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TITLE: Phase II study of acalabrutinib and high frequency low dose subcutaneous rituximab in patients with previously untreated CLL/SLL

Study Chair:	Paul M. Barr, MD University of Rochester 601 Elmwood Ave, Box 704 Rochester NY 14642
IND Number:	**Acalabrutinib:** **Rituximab:** FDA Approved
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AMENDMENTS

Version 2.0 (Dated 06 October 2022) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

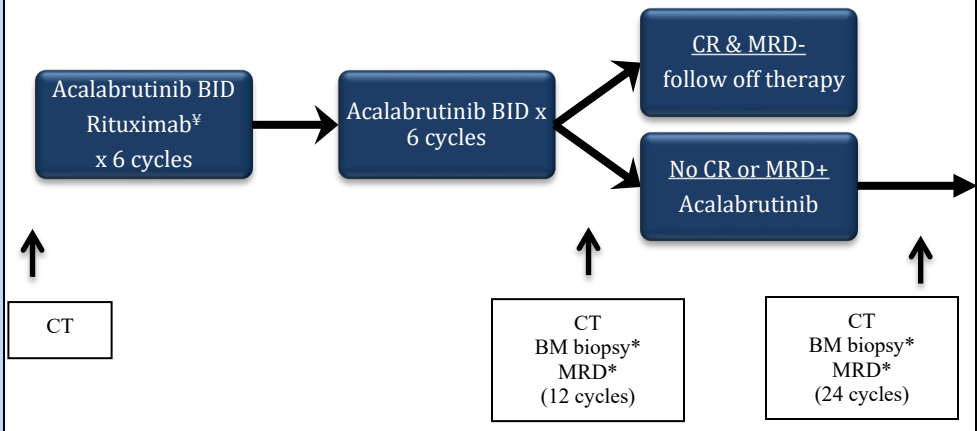
- The formulation of acalabrutinib has changed. The tablet formulation will be used in all paitents going foward;
- The previous version included peripheral blood sample collection in a 10ml purple top tube for lymphocytes, on D1 of cycles 3, 6, 9, 12, 15, 18, 21, 24. This has been changed to 3, 6, 9, 12, 16, 18, 22, 25 (+/- 4 weeks) to align with patient visits and include flexibility for these correlative studies
- Response assessments are clarified. Following cycles 12 and 24, patients who have attained a radiographic complete response will undergo a BM biopsy to confirm CR. Patients in CR will also have MRD testing performed on peripheral blood and marrow. Patients in CR and undetectable for MRD, will stop therapy and be followed until disease progression. Patients not in a MRD negative CR, will continue acalabrutinib.
- Patient assessments following cycle 24 are clarified. After this point, patients will be evaluated as per institutional standards (typically every 3-4 months). Physical exam data, vital signs, laboratory values and patient diaries will no longer be collected. Patients continuing on acalabrutinib will continue with adverse event assessments at each evaluation and be followed for progression and survival events.

Protocol no.	
Study Title	**Phase II study of acalabrutinib and high frequency low dose subcutaneous rituximab in patients with previously untreated CLL/SLL**
Principle Investigator and Study Chair	Paul M. Barr, MD Wilmot Cancer Institute, University of Rochester, Rochester NY USA
Study Site & Enrollment	University of Rochester Medical Center 40 evaluable patients
Study Rationale	Despite an array of available therapies, CLL/SLL remains an incurable disease. Furthermore, the presence of certain cytogenetic abnormalities and high-risk mutational features predicts for a reduced response to treatment, and as a result, a shorter period of progression-free survival. The development of a well-tolerated more effective, easily administered and limited duration therapy would be a major contribution to the management of CLL and other B cell malignancies. Acalabrutinib is an imidazopyrazine analogue and a potent inhibitor of BTK in vitro and in vivo. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib. Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations. Rituximab is a chimeric monoclonal antibody targeting CD20 FDA approved for the treatment of CLL/SLL using intravenous or subcutaneous formulations. Antibody dependent cellular phagocytosis may be optimized using high frequency subcutaneous administration of anti-CD20 monoclonal antibodies. Unlike ibrutinib, acalabrutinib does not cause significant in vitro inhibition of rituximab induced antibody dependent cellular phagocytosis in vitro. We thus propose that acalabrutinib would be an ideal partner drug with high frequency low dose SQ rituximab in the treatment of CLL and that the combination will increase the efficacy of therapy for CLL patients by decreasing the time to achievement of complete response and allowing for shorter and less toxic therapy.

Study Objectives	**Primary objective:** • Define the clinical efficacy as defined by complete remission rate of acalabrutinib and high frequency low dose subcutaneous rituximab in patients with previously untreated CLL/SLL **Secondary objectives:** • Describe the rate of minimal residual disease (MRD) negativity using 6-color flow cytometry. • Define the progression free survival and duration of response in patients treated with the combination. • Determine the safety of acalabrutinib and high frequency low dose subcutaneous rituximab in this population. **Exploratory objectives:** • Determine the effect of high frequency low dose SQ rituximab on circulating CLL cell CD20 expression before and after the addition of acalabrutinib. • Determine the effects of in vivo exposure of circulating target and effector cells to acalabrutinib on subsequent in vitro anti-CD20 mAb induced ADCP, ADCC and CDC. • Determine the effect of treatment with acalabrutinib and HFLD SQ rituximab on T, B, NK and monocyte immunophenotypes in CLL/SLL patients
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Diagnosis of B-cell CLL or SLL, with diagnosis established according to IWCLL criteria and documented within medical records. Patients must not have received previous CLL/SLL directed therapy 2. CLL/SLL that warrants treatment consistent with accepted IWCLL criteria for initiation of therapy. Any one of the following conditions constitute CLL/SLL that warrants treatment: a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or b) Massive (i.e., lower edge of spleen ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or c) Massive (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/L), or e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or f) Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:

	i. Unintentional weight loss of ≥10% within the previous 6 months, or ii. Significant fatigue (≥Grade 2), or iii. Fevers >100.5°F or 38.0°C for ≥2 weeks, or iv. Drenching night sweats for >1 month. 3. Adequate organ system function, defined as follows: a) Absolute neutrophil count (ANC) ≥ 0.5 x10^9/L and platelet count ≥ 30x10^9/L b) Total bilirubin ≤2.5 times the upper limit of normal (ULN), unless due to Gilbert's disease c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement d) Calculated creatinine clearance >30mL/min (as calculated by the Cockcroft-Gault formula) e) Patients with PT/INR or aPTT ≤ 2xULN. 4. ECOG performance status ≤ 2, or ≤ 3 if related to CLL. 5. Male or female ≥ 18 years of age. 6. Ability to swallow and retain oral medication. 7. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib and for 12 months following last dose of rituximab. (see Appendix 3 for examples) 8. Willingness and ability to comply with study and follow-up procedures and give written informed consent.
Exclusion Criteria	Patients who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Patients receiving cancer therapy a. Systemic corticosteroid therapy started prior to study entry is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted. 2. Serologic status reflecting active hepatitis B or C infection. Patients who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded. 3. Known history of HIV. 4. Known histological transformation from CLL to an aggressive lymphoma. 5. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. 6. Live virus vaccines within 4 weeks prior to C1D1 or during rituximab therapy. 7. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration or acalabrutinib.

