in Appendix 1 to Appendix 4. For each variable, descriptive statistics will be presented at each scheduled postbaseline assessment by treatment arm. Subjects who received IV immunoglobulin on the study will be excluded from the summary for IgG.

ECOG Performance Status

The ECOG performance status will be collected as scheduled in Appendix 1 to Appendix 4. The ECOG performance status grade ranges from 0 to 5. Descriptive statistics will be provided for each visit over time.

Vital Signs and Weight

Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and weight will be collected for this study. Those parameters will be collected as scheduled in Appendix 1 to Appendix 4. For each parameter, descriptive statistics will be provided over time.

13 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

13.1 Direct Access to Source Data/Documents

13.1.1 Study Monitoring

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

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

13.1.2 Audits and Inspections

Authorized representatives of Acerta, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Acerta audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Acerta immediately if contacted by a regulatory agency about an inspection.

13.1.3 Institutional Review Board and Independent Ethics Committee

The Investigator will submit this protocol, the informed consent, Acalabrutinib 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 GCP guidelines and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Form FDA 1572 (Statement of

Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

13.2 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 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

13.3 Ethics

13.3.1 Ethical Conduct of the Study

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 United States 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).

13.3.2 Written Informed Consent

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 § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before study participation. If allowed by the protocol, a legal representative may sign the ICF for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance 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.

13.4 Data Handling and Recordkeeping

13.4.1 Subject Screening Log

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

13.4.2 CRFs

Authorized study site personnel (see Section 13.8) 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 13.4.4 for record retention requirements.

13.4.3 Inspection of Records

Acerta or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

13.4.4 Retention of Records

The Investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source

documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

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

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

13.5 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.

13.6 Publication Policy

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

13.7 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.

13.8 General Investigator Responsibilities

The principal Investigator must ensure that:

1. He or she will conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the Investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. CRF pages are completed promptly.
11. All Investigational New Drug (IND) Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to the Study Representative within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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15 APPENDICES

Appendix 1. Schedule of Assessments – Acalabrutinib Treatment

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT Visit[c]	SFU Visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Assessed Q12W/ Q24W[g]**		**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**							
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days			± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
Study Drug Administration																x
ARM A Acalabrutinib 100 mg BID PO		Continuous Twice-Daily Dosing														
Procedures																
Informed consent	x															
Confirm eligibility & randomize	x															
Medical history	x															
Physical exam[h]	x	x			x		x		x	x	x	x	x	x		
ECOG PS	x	x			x		x		x	x		x	x			
Weight	x	x		x	x	x	x	x	x	x		x	x			
CCI																
Vital signs[i]	x	x	x	x	x	x	x	x	x	x		x	x			
ECG	x[j]															
PRO assessments[k]		x			x		x		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
Concomitant medications	x	x	x	x	x	x	x	x	x	x		x	x	x		
Adverse events[m]	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Serum pregnancy test[n]	x	x[o]			x		x		x	x		x	x			
HIV testing (for study sites in Germany)	x[p]															
Hepatitis serology[q]	x															

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT Visit[c]	SFU Visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Assessed Q12W/ Q24W[g]**		**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**							
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days			± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
HBV PCR[r]	x				x		x		x	QM through Cycle 19, then Q12W thereafter				QM/ Q12W, as appropriate	QM/ Q12W, as appropriate	
HCV PCR[s]	x															
Cytogenetics and FISH panel	x								x[t]			x[u]	x[u]			
CMV testing[v]	x															
Hematology[w]	x	x	x	x	x	x	x		x	x	ANC, ALC, PLT, Hgb (within 7 days of CT)	x	x	x		
Coagulation tests[x]	x															
Serum chemistry[y]	x	x	x	x	x	x	x		x	x		x	x	x		
Urinalysis[z]	x															
Serum immunoglobulins, T/B/NK/monocyte counts		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
β2-microglobulin		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
CCI																
CT/MRI scans[cc]	x[dd]										x[ee,ff]			x		
Overall response assessment											x					
Bone marrow biopsy and aspirate[gg]	x										To confirm CR			As clinically indicated		

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT Visit[c]	SFU Visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
		Cycle 1			Cycle 2		Cycles 3 to 6		Cycle 7							
Days		1	8	15	1	15	1	15	1	Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Assessed Q12W/ Q24W[g]		30 days after last dose	Q12W	Q12W	
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days			± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
MRD assessment[hh]											At time of bone marrow biopsy/post CR					
New anticancer therapy														x	x	
Survival status															x	

Abbreviations: AE=adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; aPTT = activated partial thromboplastin time; BID = twice daily; BTK = Bruton tyrosine kinase; CBC = complete blood count; CMV = cytomegalovirus; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; HIV = human immunodeficiency virus; IGHV = immunoglobulin heavy-chain variable; INR = international normalized ratio; IVIG = intravenous immunoglobulins; MRD = minimal residual disease; PCR = polymerase chain reaction; PLCγ = phospholipase C gamma; PLT = platelet count; PO = oral; PRO = patient reported outcomes; Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; TT = treatment termination; SAE=serious adverse event; SFU = safety follow-up.

Footnotes for ACE-CL-309 Schedule of Study Activities for Acalabrutinib Monotherapy:

a. Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

b. Subjects will have visits on Days 1, 8 and 15 of Cycle 1, on Days 1 and 15 of Cycles 2 to 6, on Day 1 of Cycle 7, and on Day 1 of every third cycle thereafter, starting with Cycle 10; each cycle is 28 days. There is no restriction on maximum treatment allowed with acalabrutinib.

c. A treatment termination (TT) visit is required for subjects who permanently discontinue treatment early for any reason, including disease progression. A 30-day (+ 7 days) SFU visit after the last dose of all study drugs is required when subjects discontinue all study drugs. The TT 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 study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit. In addition to the TT visit, each subject should be followed until the SFU visit at 30 (+ 7) days after his or her last dose of 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 timeframe.

d. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, complete blood count (CBC) with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival until death or lost to follow-up.

f. After the final data cutoff, for subjects who are still on treatment and deriving clinical benefit, all procedures and assessments will be performed as standard of care. For continued access to study drug, see Section 7.3. All AEs, SAEs, irrespective of attribution of causality, and periodic laboratory results will be collected and recorded in the subject's medical records. Only the SAEs will be reported to the sponsor using a paper form.

g. 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/MRI scans. Bone marrow biopsies/aspirates to confirm a CR must be done within 8-12 weeks of the CT/MRI scan which showed CR.

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

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

j. Subjects should be in supine position and resting for ≥ 10 minutes before the baseline ECG.