	8. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) b. Uncontrolled cardiac arrhythmia (Patients with controlled atrial fibrillation/flutter are eligible) c. Myocardial infarction within 3 months of enrollment d. Angina not well-controlled by medication e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 3 months of enrollment. f. Active bleeding or history of bleeding diathesis (eg, hemophilia or von Willebrand disease). g. Any history of intracranial bleed or stroke within 6 months of first dose of study drug h. Patients with suspected or confirmed PML i. Patients with malabsorption syndrome or gastrointestinal disease that limits absorption of oral medication 9. Malignancy within 2 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry. 10. Patients with active uncontrolled autoimmune hemolytic anemia or ITP. 11. Inability to discontinue use of strong CYP3A inhibitors. Patients taking moderate CYP3A inhibitors or strong CYP3A inducers are eligible. 12. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug. 13. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) at study entry. Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study. 14. Women who are pregnant or breastfeeding.
Efficacy Endpoints	The primary objective of the study is to determine the efficacy of acalabrutinib and subcutaneous rituximab as defined by complete response rate at 1 year of therapy. The complete response rate will be presented with an associated 95% two-sided exact binomial confidence interval.
Study Design	Single center, open label, Phase II trial of acalabrutinib and high frequency low dose subcutaneous rituximab in previously untreated CLL patients requiring therapy.

Premedication	Pre-medicate patients approximately 30 minutes prior to the first dose of rituximab (administered IV) and second dose of rituximab (administered subcutaneously) with acetaminophen 650 mg (or equivalent), an antihistamine (diphenhydramine 50 mg or equivalent). Premedications will be optional prior to subsequent subcutaneous doses. Use of anti-pneumocystis (PJP) and antiviral prophylaxis is optional.
Dosing Regimen & Treatment Study Visits	All cycles will be 28 days. Rituximab: administered 2 times weekly for 6 cycles. Initial dose day 1: 50 mg IV, Then 50 mg SQ thereafter. Acalabrutinib: 100 mg po BID starting on day 8 of cycle 1. First dose prior to rituximab on day 8. • Response assessments will be performed prior to the completion of cycle 12. Patients who have attained a radiographic complete response will undergo a BM biopsy to confirm CR. Patients in CR will also have MRD testing performed on peripheral blood and marrow. Patients in CR and undetectable for MRD, will stop therapy and be followed until disease progression. • Patients not in a MRD negative CR, will continue acalabrutinib. • Repeat response assessments will be performed at 24 cycles of therapy for those continuing on acalabrutinib. Patients in CR and undetectable for MRD, will stop therapy and be followed until disease progression, .unacceptable toxicity or physician/patient discretion. **SCHEMA**  *If otherwise in CR ¥ Administered twice weekly, 1st dose of rituximab will be administered intravenously, subsequently doses will be administered subcutaneously
Correlative Experiments	Study labs (peripheral blood) will be collected immediately before initiation of the first dose of rituximab (50 mg IV), at 1 hour and at completion of the infusion. Peripheral blood will also be sampled immediately before and 2 hours after the subcutaneous administration 50 mg of rituximab on days 3, 8,

	and 15 of cycle 1, on day 1 of cycles 2-6 of rituximab, at 4 weeks after the administration of the last dose of rituximab, and then every 3 months until 24 months after initiation of therapy (see section 12). These samples will be analyzed in the laboratory of Dr. Clive Zent at the University of Rochester. At the post cycle 12 and/or cycle 24 response assessment, peripheral blood and bone marrow samples will be analyzed for MRD
Statistical Considerations	The complete response rate will be estimated from forty enrolled subjects. An associated 95% two-sided confidence interval will be calculated using exact binomial methods. We anticipate a CR rate of 20%, which would result in a 95% two-sided confidence interval with a width of 26.6% (from 9.1% to 35.6%) for a sample size of 40 subjects.

1 . INTRODUCTION

1.1 CLL/SLL

In the US, an estimated 18,960 new cases of Chronic Lymphocytic Leukemia (CLL) will be reported for 2016 with deaths totaling 4,660 due to the disease according to American Cancer Society estimates (American Cancer Society, 2016). Small lymphocytic lymphoma (SLL) is same disease as CLL, predominantly affecting the nodal compartment whereas the bone marrow and peripheral blood have a higher degree of disease involvement in CLL. CLL affects mainly older adults and is characterized by the accumulation of clonal mature B lymphocytes in the blood, bone marrow, and secondary lymphoid tissues. CLL is a heterogeneous disease, with several higher risk cytogenetic abnormalities which are generally more difficult to treat, including 17p deletion, *TP53* gene mutation, and 11q deletion. [1] Chemotherapy regimens in combination with monoclonal antibody therapy have historically comprised the standard of care for patients with CLL. Frontline therapy for patients with CLL had consisted of the anti-CD20 monoclonal antibody rituximab, in combination with either fludarabine and cyclophosphamide, or bendamustine. Depending on the age and comorbidities of the patient, chlorambucil in combination with an anti-CD20 monoclonal antibody is also considered. In addition to rituximab, other anti-CD20 antibodies have also been approved for the treatment of CLL, including ofatumumab and obinutuzumab. [2-4] Recently the BTK inhibitor, ibrutinib was approved by the FDA for the treatment of patients with CLL in the relapsed or refractory setting or more recently as first-line therapy. [5, 6]

Despite these advancements, CLL remains an incurable disease, and many patients will progress and eventually die from their disease or the complications of its therapies such as infection. Furthermore, patients with higher risk cytogenetic abnormalities still present with a less than optimal response to approved therapies and shorter duration of response and progression free survival. As such, there is a pressing need for new, innovative, targeted therapies (and novel combinations of these therapies) for the treatment of patients with relapsed/refractory CLL. Despite this progress treatment of CLL remains suboptimal. Patients do not recover immune competency resulting in complications including infections, second malignancies, and autoimmune cytopenias. Currently therapies using B cell receptor pathway inhibitors are continued until disease progression or intolerance. About 30% of patients stop therapy because of adverse events and a smaller percentage stop because of disease progression.[7] The development of a well-tolerated more effective, easily administered and limited duration therapy combining a specifically targeted BTK inhibitor and an anti-CD20 mAb would be a major contribution to the management of CLL and other B cell malignancies.

1.2 B-CELL RECEPTOR SIGNALING

Since its discovery, the biological role of the BCR signal transduction pathway has been described, including the respective functions of BCR itself, several other tyrosine kinases, tyrosine phosphatases, adaptor molecules, lipid-modifying enzymes, modular binding domains, and transcription factors. [8] Together, the components of the BCR signaling pathway tell the eloquent story of a signaling cascade starting at the level of the BCR and resulting in the activation/modulation of an array of diverse intracellular signaling pathways responsible for mounting an effective humoral response by the BCR-activated B cells. It is now widely accepted that BCR signaling is an important contributor to malignant transformation of B lymphocytes. In CLL, there is mounting evidence to support the role of BCR signaling as a central component of the oncogenic process. [9] Overall, the accumulated evidence suggests that

CLL has powerful addiction to BCR signaling and, hence, supports the concept of BCR signal inhibition as a novel treatment approach.

1.3 BTK INHIBITION IN LYMPHOID MALIGNANCIES

Bruton tyrosine kinase (BTK) is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B-cells, myeloid cells, mast cells, and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration.[10, 11] In addition, BTK-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumors.[12, 13] Taken together, these findings suggested inhibition of BTK offered an attractive strategy for treating B-cell neoplasms.

1.4 ACALABRUTINIB (ACP-196)

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is a potent inhibitor of BTK in vitro and in vivo and is approved in the US for the treatment of adult patients with MCL who have received at least 1 prior therapy. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK and does not appreciably inhibit non-BTK TEC family kinases, compared with ibrutinib.[14] Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations. As such, acalabrutinib does not cause significant in vitro inhibition of rituximab induced ADCP in vitro (unpublished data from the Zent lab). We thus propose that acalabrutinib would be an ideal partner drug with high frequency low dose SQ rituximab in the treatment of CLL.

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. The systemic toxicity of acalabrutinib has been investigated in 6 repeat-dose toxicology studies. The NOAEL in the dog was 30 mg/kg/day, which was the highest dose evaluated. Pharmacokinetic and pharmacodynamics studies have been conducted in healthy volunteers investigating dose-ranging, food-effect, and drug-drug interactions of acalabrutinib dosing for 1 or 2 days. Minimal low-grade side effects were noted. Median plasma Tmax values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma ACP-196 Cmax values decreased to 27.3% of the values observed in the fasted state. In contrast, the relative exposure of ACP-196 (AUC) remained mostly unchanged in both states. The effect of coadministration of a potent CYP3A4 inhibitor, itraconazole, on the plasma levels of ACP-196 was also evaluated. The mean plasma ACP-196 Cmax values increased 3.7-fold in the presence of itraconazole. The mean plasma AUC0-last, AUC0-24, and AUC0-inf values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole. Additionally, administration of the gastric pH modifiers, calcium carbonate or omeprazole, decreased mean Cmax to 25% and 21% and AUC to 47% and 43%, respectively, of values obtained with ACP-196 dosed alone. Rifampin dosed at 600 mg QD for 9 days decreased AUC to 23% of values obtained with ACP-196 dosed alone.

In August of 2022, AstraZeneca informed all sponsors that the new tablet formation of acalabrutinib would be used in the future. The tablets consist of *acalabrutinib maleate*, a salt form of *acalabrutinib* freebase that is used in capsules, and delivers an equivalent dose of *acalabrutinib* compared to the

capsules (100mg). Therefore, the tablets can be switched directly for capsules on a 1:1 basis. This new tablet formulation was developed to overcome the interactions between acalabrutinib capsules and acid reducing agents (ARAs). Acalabrutinib tablets can be co-administered with all acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids). Since the formulations are bioequivalent, the same safety and efficacy can be expected, with the added benefit for patients who require co-treatment with PPIs now able to be taking acalabrutinib.

Clinical experience with acalabrutinib has included >3000 trial participants to date, justifying current FDA approval of acalabrutinib 100 mg po bid for patients with relapsed mantle cell lymphoma. Regarding CLL/SLL, clinical efficacy results are available for a subset of subjects with relapsed CLL. [14] One hundred thirty-four subjects were sequentially enrolled and continuously treated with acalabrutinib 100 to 400 mg once daily in the dose-escalation portion of the study, and 100 mg twice daily in the expansion portion. Clinical activity of acalabrutinib was robust. The ORR, including PR and PRL, was 96.9% based on the efficacy evaluable population. The rate of progression-free survival at 12 months and 18 months was 95.4% and 89.6%, respectively. Subjects could be enrolled in the treatment-naive subgroup if they did not want to receive chemoimmunotherapy or if they had comorbidities that would have precluded chemoimmunotherapy. A total of 99 subjects were treated in the treatment-naive subgroup with a median time on study for this population of 24.8 months. The ORR, including PR and PRL, was 99.0% based on the efficacy evaluable population. The rate of PFS was 99% at both 12 and 18 months.

An aggregate safety analysis of acalabrutinib monotherapy was conducted in order to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. The analysis was performed on a 7-study integrated monotherapy population. The most commonly reported AEs of any grade were headache (42.3%), diarrhea (40.4%), fatigue (24.6%), nausea (23.6%), contusion (23.5%), cough (22.1%), and upper respiratory tract infection (21.7). The most frequently reported Grade ≥3 AEs were neutropenia (10.4%), anemia (7.5%), pneumonia (6.5%), thrombocytopenia (3.7%), and hypertension (3.1%). Grade 5 AEs were reported for 27 (4.4%) subjects in the monotherapy population. Of these 27 subjects, 13 (2.1%) subjects had an infection event, including 6 (1.0%) subjects with Grade 5 pneumonia, which was the only Grade 5 event reported for more than 1 subject. The remaining reported Grade 5 infection events include Aspergillus infection, brain abscess, Candida sepsis, lower respiratory tract infection, lung infection, sepsis, and septic shock.

Safety data is available combining acalabrutinib with anti-CD20 therapy as well. A phase 1b study of acalabrutinib with obinutuzumab in patients with relapsed as well as previously untreated CLL has enrolled 45 patients to date. (acalabrutinib investigator brochure 7.1) The most frequently reported adverse events were upper respiratory tract infection (68.9%), weight increased (64.4%), diarrhea (62.2%), rash maculopapular (62.2%), cough (55.6%), nausea (51.1%), headache (44.4%), infusion related reaction (44.4%), contusion (42.2%), dizziness (40.0%), vomiting (40.0%), arthralgia, constipation, hypertension, and skin lesion (37.8% each), fatigue (35.6%), decreased appetite, edema peripheral, and sinusitis (33.3% each), fall and oral pain (31.1% each), myalgia (28.9%), and dyspepsia and paresthesia (26.7% each). The most frequently reported Grade ≥3 AEs were neutrophil count decreased in 11 (24.4%) subjects, platelet count decreased and syncope in 4 (8.9%) subjects each, and weight increased in 3 (6.7%) subjects. There were no Grade 5 (fatal) AEs reported.