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

l. After Cycle 7 Day 1, PRO assessments (through Amendment 5.0), serum immunoglobulins, β2-microglobulin, and T/B/NK/monocyte counts should be collected every 12 weeks at Cycle 10 and Cycle 13, and every 24 weeks thereafter.

m. 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. After the end of the protocol-defined AE reporting period (see Section 11.8.1), only SAEs or other AEs of concern that are believed to be related to prior treatment with study drug are required to be collected.

n. Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. More frequent pregnancy testing than delineated in the Schedule of Assessments may be done if required by local regulatory authorities.

o. This serum pregnancy test is to be performed on Cycle 1 Day 1 (- 3 days).

p. For study sites in Germany: Screening peripheral blood samples to be sent to a central vendor to be tested for seropositivity for HIV-1 antibody, HIV-2 antibody, and if positive, reactivity for the HIV-specific p24 antigen.

q. 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 any hepatitis serology must have polymerase chain reaction (PCR) testing (see exclusion criterion #16).

r. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and monthly during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV 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, PCR testing monthly is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

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

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

u. Peripheral blood samples will be taken at screening and at disease progression (if the progression peripheral blood sample is not taken at the TT visit, then it can be drawn at the SFU visit).

v. CMV testing at screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at screening. Subjects assigned to Arm B must have monthly CMV DNA PCR testing while on treatment. Monthly monitoring for CMV should continue by CMV DNA PCR testing for Arm B subjects until 12 months after the last dose of idelalisib or bendamustine, including the crossover period. The screening CMV serologies will be advisory only, to guide Investigators in assessing risk of new infection or reactivation of CMV while on study.

w. Hematology includes CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

x. Coagulation tests at screening include Prothrombin time/INR and aPTT.

y. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

z. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

aa. CCI

bb. CCI

cc. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous (IV) CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. CT/MRI scan can be performed up to 7 days before response evaluation.

dd. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. 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 30 days of first dose and was acquired in accordance with the guidelines outlined in Section 11.1.22.

ee. Bone marrow and radiologic assessments are both required for confirmation of a CR. Testing for minimal residual disease (bone marrow aspirate) will be done on subjects with confirmed CRs. Clinical assessments of tumor response should be done at every visit. A central radiology vendor will be used to collect and store images for Independent Review Committee (IRC) review.

ff. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done at a central laboratory for confirmation of Richter's transformation. If a whole body PET-CT scan is obtained by the Investigator as an ancillary diagnostic tool, the results of this scan should be captured in the EDC as an unscheduled visit (these scans are not required, as biopsy of the affected site is diagnostic and sufficient for confirmation).

gg. A bone marrow aspirate and biopsy will be done at screening or ≤ 3 months before enrollment, to confirm CR, and as clinically indicated during the post-treatment disease follow-up period.

hh. 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 to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT/MRI imaging of suspected CR.

Appendix 2. Schedule of Assessments – Idelalisib/Rituximab Treatment

		Screening[a]	Treatment Phase[b]									Response Evaluation	TT visit[c]	SFU visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days			**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Assessed Q12W/ Q24W[g]**		**30 days after last dose**	**Q12W**	**Q12W**	
			1	8	15	1	15	1	15	1							
Study Windows		- 30 days		± 3 days		± 3 days		± 3 days		± 3 days	± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
Study Drug Administration																	x
ARM B	Idelalisib 150 mg BID PO		Continuous Twice-Daily Dosing														
	Rituximab IV (first dose 375 mg/m^2; 500 mg/m^2 subsequently)		x		x	x	x	x										
Procedures																	
Informed consent		x															
Confirm eligibility & randomize		x															
Medical history		x															
Physical exam[h]		x	x			x		x		x	x	x	x	x	x		
ECOG PS		x	x			x		x		x	x		x	x			
Weight		x	x		x	x	x	x	x	x	x		x	x			
CCI																	
Vital signs[i]		x	x	x	x	x	x	x	x	x	x		x	x			
ECG		x[j]															
PRO assessments[k]			x			x		x		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
Concomitant medications		x	x	x	x	x	x	x	x	x	x		x	x	x		
Adverse events[m]		x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Serum pregnancy test[n]		x	x[o]			x		x		x	x		x	x			
HIV testing (for study sites in Germany)		x[p]															

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT visit[c]	SFU visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		Cycle 1			Cycle 2		Cycles 3 to 6		Cycle 7	Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Assessed Q12W/ Q24W[g]		30 days after last dose	Q12W	Q12W	
		1	8	15	1	15	1	15	1							
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days		± 3 days	± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
Hepatitis serology[q]	x															
HCV PCR[r]	x															
HBV PCR[s]	x				x		x		x	QM through Cycle 19, then Q12W thereafter				QM/ Q12W, as appropriate	QM/ Q12W, as appropriate	
CMV testing[t]	x				x		x		x	QM			QM	QM	QM	
Cytogenetics and FISH panel	x								x[u]			x[v]	x[v]			
Hematology[w]	x	x	x	x	x	x	x	x	x	x	ANC, ALC, PLT, Hgb (within 7 days of CT)	x	x	x		
Coagulation tests[x]	x															
Serum chemistry[y]	x	x	x	x	x	x	x	Cycle 3 only	x	x		x	x	x		
Urinalysis[z]	x															
Serum immunoglobulins, T/B/NK/monocyte counts		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
β2-microglobulin		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
CCI																
CT/MRI scans[cc]	x[dd]										x[ee,ff]			x		
Overall response assessment											x					
Bone marrow biopsy and aspirate[gg]	x										To confirm CR			As clinically indicated		

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT visit[c]	SFU visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Assessed Q12W/ Q24W[g]**		**30 days after last dose**	**Q12W**	**Q12W**	
		1	8	15	1	15	1	15	1							
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days		± 3 days	± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
MRD assessment[hh]											At time of bone marrow biopsy/post CR					
New anticancer therapy														x	x	
Survival status															x	

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; anti-HBs = hepatitis B surface antibody; BTK = Bruton tyrosine kinase; CBC = complete blood count; CMV = cytomegalovirus; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; HIV = human immunogenicity virus; IGHV = immunoglobulin heavy-chain variable; INR = international normalized ratio; IV = intravenous; IVIG = intravenous immunoglobulin; MRD = minimal residual disease; PCR = polymerase chain reaction; PLCγ = phospholipase C gamma; PLT = platelet count; PO = oral; PRO = patient reported outcomes; Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; TT = treatment termination; SAE = serious adverse event; SFU = safety follow-up.