1.5 HIGH FREQUENCY LOW DOSE SQ RITUXIMAB IN CLL

Unconjugated anti-CD20 mAb are effective and tolerable therapy for CLL and other B cell malignancies but rarely achieve complete remission as single agents and are not curative. Anti-CD20 mAb primary kills B cells by activating the innate immune system i.e. cell mediated cytotoxicity and complement dependent cytotoxicity (CDC). There is appreciable in vivo murine and in vivo primary human cell data showing that the primary mechanism of removal of opsonized B cells in the circulation is phagocytosis by fixed macrophages in the liver (Kupffer cells) and spleen. [15-23](and unpublished data from Zent lab) The mechanism of cellular cytotoxicity in malignant lymphoid tissue is less well understood but could involve activation of tumor associated macrophages that converts them from supportive to cytotoxic cells. NK cell mediated ADCC has a limited capacity to kill CLL cells in vitro and there is no documented cytotoxic role for NK cells in lymphoid tissue. In summary, most anti-CD20 mAb cytotoxicity is mediated by the innate immune system via CDC and macrophage ADCP.
Mechanisms of resistance of B cells to anti-CD20 mAb therapy are not well understood. Circumstantial evidence suggests that treatment efficacy is limited by the finite cytotoxic capacity of the innate immune system. Studies of complement levels after treatment in patients with circulating B cells suggests that depletion of complement is not a major limitation of CDC but are not conclusive. [24, 25] Intrinsic resistance to activated complement system generated membrane attack complexes activated by anti-CD20 mAb has been demonstrated in vitro. [26, 27] There is limited data on the cytotoxic capacity of fixed macrophages in humans and no published data on target B cell resistance to ADCP. An important and well documented mechanism of acquired resistance to anti-CD20 mAb therapy is loss of CD20 expression by target cells by trogocytosis as recently reviewed. [28] In brief, administration of large doses of aCD20 mAb rapidly activates the innate immune cytotoxic mechanism followed by rapid loss of cell membrane CD20 (~99%) by the surviving cells. [24] Loss of CD20 occurs by trogocytosis, a mechanism of non-lethal removal of membrane bound immune complexes (e.g. CD20-anti-CD20 mAb) from target cells by effector cells including macrophages, monocytes, and neutrophils. [29] In clinical trials therapy with higher frequency (2-3 x week) lower (20 mg/m^2) doses of rituximab did not cause significant loss of CD20. [30, 31] These data support further trials of high frequency low dose rituximab in the management of CLL and other B cell malignancies.
Rituximab is FDA approved for the treatment of CLL based on an overall survival benefit when combined with standard therapy in the first line setting. [3] Subcutaneously administered rituximab is also approved for use in CLL based on non-inferior pharmacokinetics and comparable efficacy. [32-34] Additionally, in a randomized phase 3 trial comparing intravenous vs. subcutaneous rituximab, 77% of patients preferred subcutaneous administration. [35] The most common adverse events (≥20%) observed in patients with FL include infections, neutropenia, nausea, constipation, cough, and fatigue. The most common adverse events (≥20%) observed in patients with DLBCL include infections, neutropenia, alopecia, nausea, and anemia. The most common adverse events (≥20%) observed in patients with CLL were infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

1.6 HYPOTHESIS

Combined BTK inhibitor and anti-CD20 mAb therapy has been shown to be safe and effective for treatment of CLL. [36] The rationale for use of this combination is the disparate mechanisms of actions and assumed differences in tumor cell resistance to cytotoxicity of these drugs. In addition, initiation of therapy with BTK inhibitors frequently causes lymphocytosis by mobilizing CLL cells from lymphoid tissue into the circulation where they are more susceptible to mAb mediated cytotoxicity. We propose that the combination of a BTK inhibitor and kinetically optimized high frequency low dose rituximab therapy will increase the efficacy of therapy for CLL by decreasing the time of achievement of complete response and allowing for shorter and less toxic therapy.

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

- To define the clinical efficacy as defined by complete remission rate of acalabrutinib and high frequency low dose subcutaneous rituximab in patients with previously untreated CLL/SLL

2.2 SECONDARY OBJECTIVES

- To describe the rate of MRD negativity using 6-color flow cytometry.
- To define the progression free survival and duration of response in patients treated with the combination.
- To determine the safety of acalabrutinib and high frequency low dose subcutaneous rituximab in this population.

2.3 EXPLORATORY OBJECTIVES

- To determine the effect of high frequency low dose SQ rituximab on circulating CLL cell CD20 expression before and after the addition of acalabrutinib.
- To determine the effects of in vivo exposure of circulating target and effector cells to acalabrutinib on subsequent in vitro anti-CD20 monoclonal antibody induced ADCP, ADCC and CDC.
- To determine the effect of treatment with acalabrutinib and HFLD SQ rituximab on T, B, NK and monocyte immunophenotypes in CLL/SLL patients

Response and efficacy endpoints will be defined as per the guidelines for the diagnosis, response assessment and supportive management of chronic lymphocytic leukemia. [37]

3 ELIGIBILITY CRITERIA

Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

3.1 INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Diagnosis of B-cell CLL or SLL, with diagnosis established according to IWCLL criteria and documented within medical records. Patients must not have received previous therapy for CLL/SLL
2. CLL/SLL that warrants treatment consistent with accepted IWCLL criteria for initiation of therapy. Any one of the following conditions constitutes CLL/SLL that warrants treatment:
    a. Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
    b. Massive (i.e., lower edge of spleen ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or
    c. Massive (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
    d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/L), or
    e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
    f. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
        i. Unintentional weight loss of ≥10% within the previous 6 months, or
        ii. Significant fatigue (≥Grade 2), or
        iii. Fevers >100.5°F or 38.0°C for ≥2 weeks, or
        iv. Drenching night sweats for >1 month.
3. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) ≥ 0.5×10^9/L and platelet count ≥ 30×10^9/L
    b. Total bilirubin ≤2.5 times the upper limit of normal (ULN) unless due to Gilbert's disease
    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement
    d. Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault formula)
    e. Patients with PT/INR or aPTT ≤2xULN.
4. ECOG performance status ≤ 2 unless related to CLL.
5. Male or female ≥ 18 years of age.
6. Ability to swallow and retain oral medication.

7. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib and for 12 months following last dose of rituximab. (see Appendix 3 for examples)
8. Willingness and ability to comply with study and follow-up procedures, and give written informed consent.

3.2 EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria are not to be enrolled to this study:

1. Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery).
    a. Systemic corticosteroid therapy started prior to study entry is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
2. Serologic status reflecting active hepatitis B or C infection. Patients who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.
3. Known history of HIV.
4. Known histological transformation from CLL to an aggressive lymphoma.
5. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion.
6. Live virus vaccines within 4 weeks prior to C1D1 or during rituximab therapy.
7. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration or acalabrutinib.
8. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV)
    b. Uncontrolled cardiac arrhythmia (Patients with controlled atrial fibrillation/flutter are eligible)
    c. Myocardial infarction within 3 months of enrollment
    d. Angina not well-controlled by medication
    e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 3 months of enrollment.
    f. Active bleeding or history of bleeding diathesis (eg, hemophilia or von Willebrand disease).
    g. Any history of intracranial bleed or stroke within 6 months of first dose of study drug
    h. Patients with suspected or confirmed PML
    i. Patients with malabsorption syndrome or gastrointestinal disease that limits absorption of oral medication
9. Malignancy within 2 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry.

10. Patients with active uncontrolled autoimmune hemolytic anemia or ITP.
11. Inability to discontinue use of strong CYP3A inhibitors. Patients taking moderate CYP3A inhibitors or strong CYP3A inducers are eligible.
12. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
13. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) at study entry. Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is an open label, Phase II trial of acalabrutinib and high frequency low dose subcutaneous rituximab in previously untreated CLL patients requiring therapy. Subjects will be recruited from the James P. Wilmot Cancer Center, University of Rochester in Rochester, New York. Patients seen in the inpatient or outpatient setting with histologically confirmed untreated CLL will be evaluated for this study.

Patients will be treated with the following combination:
Rituximab: day 1 = 50 mg IV, then 50 mg SQ 2 x weekly for 6 cycles. Note that in the event of a first dose infusion reaction, subsequent doses may be given IV if felt necessary by the treating investigator.
Acalabrutinib: 100 mg po BID starting on day 8 of cycle 1. First dose prior to rituximab on day 8.

- Response assessments will be performed prior to the completion of cycle 12. Patients who have attained a radiographic complete response will undergo a BM biopsy to confirm CR. Patients in CR will also have MRD testing performed on peripheral blood and marrow. Patients in CR and undetectable for MRD, will stop therapy and be followed until disease progression.
- Patients not in a MRD negative CR, will continue acalabrutinib.
- Repeat response assessments will be performed at 24 cycles of therapy for those continuing on acalabrutinib. Patients in CR and undetectable for MRD, will stop therapy and be followed until disease progression, unacceptable toxicity or physician/patient discretion.

All cycles will be 28 days.

Patients will be followed until the occurrence of definitive disease progression and may discontinue therapy early for unacceptable toxicity or withdrawal from the study due to investigator decision or other reasons.

4.2 REGISTRATION

Patients registered to the study must sign consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Patients should begin study treatment within 30 days of consent.

4.3 DISCONTINUATION FROM STUDY TREATMENT

Patients will be discontinued from study treatment for any of the following reasons:

- MRD negative CR or CRi at completion of cycle 12 or cycle 24 (MRD negativity is defined as <1 CLL cell/10,000)
- Disease progression
- Severe toxicity
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy

- Inability of the patient to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Non-compliance/lost to follow-up
- Investigator discretion
- Study termination

Patients who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression. After withdrawal from protocol treatment, patients should be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigators must record his or her reasoning for this decision in the patient's medical records. All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the investigator, it is not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patient's medical records.

4.4 CRITERIA FOR STUDY TERMINATION

This study will be considered terminated when 1 or more of the following conditions are met:

- All subjects have completed all required study visits;
- All subjects have discontinued from the study;
- The University of Rochester Data Safety Monitoring Committee or Institutional Review Board (IRB) discontinues the study because of safety considerations.

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Table 5.1 below lists all of the required assessments that should be performed at each study visit.

TABLE 5.1: STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Cycle = 28 days	Screening	Cycle 1[1]				Cycle 2-6[2]	Cycle 7-12[2]	Cycles 12-24[2]	Follow up[3]
	D-28 to -1	D1	D3,4 or 5	D8	D15	D1	D1	q3 mo	
Informed consent	X								
Medical history	X								
ECOG Performance Status	X								
Physical Examination	X	X		X		X	X	X	
Vital signs	X	X	X	X		X	X	X	
Hematology[14]	X	X	X	X	X	X	X	X	
Chemistry [15]	X	X[16]				X	X	X	
LDH, Uric acid	X	X[16]							
B2mcg	X								
Pregnancy Test	X[8]								
Hep B/C serology, quant Igs	X								
FISH	X[5]								
IGHV, TP53, NOTCH1, SF3B1	X[5]								
CT imaging (neck, chest, abdomen, pelvis)	X[6]						X[6]	X[6]	
BM aspirate &biopsy							X[9]	X[9]	
Flow cytometry for MRD							X[10] (PB/BM)	X[10] (PB/BM)	
Correlative Labs [4]		X	X	X	X	X	X	X	
Rituximab 50 mg* twice weekly		X*	X	X	X	X			
Acalabrutinib 100 mg BID				X[13]	X	X	X	X[12]	X[12]
Response Assessment							X	X	
Adverse Event Assessment		X	X	X	X	X	X	X	X [11]
Concomitant Medications		X	X	X	X	X	X	X	

**1st dose of rituximab will be administered intravenously, subsequently doses will be administered subcutaneously*

[1] Treatment Administration +/- 1 day window. Physical Exam, Vital Signs, Hematology and Chem visit days have - 1 day window

[2] Treatment Administration +/- 3 day window. Physical Exam, Vital Signs, Hematology and Chem visit days have a - 3 day window

[3] Following completion of cycle 24 or upon discontinuation of therapy in the absence of disease progression, patients will be evaluated as per institutional standards (typically every 3-4 months). Physical exam data, vital signs, laboratory values and patient diaries will no longer be collected. Patients continuing on acalabrutinib will continue with adverse event assessments at each evaluation and be followed for progression and survival events.

[4] See section 12

[5] FISH for del17p, del11q, del13q, trisomy 12 will be performed on peripheral blood or marrow within 6 months of C1D1. IGHV, TP53, NOTCH1, SF3B1 mutation analysis to be performed at screening (if feasible) unless previously tested.

[6] Baseline CT scan within 60 days prior to Cycle 1/Day 1. CT Scan/Response Assessment +/- 7 day window. CT Scan/Response assessment end of cycle 12 and at the end of cycle 24 for patients continuing on acalabrutinib. Follow up CTs to be done at investigator discretion/ per standard of care. CTs at cycle 12 and 24 will not be required if a patient does not have measurable disease at baseline.

[7] Visits every 3 months (+/- 1 month) or as per investigator discretion. Treatment Administration and labs or other assessments +/- 7 day window from visit.

[8] Serum or urine pregnancy test prior to Cycle 1 / Day 1 and within 30 days following discontinuation for females of childbearing potential. If patient has experienced menopause or no longer has uterus / ovaries this can be omitted.

[9] Bone Marrow sample performed prior to completion of cycle 12 and/or cycle 24 to confirm a complete response / MRD negativity

[10] Flow cytometry of peripheral blood for minimal residual disease assessment is being performed prior to completion of cycle 12 and at cycle 24 for patients continuing on acalabrutinib. A patient in CR will undergo a bone marrow biopsy to confirm the response. Bone marrow and peripheral blood samples will be analyzed and stored in the laboratory of Dr. Richard Burack at the University of Rochester.

[11] Follow-up for SAEs should continue until resolution, stabilization, the subject has withdrawn consent or has been lost to follow-up.

[12] Patients not in a MRD negative complete remission will continue acalabrutinib.

[13] Acalabrutinib is dosed twice daily every day, unless treatment is held or discontinued, starting Cycle 1 Day 8.

[14] At a minimum, hematology includes white blood cells and differential, hemoglobin, hematocrit, mean corpuscular volume, platelets.

[15] At a minimum, chemistry includes sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, calcium, phosphorus, albumin

[16] Chemistry, uric acid and LDH will be repeated 6-8 hours after treatment initiation and as further clinically indicated for patients with a high tumor burden, which is defined as having any lymph nodes >10cm or lymph nodes >5cm with an absolute lymphocyte count>25 $x10^9$/L

6 AGENT GUIDANCE

6.1 GUIDELINES FOR RITUXIMAB

- *Method of Administration:* Rituximab will be administered as an intravenous for the first dose.
- Subsequent doses will be subcutaneous. Note that in the event of a first dose infusion reaction, subsequent doses may be given IV if felt necessary by the treating investigator.
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* Pre-medicate approximately 30 minutes prior to rituximab with an antihistamine (oral diphenhydramine 50 mg or equivalent) and oral acetaminophen 650 mg (or equivalent). Premedications will be optional prior to subsequent subcutaneous doses. Use of anti-pneumocystis (PJP) and antiviral prophylaxis is optional.
- *Hypersensitivity and Infusion Reaction Precautions*: Medication and resuscitation equipment must be available per institutional guidelines prior to first rituximab administration for the emergency management of potential anaphylactic reactions.
- *Supply:* Rituximab intravenous solution (Rituxan® 100 mg/10 mL or 500 mg/50 mL vials) and rituximab/hyaluronidase (Rituxan Hycela® rituximab 1400 mg/hyaluronidase 23,400 units per 11.7 mL vials) will be sourced by study sites from commercially-available supplies.
- *Storage and handling:* Rituximab intravenous solution and rituximab/hyaluronidase should be stored in a refrigerator between 2-8 degrees Celsius (36-46 degrees Fahrenheit). During storage, vials should be kept in their original packaging to protect them from light. Do not freeze or shake vials.
- *Potential risks: T*reatment with rituximab (a standard treatment modality for this clinical situation) may cause serious side effects. While unlikely to occur, some of which can be life-threatening or cause death, including the following, listed according to their frequency/risk. Please refer to rituximab prescribing information for additional details.
- *Contraception recommendations:* Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 12 months following last dose of rituximab. (see Appendix 3 for examples)