Footnotes for ACE-CL-309 Schedule of Study Activities for Idelalisib in Combination With Rituximab:

a. Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

b. Subjects will have visits on Days 1, 8, and 15 of Cycle 1, on Days 1 and 15 of Cycles 2 to 6, on Day 1 of Cycle 7, and on Day 1 of every third cycle thereafter, starting with Cycle 10; each cycle is 28 days. Rituximab is to be administered for a maximum of 8 infusions (6 cycles). Idelalisib treatment will continue until disease progression or unacceptable toxicity.

c. A treatment termination (TT) visit is required for subjects who permanently discontinue treatment early for any reason, including disease progression. A 30-day (+ 7 days) SFU visit is required after subjects receive their last dose of all study drugs. The TT 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 study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit. In addition to the TT visit, each subject should be followed until the SFU visit at 30 (+ 7) days after his or her last dose of 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 timeframe.

d. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, complete blood count (CBC) with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival until death or lost to follow-up.

f. After the final data cutoff, for subjects who are still on treatment and deriving clinical benefit, all procedures and assessments will be performed as standard of care. For continued access to study drug, see Section 7.3. All AEs, SAEs, irrespective of attribution of causality, and periodic laboratory results will be collected and recorded in the subject's medical records. Only the SAEs will be reported to the sponsor using a paper form.

g. 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/MRI scans. Bone marrow biopsies/aspirates to confirm a CR must be done within 8-12 weeks of the CT/MRI scan which showed CR.

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

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

j. Subjects should be in supine position and resting for ≥ 10 minutes before the baseline ECG.

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

l. After Cycle 7 Day 1, PRO assessments (through Amendment 5.0), serum immunoglobulins, β2-microglobulin, and T/B/NK/monocyte counts should be collected every 12 weeks at Cycle 10 and Cycle 13, and every 24 weeks thereafter.

m. 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. After the end of the protocol-defined AE reporting period (see Section 11.8.1), only SAEs or other AEs of concern that are believed to be related to prior treatment with study drug are required to be collected.

n. Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. More frequent pregnancy testing (either urine or serum) than delineated in the Schedule of Assessments may be done if required by local regulatory authorities.

o. This serum pregnancy test is to be performed on Cycle 1 Day 1 (-3 days).

p. For study sites in Germany: Screening peripheral blood to be sent to a central vendor to be tested for seropositivity for HIV-1 antibody, HIV-2 antibody, and if positive, reactivity for the HIV-specific p24 antigen.

q. 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 any hepatitis serology must have PCR testing (see exclusion criterion #16).

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

s. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV 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, PCR testing every month 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).

t. CMV testing at screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at screening. Subjects assigned to Arm B must have monthly CMV DNA PCR testing while on treatment. Monthly monitoring for CMV should continue by CMV DNA PCR testing for Arm B subjects until 12 months after the last dose of idelalisib or bendamustine, including the crossover period. The screening CMV serologies will be advisory only, to guide Investigators in assessing risk of new infection or reactivation of CMV while on study.

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

v. Peripheral blood samples will be taken at screening and at disease progression (if the progression peripheral blood sample is not taken at the TT visit, then it can be drawn at the SFU visit).

w. Hematology includes CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

x. Coagulation tests at screening include Prothrombin time/INR and aPTT.

y. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

z. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

aa. CCI

bb. CCI

cc. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous (IV) CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. CT/MRI scan can be performed up to 7 days before response evaluation.

dd. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. 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 30 days of first dose and was acquired in accordance with the guidelines outlined in Section 11.1.22.

ee. Bone marrow and radiologic assessments are both required for confirmation of a CR. Testing for minimal residual disease (bone marrow aspirate) will be done on subjects with confirmed CRs. Clinical assessments of tumor response should be done at every visit. A central radiology vendor will be used to collect and store images for Independent Review Committee (IRC) review.

ff. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done at a central laboratory for confirmation of Richter's transformation. If a whole body PET-CT/MRI scan is obtained by the Investigator as an ancillary diagnostic tool, the results of this scan should be captured in the EDC as an unscheduled visit (these scans are not required, as biopsy of the affected site is diagnostic and sufficient for confirmation).

gg. A bone marrow aspirate and biopsy will be done at screening or ≤ 3 months before enrollment, to confirm CR, and as clinically indicated during the post-treatment disease follow-up period.

hh. For subjects on treatment with idelalisib plus rituximab, 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 to evaluate MRD should be done no earlier than between 8-12 weeks after the completion of rituximab treatment (e.g., earliest bone marrow biopsy would be start of Cycle 9). For subjects who completed all 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 to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT/MRI imaging of suspected CR.

Appendix 3. Schedule of Assessments – Bendamustine/Rituximab Treatment

		Screening[a]	Treatment Phase[b]						Response Evaluation	TT visit[c]	SFU visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days			Cycle 1				Cycles 2 to 6		Assessed Q12W/Q24W[g]		30 days after last dose	Q12W	Q12W	
			1	2	8	15	1	2						
Study Windows		- 30 days			± 3 days		± 3 days		± 14 days		+ 7 days	± 7 days	± 7 days	
Study Drug Administration														x
ARM B	Bendamustine 70 mg/m^2 IV[h]		x	x			x	x						
	Rituximab IV (first dose 375 mg/m^2; 500 mg/m^2 subsequently)		x				x							
Procedures														
Informed consent		x												
Confirm eligibility & randomize		x												
Medical history		x												
Physical exam[i]		x	x				x		x	x	x	x		
ECOG PS		x	x				x			x	x			
Weight		x	x	x		x	x	x		x	x			
CCI														
Vital signs[j]		x	x	x	x	x	x	x		x	x			
ECG		x[k]												
PRO assessments[l]			x				x[m]					Q12W/ Q24W, as appropriate[m]		
Concomitant medications		x	x	x	x	x	x	x		x	x	x		
Adverse events[n]		x	x	x	x	x	x	x		x	x	x	x	x
Serum pregnancy test[o]		x	x[p]				x			x	x			
HIV testing (for study sites in Germany)		X[q]												
Hepatitis serology[r]		x												

	Screening[a]	Treatment Phase[b]						Response Evaluation	TT visit[c]	SFU visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		Cycle 1				Cycles 2 to 6		Assessed Q12W/Q24W[g]		30 days after last dose	Q12W	Q12W	
		1	2	8	15	1	2						
HBV PCR[s]	x					x					QM/ Q12W, as appropriate	QM/ Q12W, as appropriate	
HCV PCR[t]	x												
CMV testing[u]	x					x				QM	QM	QM	
Cytogenetics and FISH panel	x								x[v]	x[v]			
Hematology[w]	x	x	x	x	x	x		ANC, ALC, PLT, Hgb (within 7 days of CT)	x	x	x		
Coagulation tests[x]	x												
Serum chemistry[y]	x	x	x	x	x	x			x	x	x		
Urinalysis[z]	x												
Serum immunoglobulins, T/B/NK/monocyte counts		x				Cycle 3 only[m]					Q12W/ Q24W, as appropriate[m]		
β2-microglobulin		x				Cycle 3 only[m]					Q12W/ Q24W, as appropriate[m]		
CCI													
CT/MRI scans[dd]	x[ee]							x[ff,gg]			x		
Overall response assessment								x					
Bone marrow biopsy and aspirate[hh]	x							To confirm CR			As clinically indicated		
MRD assessment[ii]								At time of bone marrow biopsy/post CR					
New anticancer therapy											x	x	
Survival status												x	

Abbreviations: AE=adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; aPTT = activated partial thromboplastin time; BTK = Bruton tyrosine kinase; CBC = complete blood count; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; HIV = human immunogenicity virus; IGHV = immunoglobulin heavy-chain variable; INR = international normalized ratio; IV = intravenous; IVIG = intravenous immunoglobulin; MRD = minimal residual disease; PCR = polymerase chain reaction; PLCγ = phospholipase C gamma; PLT = platelet count; PO = oral; PRO = patient reported outcomes; Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; TT = treatment termination; SAE = serious adverse event; SFU = safety follow-up.

Footnotes for ACE-CL-309 Schedule of Study Activities for Bendamustine in Combination With Rituximab:

a. Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

b. Subjects will have visits on Days 1, 2, 8, and 15 of Cycle 1, on Days 1 and 2 of Cycles 2 to 6, and on Day 1 of the next 12-week visit regardless of whether the subject is on study drug. Each cycle is 28 days. Bendamustine in combination with rituximab is to be administered for a maximum of 6 cycles.

c. A treatment termination (TT) visit is required for subjects who permanently discontinue treatment early for any reason, including disease progression. A 30-day (+ 7 days) SFU visit is required after subjects receive their last dose of all study drugs. The TT 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 study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit. In addition to the TT visit, each subject should be followed until the SFU visit at 30 (+ 7) days after his or her last dose of 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 timeframe.

d. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, complete blood count (CBC) with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival until death or lost to follow-up.

f. After the final data cutoff, for subjects who are still on treatment and deriving clinical benefit, all procedures and assessments will be performed as standard of care. For continued access to study drug, see Section 7.3. All AEs, SAEs, irrespective of attribution of causality, and periodic laboratory results will be collected and recorded in the subject's medical records. Only the SAEs will be reported to the sponsor using a paper form.

g. 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. For bendamustine-treated subjects, the second radiologic tumor assessment will occur at the next 12-week interval (± 14 days) regardless of whether the subject is on study drug. Hematology results must be done within 7 days of CT/MRI scans. Bone marrow biopsies/aspirates to confirm a CR must be done within 8-12 weeks of the CT/MRI scan which showed suspected CR.

h. Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full six cycles to be received, wherever possible. A maximum of 6 cycles can be administered. See further instructions for data entry in such cases in the eCRF guidelines.

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

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

k. Subjects should be in supine position and resting for ≥ 10 minutes before the baseline ECG.

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

m. For bendamustine-treated subjects, serum immunoglobulins, β2-microglobulin, and T/B/NK/monocyte counts will be collected 16 weeks after Cycle 3 (e.g., SFU visit), every 12 weeks for the next 2 visits, and every 24 weeks thereafter. After Cycle 6, PRO assessments (through Amendment 5.0) will be conducted at the next monthly visit (e.g., SFU visit), every 12 weeks for the next 2 visits, and then every 24 weeks thereafter.

n. 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. After the end of the protocol-defined AE reporting period (see Section 11.8.1), only SAEs or other AEs of concern that are believed to be related to prior treatment with study drug are required to be collected.

o. Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. More frequent pregnancy testing (either urine or serum) than delineated in the Schedule of Assessments may be done if required by local regulatory authorities.

p. This serum pregnancy test is to be performed on Cycle 1 Day 1 (-3 days).

q. For study sites in Germany: Screening peripheral blood to be sent to a central vendor to be tested for seropositivity for HIV-1 antibody, HIV-2 antibody, and if positive, reactivity for the HIV-specific p24 antigen.

r. 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 any hepatitis serology must have PCR testing (see exclusion criterion #16).

s. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV 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, PCR testing every month 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).

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

u. CMV testing at screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at screening. Subjects assigned to Arm B must have monthly CMV DNA PCR testing while on treatment. Monthly monitoring for CMV should continue by CMV DNA PCR testing for Arm B subjects until 12 months after the last dose of idelalisib or bendamustine, including the crossover period. The screening CMV serologies will be advisory only, to guide Investigators in assessing risk of new infection or reactivation of CMV while on study.

v. Peripheral blood samples will be taken at screening and at disease progression (if the progression peripheral blood sample is not taken at the TT visit, then it can be drawn at the SFU visit).

w. Hematology includes CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

x. Coagulation tests at screening include Prothrombin time/INR and aPTT.

y. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

z. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

aa. CCI [redacted]

bb. CCI

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

dd. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous (IV) CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. CT/MRI scan can be performed up to 7 days before response evaluation.

ee. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. 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 30 days of first dose and was acquired in accordance with the guidelines outlined in Section 11.1.22.

ff. Bone marrow and radiologic assessments are both required for confirmation of a CR. Testing for minimal residual disease (bone marrow aspirate) will be done on subjects with confirmed CRs. Clinical assessments of tumor response should be done at every visit. A central radiology vendor will be used to collect and store images for Independent Review Committee (IRC) review.

gg. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done at a central laboratory for confirmation of Richter's transformation. If a whole body PET-CT/MRI scan is obtained by the Investigator as an ancillary diagnostic tool, the results of this scan should be captured in the EDC as an unscheduled visit (these scans are not required, as biopsy of the affected site is diagnostic and sufficient for confirmation).

hh. A bone marrow aspirate and biopsy will be done at screening or ≤ 3 months before enrollment, to confirm CR, and as clinically indicated during the post-treatment disease follow-up period.

ii. For subjects on bendamustine plus rituximab, 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 to evaluate MRD should be done no earlier than between 8-12 weeks after the completion of the bendamustine plus rituximab treatment, or, if treatment has already been completed, no earlier than between 8-12 weeks from the time of the supportive clinical assessments that suggest CR.

Appendix 4. Schedule of Assessments – Crossover

		Screening[a]	Treatment Phase[b]									Response Evaluation	TT Visit[c]	SFU Visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
			Cycle 1			Cycle 2		Cycles 3 to 6		Cycle 7	Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)						
Days			1	8	15	1	15	1	15	1		Assessed Q12W/ Q24W[g]		30 days after last dose	Q12W	Q12W	
Study Windows		- 30 days		± 3 days		± 3 days		± 3 days			± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
Study Drug Administration																	x
Crossover	Acalabrutinib 100 mg BID		Continuous Twice-Daily Dosing														
Procedures																	
Physical exam[h]		x	x			x		x		x	x	x	x	x	x		
ECOG PS		x	x			x		x		x	x		x	x			
Weight		x	x		x	x	x	x	x	x	x		x	x			
CCI																	
Vital signs[i]		x	x	x	x	x	x	x	x	x	x		x	x			
ECG		x[j]															
PRO assessments[k]			x			x		x		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]						
Concomitant medications		x	x	x	x	x	x	x	x	x	x		x	x	x		
Adverse events[m]		x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Serum pregnancy test [n]		x	x[o]			x		x		x	x		x	x			
HIV testing (for study sites in Germany)		x [p]															
Hepatitis serology[q]		x															
HBV PCR[r]		x				x		x		x	QM through Cycle 19, then Q12W thereafter				QM/ Q12W, as appropriate	QM/ Q12W, as appropriate	