  Very Common (≥10% of patients) – The most common side effects (>10%) observed with rituximab treatment in patients, include:

  - Infusion/Administration related reaction
  - Fever
  - Chills
  - Infection
  - Weakness
  - Headache
  - Abdominal Pain
  - Pain
  - Low white blood cell counts
  - Low platelet count
  - Night sweats

- Rash
- Pruritus (itching)
- Rash and itching at injection site
- Cough
- Runny nose
- Angioedema (swelling, especially around the nose or mouth)
- Nausea

Common (>5-10% of patients) - Common side effects (>5-10%) observed with rituximab treatment in patients, include:

- Back pain
- Throat irritation
- Flushing (redness in face or other areas of body)
- Anemia (low hemoglobin)
- Hives (itchy red welts)
- Wheezing
- Shortness of breath
- Sinus infection
- Hyperglycemia (high blood sugar)
- Peripheral edema (swelling of extremities)
- Diarrhea
- Vomiting
- Constipation
- Dizziness
- Anxiety
- Muscle pain
- Joint pain
- Constriction ('spasm') of muscles in chest
- Hypotension (low blood pressure)
- Hypertension (high blood pressure)

6.1.1 DOSE PREPARATION AND ADMINISTRATION OF RITUXIMAB: INTRAVENOUS

PREPARATION

Per current rituximab prescribing information, final concentration of the intravenous bag of rituximab should be between 1-4 mg/mL. Instructions below will provide an intravenous solution with a final concentration of 1 mg/mL. Sites are discouraged from preparing more concentrated solutions, as it may be difficult to properly administer the required dose. Doses should be prepared under standard aseptic conditions following applicable regulatory guidelines. *Do not use rituximab/hyaluronidase for preparation of the intravenous cycle 1 day 1 rituximab dose.*

<u>Steps for Preparation of 1 mg/mL IV solution</u>

1. Prepare a 45 mL IV bag of 0.9% sodium chloride
    a. Sites may either pump a bag with 0.9% sodium chloride to a final volume of 45 mL, or withdraw overfill from a prefilled bag to achieve a final volume of 45 mL

i. Rituximab for IV use is compatible with polyethylene (PE) and polyvinyl chloride (PVC) infusion bags

2. Draw up 5 mL of rituximab intravenous solution for injection (10 mg/mL) into a syringe
3. Add 5 mL of rituximab to the 45 mL bag of 0.9% sodium chloride
4. Gently invert the prepared IV bag a few times to mix. Do NOT shake the bag.
5. Label according to applicable local, state, and federal regulations

Diluted solutions of rituximab for intravenous infusion should be used immediately. If unable to use immediately, prepared solutions for infusion may be stored for up to 24 hours between 2-8 degrees Celsius (36-46 degrees Fahrenheit).

ADMINISTRATION
After administering appropriate pre-medications, infuse the 50 mg dose intravenously at 25 mg/hr (total of 2 hours), modifying if necessary for infusion related reactions (section 6.1.3)

IV doses of rituximab should not be mixed with other solutions. Bags should not be shaken. Solutions should be administered by IV infusion – do not administer by IV push, IV bolus, or subcutaneously. If the patient develops an infusion reaction, see section 6.1.3. Permanently discontinue the infusion if the patient develops a serious or life-threatening cardiac arrhythmia.

The date of administration of rituximab must be recorded within the eCRF, patient's medical records, and/or in the drug accountability records. For the purpose of drug accountability and dosing, subjects should record the doses missed on a drug diary. Any error in drug administration should be recorded (e.g., missed dose).

6.1.2 DOSE PREPARATION AND ADMINISTRATION OF RITUXIMAB: SUBCUTANEOUS

PREPARATION
Individual 50 mg doses of rituximab/hyaluronidase should be drawn from vials into discrete syringes, under standard aseptic conditions and following applicable regulatory guidelines. At the manufacturer's standard concentration (120 mg/mL), sites will need to draw up 0.42 mL per syringe for each dose. Rituximab/hyaluronidase is compatible with polypropylene and polycarbonate syringes, and stainless steel transfer and injection needles. To avoid clogging the needle, do not attach the injection needle until immediately before administration.

Doses of rituximab hyaluronidase drawn into syringes should be used immediately. Doses not used immediately may be stored for up to 48 hours between 2-8 degrees Celsius (36-46 degrees Fahrenheit) and up to 8 hours at 30 degrees Celsius (86 degrees Fahrenheit) in diffused daylight. After drawing up doses, residual rituximab/hyaluronidase in the source vial should be discarded. If using a closed system transfer device for withdrawal of rituximab/hyaluronidase from source vials, the source vials (not doses drawn up) may be kept in a refrigerator for up to 7 days from the time of initial access.

Following successful tolerance of at least one dose of subcutaneous rituximab/hyaluronidase at the study site, the site may elect to provide the patient with pre-drawn doses for home administration, with the patient's consent. Patients receiving pre-drawn doses for home administration should be provided with:

- Detailed instructions regarding proper storage, handling, and administration technique
- A prescription for injection needles
- A sharps bin for safe disposal of used needles & syringes

- Contact information for study personnel, in the event of questions or acute issues
- Information on managing injection reactions

NOTE: If the site provides doses to patients for home administration, no more than two doses may be provided at one time. Doses of rituximab/hyaluronidase are only stable for a maximum of 48 hours when stored between 2-8 degrees Celsius (36-46 degrees Fahrenheit) and up to 8 hours at 30 degrees Celsius (86 degrees Fahrenheit) in diffused daylight. Patients should be educated on the importance of storing doses in a refrigerator at home. Doses for home administration should be provided to patients in clean, sterile overwraps.

ADMINISTRATION
NOTE: Patients must have tolerated an IV dose of rituximab before they can be given subcutaneous rituximab/hyaluronidase.

Pre-medication is recommended as per section 6.1.

Attach stainless steel injection needle immediately prior to dose administration and inject subcutaneously into the abdomen. Rotate abdominal injection sites with each dose. Do not inject dose into any area appearing red, hard, bruised, tender, or where moles or scars are present. Do not inject doses of other subcutaneous medications at the same site.

6.1.3 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE – RITUXIMAB

Infusion related reactions, including severe reactions, have been reported with rituximab administration in patients with CLL. Guidelines are provided below for patients who experience such reactions. Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen, and bronchodilators.

The following are recommended infusion rate reduction/delay guidelines for patients who experience severe Infusion Related Reactions (IRR's) in which treatment should be interrupted. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitored patient, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the Investigator, and provided the patient is stable, the infusion may be resumed at ½ the previous rate and escalated at 30 minutes if tolerated.
- If the patient does not experience any further IRR symptoms, infusion may resume.

3rd Infusion Interruption (same day):

- Discontinue infusion for that day – monitor patient for resolution of all symptoms. Patient should have all vital signs completed as well as any other standard of care procedures completed as warranted by the Investigator prior to release of patient from study site.

- Any remaining diluted product should be discarded.

If at any time during rituximab treatment, an infusion related reaction is observed, the treating investigator may reduce the infusion flow rate at their discretion.