	Screening[a]	Treatment Phase[b]									Response Evaluation	TT Visit[c]	SFU Visit[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Continued Access to Study Drug[f]
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Assessed Q12W/ Q24W[g]**		**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**							
Study Windows	- 30 days		± 3 days		± 3 days		± 3 days			± 3 days	± 14 days		+ 7 days	± 7 days	± 7 days	
HCV PCR	x															
CMV testing[s]	x	x			x		x		x	QM			x	QM	QM	
Cytogenetics and FISH panel	x								x[t]			x[u]	x[u]			
Hematology[v]	x	x	x	x	x	x	x		x	x	ANC, ALC, PLT, Hgb (within 7 days of CT)	x	x	x		
Serum chemistry[w]	x	x	x	x	x	x	x		x	x		x	x	x		
Urinalysis[x]	x															
Serum immunoglobulins, T/B/NK/monocyte counts		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
β2-microglobulin		x					Cycle 3 only		x	Q24W starting at Cycle 13 (e.g., Cycles 13, 19)[l]				Q24W		
CCI																
CT/MRI scans[aa]	x[bb]										x[cc,dd]			x		
Overall response assessment											x					
Bone marrow biopsy and aspirate[cc]											To confirm CR			As clinically indicated		
MRD assessment[ee]											At time of bone marrow biopsy/post CR					
Survival status and new anticancer therapy															x	

Abbreviations: AE=adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; BID = twice daily; BTK = Bruton tyrosine kinase; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; HIV = human immunodeficiency virus; IGHV = immunoglobulin heavy-chain variable; IVIG = intravenous immunoglobulin; MRD = minimal residual disease; PCR = polymerase chain reaction; PLCγ = phospholipase C gamma; PLT = platelet count; PO = oral; PRO = patient reported outcomes; Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; TT = treatment termination; SAE = adverse event; SFU = safety follow-up.

Footnotes for ACE-CL-309 Schedule of Study Activities for Crossover to Acalabrutinib Monotherapy:

a. Screening tests should be performed within 30 days before the administration of study drug, unless otherwise indicated. However, screening hematology and serum chemistry tests do not need to be repeated if they had been done at a prior study visit within 10 days of crossing over (i.e., receiving acalabrutinib). Cytogenetics and FISH panel, serum immunoglobulins and genetic and molecular prognostic factors do not need to be repeated if they had been done at a prior study visit within 30 days of crossing over (i.e., receiving acalabrutinib).

b. Subjects will have visits on Day 1 of every third cycle, starting with Cycle 1; each cycle is 28 days. There is no restriction on maximum treatment allowed with acalabrutinib.

c. A treatment termination (TT) visit is required for subjects who permanently discontinue treatment early for any reason, including disease progression. A 30-day (+ 7 days) SFU visit after the last dose of all study drugs is required when subjects discontinue all study drugs. The TT 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 study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit. In addition to the TT visit, each subject should be followed until the SFU visit at 30 (+ 7) days after his or her last dose of 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 timeframe.

d. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, complete blood count (CBC) with differential, physical exams, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival until death or lost to follow-up.

f. After the final data cutoff, for subjects who are still on treatment and deriving clinical benefit, all procedures and assessments will be performed as standard of care. For continued access to study drug, see Section 7.3. All AEs, SAEs, irrespective of attribution of causality, and periodic laboratory results will be collected and recorded in the subject's medical records. Only the SAEs will be reported to the sponsor using a paper form.

g. 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/MRI scans. Bone marrow biopsies/aspirates to confirm a CR must be done within 8-12 weeks of the CT/MRI scan which showed CR.

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

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

j. Subjects should be in supine position and resting for ≥ 10 minutes before the baseline ECG.

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

l. After Cycle 7 Day 1, PRO assessments (through Amendment 5.0), serum immunoglobulins, β_2-microglobulin, and T/B/NK/monocyte counts should be collected every 12 weeks at Cycle 10 and Cycle 13, and every 24 weeks thereafter.

m. 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. After the end of the protocol-defined AE reporting period (see Section 11.8.1), only SAEs or other AEs of concern that are believed to be related to prior treatment with study drug are required to be collected.

n. Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. More frequent pregnancy testing (either urine or serum) than delineated in the Schedule of Assessments may be done if required by local regulatory authorities.

o. This serum pregnancy test is to be performed on Cycle 1 Day 1 (- 3 days).

p. For study sites in Germany: Screening peripheral blood to be sent to a central vendor to be tested for seropositivity for HIV-1 antibody, HIV-2 antibody, and if positive, reactivity for the HIV-specific p24 antigen.

q. 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 any hepatitis serology must have PCR testing (see exclusion criterion #16).

r. Subjects who are hepatitis B core antibody (anti-HBc) positive should be monitored every month with a quantitative polymerase chain reaction (PCR) test for HBV DNA during treatment Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV 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, PCR testing every month is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

s. During crossover, monthly monitoring for CMV should continue by CMV DNA PCR testing for previously treated Arm B subjects until 12 months after the last dose of idelalisib or bendamustine.

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

u. Peripheral blood samples will be taken at screening and at disease progression (if the progression peripheral blood sample is not taken at the TT visit, then it can be drawn at the SFU visit).

v. Hematology includes complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

w. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

x. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

y. CCI [redacted]

z. CCI [redacted]

aa. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous (IV) CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. CT/MRI scan can be performed up to 7 days before response evaluation.

bb. CT/MRI scans that showed disease progression from Arm B can be used for the crossover screening CT/MRI scan, if obtained within 30 days prior to crossover dosing Cycle 1 Day 1.

cc. Bone marrow and radiologic assessments are both required for confirmation of a CR. Testing for minimal residual disease (bone marrow aspirate) will be done on subjects with confirmed CRs. Clinical assessments of tumor response should be done at every visit. A central radiology vendor will be used to collect and store images for Independent Review Committee (IRC) review.

dd. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done at a central laboratory for confirmation of Richter's transformation. If a whole body PET-CT/MRI scan is obtained by the Investigator as an ancillary diagnostic tool, the results of this scan should be captured in the EDC as an unscheduled visit (these scans are not required, as biopsy of the affected site is diagnostic and sufficient for confirmation).

ee. 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 to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT/MRI imaging of suspected CR.

Appendix 5. Known Strong in Vivo Inhibitors or Inducers of CYP3A

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

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the area under the concentration-time curve (AUC) of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
e. In vivo inducer of P-glycoprotein.

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

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

Appendix 6. Performance Status Scores

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

As published in Am J Clin Oncol:

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

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

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

Appendix 7. FACIT-Fatigue

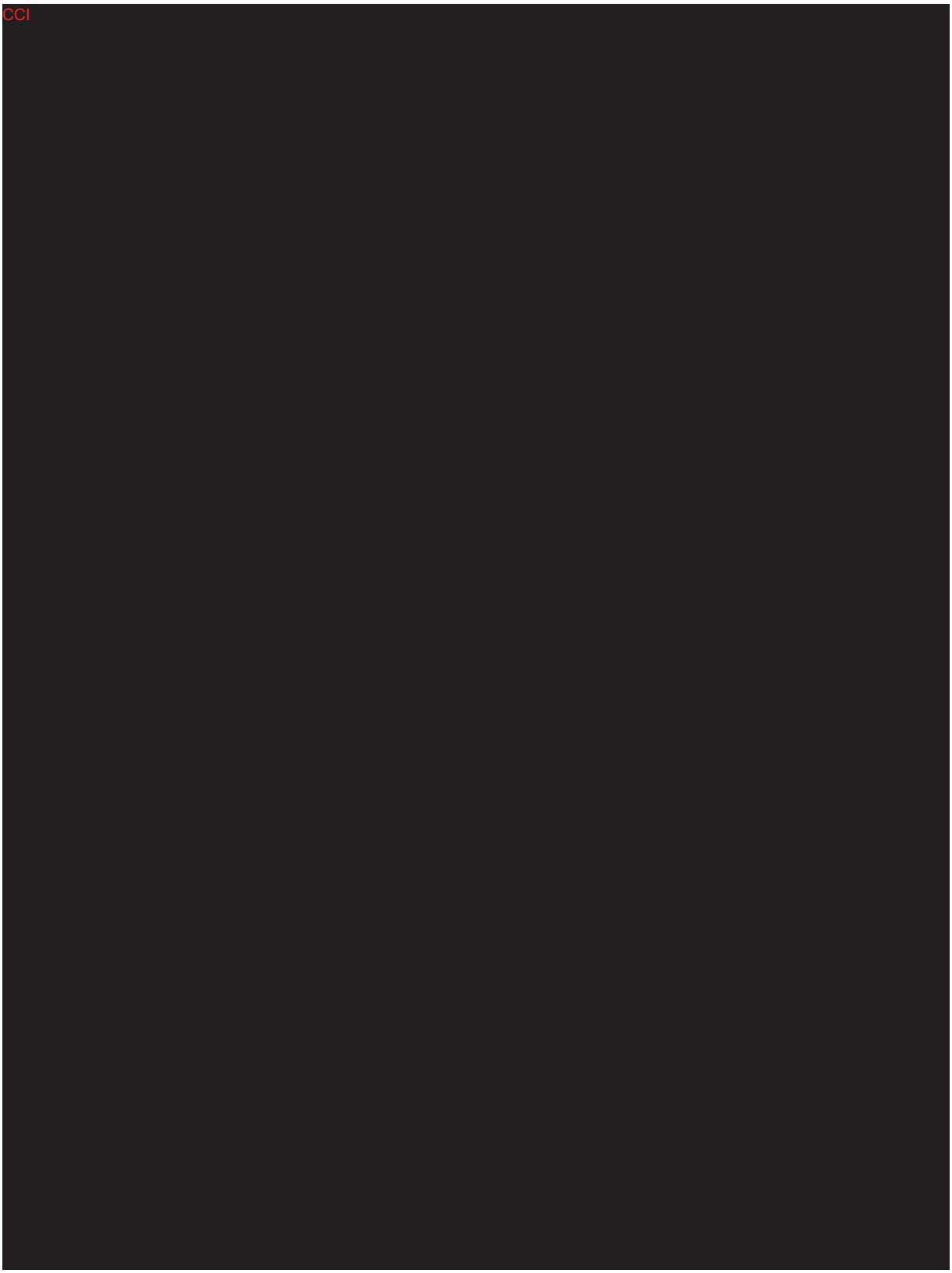
FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

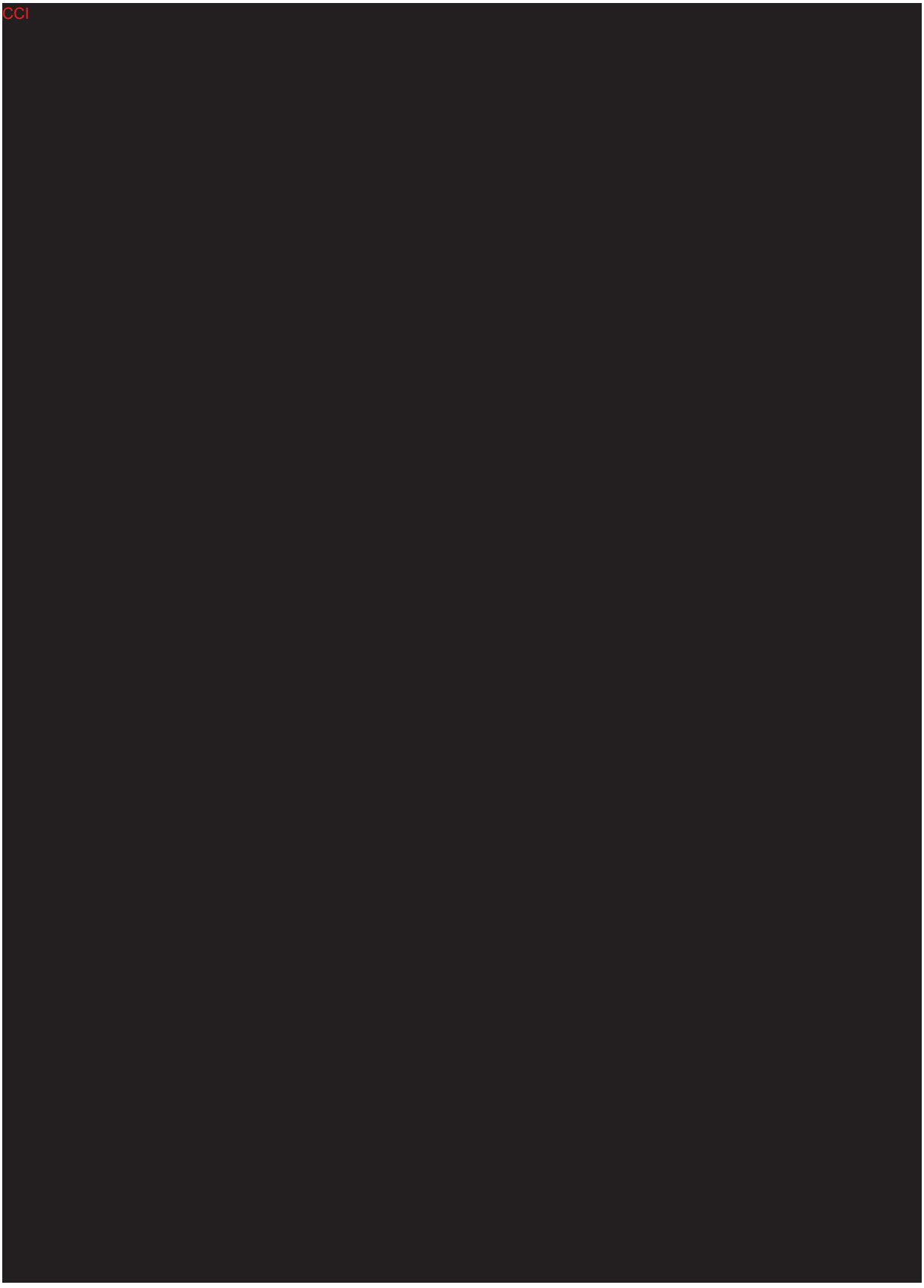
		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual a ities	0	1	2	3	4
An8	I need to sleep during the d	0	1	2	3	4
An12	I am too tire o eat	0	1	2	3	4
An14	I need help doing my us activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 8. CCI