6.2 GUIDELINES FOR ACALABRUTINIB

- *Formulation, Packaging, and Storage*: Acalabrutinib is manufactured according to current Good Manufacturing Practice (cGMP) regulations and will be provided to the investigational site by Acerta Pharma/AstraZeneca or designee. It should be stored according to the instructions on the label that is affixed to the package containing each respective drug product. Acalabrutinib should be kept in a low-humidity place at room temperature between 20-25 degrees Celsius (68-77 degrees Fahrenheit). Excursions between 15-30 degrees Celsius (59-86 degrees Fahrenheit) are permitted. The drug product is provided as capsules intended for oral administration.
- *Supply:* Acalabrutinib (Calquence®) will be supplied to sites as 100 mg capsules (60 capsules/bottle) by Acerta Pharma/AstraZeneca. Sites approved for study participation will receive an initial shipment of of acalabrutinib following site activation.
- *Method of Administration:* acalabrutinib will be administered orally twice daily (every 12 hours) with or without food. Capsules should be swallowed whole with water; do not break, open, chew, or crush capsules. 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 next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.
- *Potential Drug Interactions*:

Acalabrutinib is not a strong direct inhibitor or inducer or CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolized by CYP3A; its exposure is affected when coadministered with strong CYP3A4 inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 1) will be avoided. 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.

The effect of agents that reduce gastric acidity (e.g. proton pump inhibitors or antacids) on acalabrutinib capsule absorption was evaluated in a healthy volunteer study. Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements and short-acting H2 receptor antagonists for a period of at least 2 hours before and 2 hours after taking acalabrutinib capsules. Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors (eg, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) while taking acalabrutinib capsules is not recommended due to a potential decrease in study drug-related exposure. The new tablet formation was developed to overcome the interactions between acalabrutinib capsules and acid reducing agents (ARAs). Acalabrutinib tablets can be co-administered with all acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids). Since the formulations are bioequivalent, the same safety and efficacy can be expected, with the added benefit for patients who require co-treatment with PPIs now able to be taking acalabrutinib,

- Table 6.2.1: Drug Interactions with acalabrutinib

Strong CYP3A Inhibitors	
Clinical Impact	Co-administration of acalabrutinib with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	*Avoid co-administration of strong CYP3A inhibitors with acalabrutinib.* Alternatively, if the inhibitor will be used short-term, interrupt acalabrutinib
Moderate CYP3A Inhibitors	
Clinical Impact	Co-administration of acalabrutinib with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	*When acalabrutinib is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.*
Strong CYP3A Inducers	
Clinical Impact	Co-administration of acalabrutinib with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations Decreased acalabrutinib concentrations may reduce acalabrutinib activity.
Prevention or Management	*Avoid co-administration of strong CYP3A inducers with acalabrutinib if feasible.* If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.
Gastric Acid Reducing Agents	

- *Pre-medications:* None
- *Prophylaxis*: none
- *Contraception recommendations:* Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. (see Appendix 3 for examples)

- *Potential risks: T*reatment with acalabrutinib may cause serious side effects. While unlikely to occur, some of which can be life-threatening or cause death, including the following, listed according to their frequency/risk. Please refer to acalabrutinib prescribing information for additional details.

  Very common (occurring in at least 10% or more of patients):
  - Headache
  - Bruising events including bruises, petechiae (pinpoint red or purple spots on the
  - skin), and increased tendency to bruise
  - Diarrhea (frequent or loose stools)
  - Nausea
  - Constipation (bowel movements that are infrequent or hard to pass)
  - Bleeding
  - Vomiting
  - Abdominal pain
  - Rash

  Common (occurring in at least 1% but less than 10% of patients):
  - Nose bleeds
  - Severe Bleeding

6.2.1 DISPENSING OF ACALABRUTINIB

The investigational product, acalabrutinib capsules for oral administration, is supplied as yellow and blue, opaque hard gelatin capsules, with 100 mg of acalabrutinib as the active ingredient. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide and indigotine (FD&C Blue 2).
Starting in October 2022, all patient transitioned to the tablet formation of acalabrutinib. The tablets consist of *acalabrutinib maleate*, a salt form of *acalabrutinib* freebase that is used in capsules, and delivers an equivalent dose of *acalabrutinib* compared to the capsules (100mg). Therefore, the tablets can be switched directly for capsules on a 1:1 basis. This new tablet formulation was developed to overcome the interactions between acalabrutinib capsules and acid reducing agents (ARAs).
Acalabrutinib tablets can be co-administered with all acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids). Since the formulations are bioequivalent, the same safety and efficacy can be expected, with the added benefit for patients who require co-treatment with PPIs now able to be taking acalabrutinib.

The following pictures provide side by side comparisons of the two products

Patients should be instructed to return any unused tablets when they return the bottle to the site. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the patients' medical record.
Before dispensing, the site pharmacist must check that the acalabrutinib is in accordance with the product specifications and the validity is within the re-test date.
The Pharmacist should record the date dispensed and patient's number and initials, as well as complete the accountability forms with information concerning the dispensation of acalabrutinib.
Acalabrutinib will be self-administered (by the patient). Tablets should be taken at approximately the same time each day with or without food. Patients should be instructed to swallow the tablets as a whole and should not chew or crush them.
Acalabrutinib capsule is administered BID and taken orally approximately every 12 hours. The tablets should be swallowed intact with water. Subjects should not attempt to open capsules or dissolve them in water. 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 next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

7 DOSE DELAYS/DOSE MODIFICATIONS

7.1 RITUXIMAB

No reduction in the dose of rituximab is permitted.
Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. Use of growth factors (such as G-CSF or pegylated G-CSF) is allowed, per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196). A maximum four (4) week delay for recovery from toxicity is allowed for both rituximab and acalabrutinib (individually or together) to allow recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If the patient withdraws consent or has documented progression, an end of study visit should be completed.

Dose delay and/or modification guidance is for adverse events considered at least possibly related to the study drug. If cytopenias are deemed related to the underlying disease rather than study drug, dose modifications are not required, or are per investigator discretion. If a patient discontinues only one study drug, the patient may continue treatment with the other study drug per the protocol.

7.2 STUDY DRUG MODIFICATIONS

- The actions should be taken for any Grade 4 toxicity or unmanageable Grade 3 toxicity. In addition, the actions in Table 7.2.1 should be taken when modification of acalabrutinib dose is recommended for specific treatment-related adverse events as listed in Table 7.2.2.
- If the dose of acalabrutinib is reduced, at the Investigator's discretion, the dose of acalabrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.
- Dose modifications are for adverse events attributed to study treatment. Dose modifications are not required for adverse events unrelated to study treatment.
- Guidance for dose modifications in the event of drug interactions is provided in Table 6.2.1

TABLE 7.2.1: DOSE MODIFICATION ACTIONS FOR ACALABRUTINIB

Event Occurrence	Action
1st-2nd	May restart at original dose level (100 mg BID)
3rd	Restart at 100 mg daily
4th	Discontinue acalabrutinib

TABLE 7.2.2: STUDY DRUG MODIFICATIONS

	Rituximab	Acalabrutinib
NCI-CTCAE Grade		
Neutropenia		
Grade 3 neutropenia	Maintain current dose	Maintain current dose