CCI

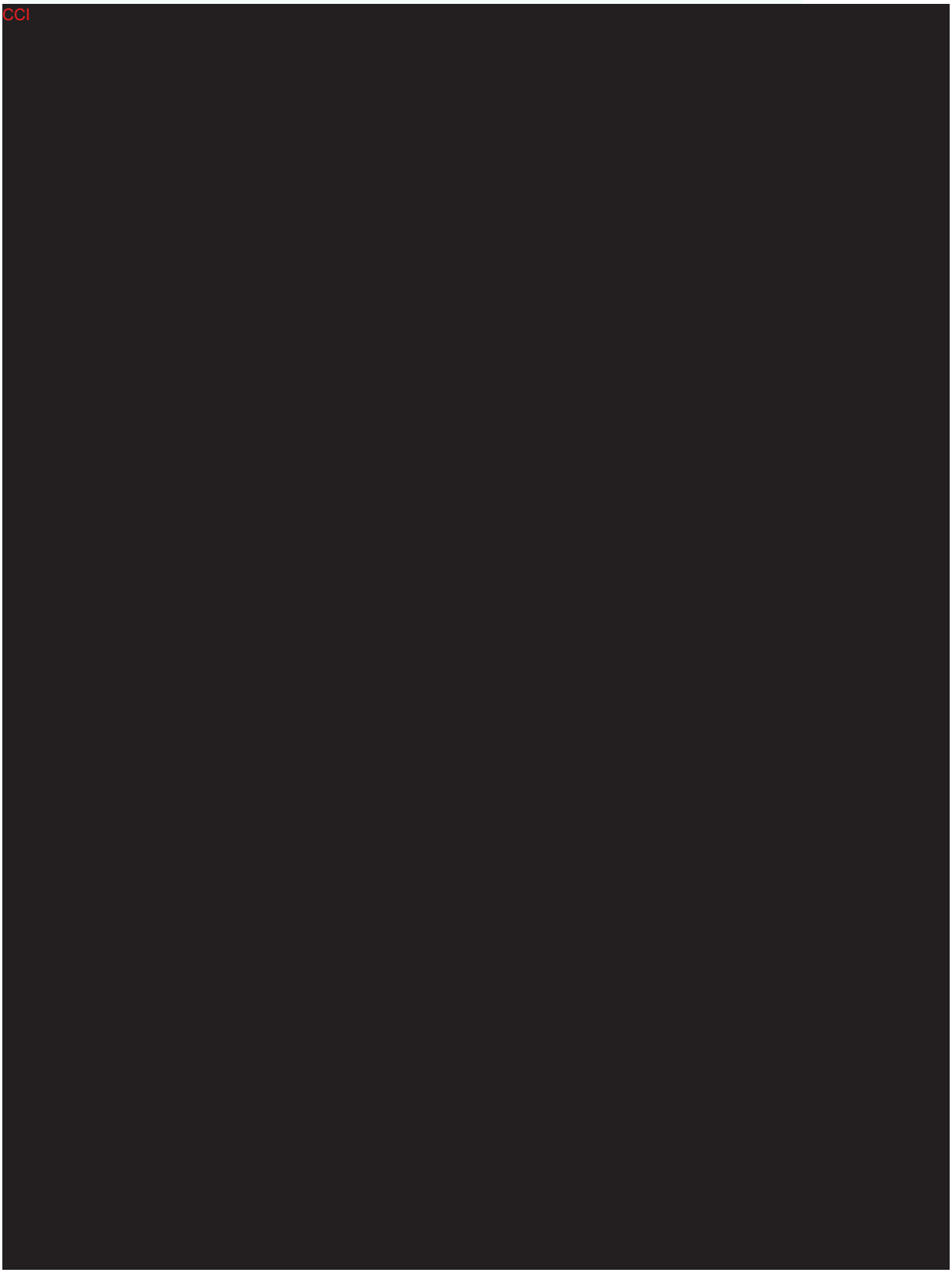


CCI



Appendix 9. CCI

CCI



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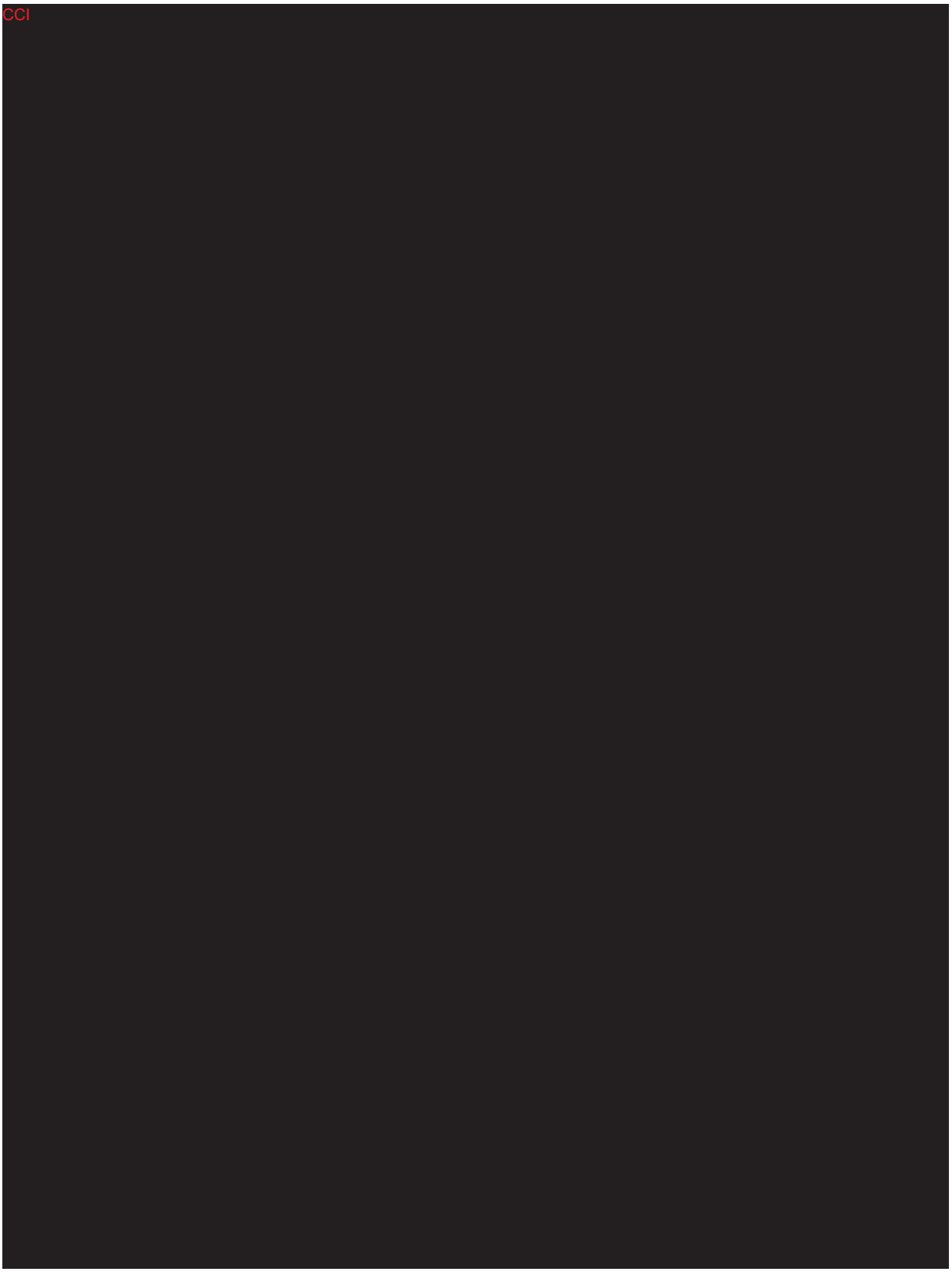

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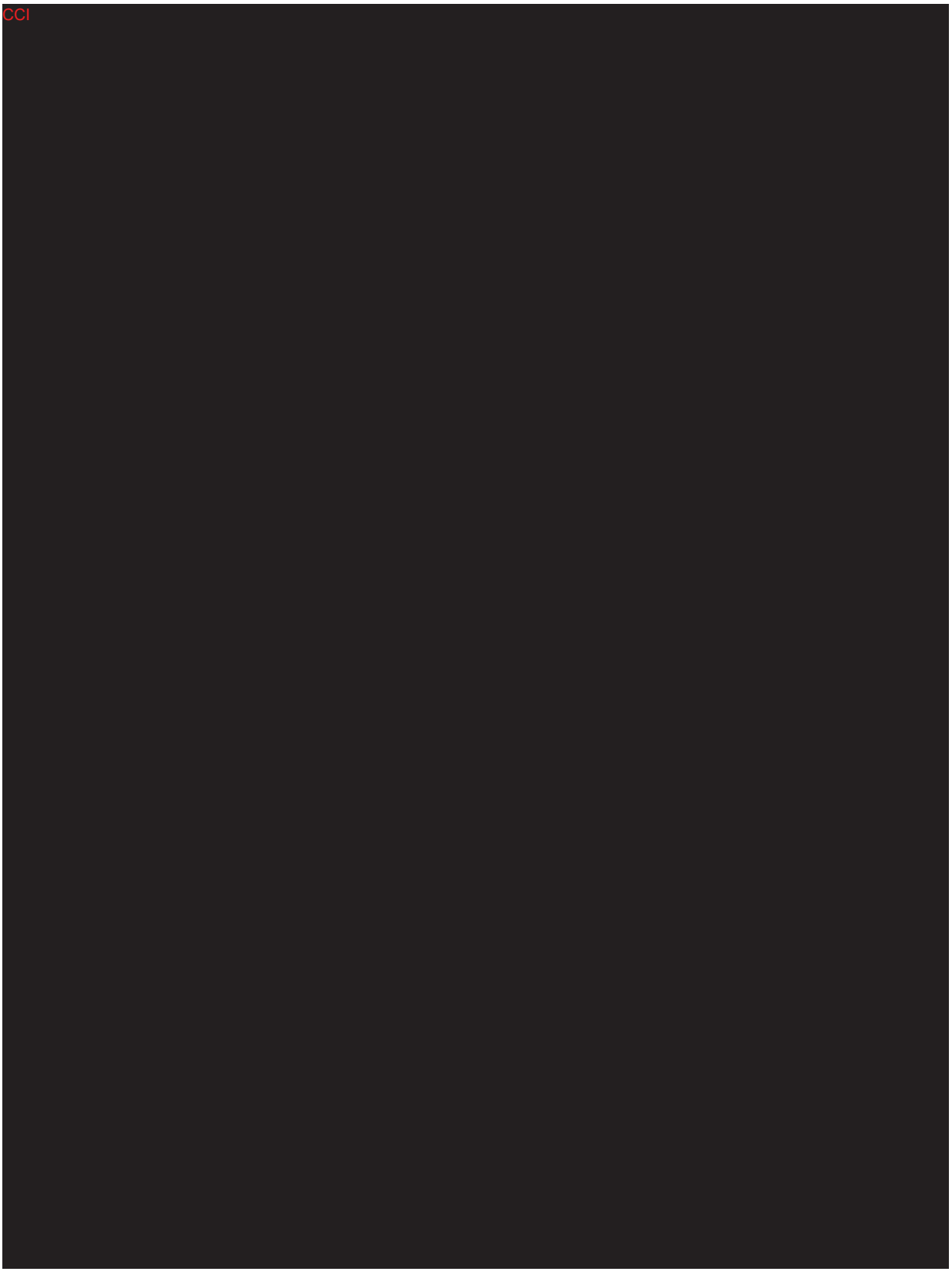

Appendix 10. Response Assessment Criteria (modified from Hallek 2008) – IWCLL Criteria (as updated for persistent lymphocytosis in Cheson 2012)

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 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			

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

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 11. 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 12. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law

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

Hy's Law

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

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

- Notify the sponsor representative/medical monitor by telephone and report the 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 is initially detected, the study medical monitor and the Investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP

and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met.

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

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

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

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

- Send updated SAE (report term "Hy's law") according to the sponsor's standard processes:

  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - Because there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

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

- Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.

- Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

- If the answer is **No:**

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

- If the answer is **Yes**:

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

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

LABORATORY TESTS

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

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

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

Reference

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

Appendix 13. 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 patient is unable or unwilling to visit the study site due to COVID-19 related reasons, investigators may ask enrolled patients to use healthcare facilities local to the patient 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 patient, 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 patient.
- A procedure is defined with the carrier to confirm the receipt of the drug by the subject and that it is received in good condition.
- The site contacts the subject to confirm the receipt and integrity of the drug and gives instructions about the drug administration.
- The pharmacy completes its accountability with each shipment made directly to a subject.

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