	Rituximab	Acalabrutinib
Grade 4 neutropenia lasting >7 days or occurrence of neutropenic fever or infection	Delay rituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. If delay is > 4 weeks, discontinue rituximab.	Hold acalabrutinib until recovery of Grade ≤ 3 or baseline. Follow dose modification actions in TABLE 7.2.1.
Thrombocytopenia		
Grade 3 thrombocytopenia	Maintain current dose	Maintain current dose
Grade 4 thrombocytopenia	Delay rituximab until Grade ≤ 3; thereafter resume at full dose. If delay is > 4 weeks, discontinue rituximab.	Hold acalabrutinib until recovery of Grade ≤ 3 or baseline. Follow dose modification actions in TABLE 7.2.1.
Diarrhea (non-infectious)		
Grade 1: increase of <4 stools per day over baseline	n/a	Provide antidiarrheal (eg, loperamide) and maintain current acalabrutinib dose level and schedule.
Grade 2: increase of 4-6 stools per day over baseline	n/a	Provide antidiarrheal (eg, loperamide). Withhold acalabrutinib until Grade ≤ 1. Resume acalabrutinib at current dose level. If rechallenge results in recurrence, may resume at initial or lower dose level at investigator discretion (if applicable). Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).
Grade 3: increase of >7 stools per day over baseline	n/a	Provide antidiarrheal (eg, loperamide). Withhold acalabrutinib until Grade ≤ 1. Resume at lower dose level (if applicable). Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).
Grade 4: life-threatening	n/a	Provide antidiarrheal (eg, loperamide). Withhold acalabrutinib until Grade ≤ 1. May resume at lower dose level (if applicable) or discontinue acalabrutinib at investigator discretion. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).
Immune related pneumonitis		
Grade 1	Withhold rituximab until resolved. Resume at full dose or if delay >4 weeks, discontinue rituximab	Maintain current dose. Consider pneumocystis prophylaxis
Grade ≥2	Discontinue rituximab, consider systemic corticosteroids and pneumocystis treatment.	Discontinue acalabrutinib, consider systemic corticosteroids and pneumocystis treatment.
Rash or injection site reaction		
Grade 1	Maintain current dose	Maintain current dose
Grade 2	Withhold rituximab until Grade ≤ 1. Resume at full dose or if delay >4 weeks, discontinue rituximab.	Maintain current dose

	Rituximab	Acalabrutinib
Grade 3 or 4	Withhold rituximab until Grade ≤ 1. Resume at full dose or if delay >4 weeks, discontinue rituximab.	Withhold acalabrutinib until Grade ≤ 1, consider systemic corticosteroids. Follow dose modification actions in TABLE 7.2.1.
All Other Non-Hematological Adverse Events		
Grade 3	Withhold rituximab until Grade ≤ 1. Resume at full dose or if delay >4 weeks, discontinue rituximab.	Hold acalabrutinib until recovery of Grade ≤ 1 or baseline. Follow dose modification actions in TABLE 7.2.1.
Grade 4	Discontinue rituximab.	Hold acalabrutinib until recovery of Grade ≤ 1 or baseline. Follow dose modification actions in TABLE 7.2.1.

7.2.1 DISCONTINUATION CRITERIA

Regardless of the inciting agent, the following warrant treatment discontinuation:

- Treatment related adverse reactions that are life-threatening.
- Treatment related diarrhea or colitis, grade 4; also administer high-dose systemic corticosteroids.
- Infusion-related reaction, grade 4.
- Treatment related immune-related Pneumonitis, Grade 2 or higher; also administer high-dose systemic corticosteroids.

7.2.2 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that patient has:

- No intolerable toxicities related to study drug.
    - Treatment may be delayed to recover from toxicity.
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

7.3 CONCOMITANT MEDICATIONS

Concomitant use of acalabrutinib with strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole) is not allowed.

Avoid concomitant use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) with acalabrutinib if feasible. If a moderate CYP3A inhibitor must be used, reduce the acalabrutinib dose to 100 mg once daily.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) if feasible. If a strong CYP3A inducer must be used, increase the acalabrutinib dose to 200 mg twice daily.

7.4 ORDERING RITUXIMAB AND ACALABRUTINIB

Acalabrutinib will be supplied at no charge by Acerta/Astra Zeneca.
Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms. If any abnormality on the bottles is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee**.**
Rituximab will be ordered by the trial site via commercial channels.

8 MEASUREMENT OF EFFECT

During the study period, all patients will be evaluated for response by history, examination, CT and/or MRI and bone marrow assessment. After cycle 24, all efficacy assessments should be per investigator discretion or standard of care. All efficacy assessments have a +/- 7 day window. The determination of response and progression will be based on the IWCLL criteria for CLL and SLL patients. [37]

CT scan is the preferred method of tumor assessment but MRI may be used at the investigator's discretion. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the study.

Patients will remain on study treatment until achievement of MRD negative CR at 12 or 24 months, the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for disease progression.

8.1 METHOD OF ASSESSMENT

In addition to clinical examination, imaging-based evaluation will be used in this study in all patients enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in patients for whom this may be a preferred alternative to CT scanning. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in patients for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, scanner, patient position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a patient is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the patient cannot tolerate the contrast.

8.2 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

8.2.1 TARGET LESIONS

For patients with measurable adenopathy/disease at baseline, up to 6 lymph nodes should be selected as target lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the target lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as target lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Target lesions will be measured and recorded at baseline and as per the study assessment schedule. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each target lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each target

lesion and the sum of the products (SPD) (in cm^2) for all target lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a nodal target lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be considered. Because nodal target lesions that have one or both diameters >0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2 (i.e., if all lymph nodes measure < 1.0 cm^2).

A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD will be considered progressive disease.

In cases in which a large lymph node mass has split into multiple components, all subcomponents regardless of size will be used in calculating the SPD. Progression of the lesion will be based on the SPD of sub-components. Lesion sub-components will have the true PPDs calculated. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) used in calculating the SPD.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

8.2.2 SPLEEN AND LIVER

Both the spleen and liver will be assessed by CT/MRI scan and by physical examination on deep inspiration at baseline and as per the study assessment schedule. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL during treatment. All spleen and liver LVD measurements should be recorded in centimeters.

8.2.3 NON-TARGET LESIONS

Any other measurable and abnormal nodal lesions not selected for quantitation as target lesions may be considered non-target lesions. In addition, non-measurable evidence of CLL such as nodal lesions with both diameters <1.0 cm, extra-nodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-target disease.
The presence or absence of non-target disease should be recorded at baseline and at the stipulated intervals during treatment. If present at baseline, up to 6 non-target lesions should be recorded. The non-target disease at baseline will be used as a general reference to further characterize regression or

progression of CLL during assessments of the objective tumor response during treatment. Measurements are not required and these lesions should be followed as “present” or “absent”.

8.3 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized by the IRC as CR, CRi, PR, PR-L, SD, or PD. In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

8.4 COMPLETE RESPONSE

To satisfy criteria for a CR, all of the following criteria must be met:

- No evidence of new disease
- ALC in peripheral blood of $<4 \times 10^9$/L
- Regression of all target nodal masses to normal size ≤1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-target disease and disappearance of all detectable non-nodal, non-target disease
- Morphologically negative bone marrow defined as <30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample (the presence of benign reactive nodules is still compatible with a CR)
- Absence of constitutional symptoms
- Peripheral blood counts meeting all of the following criteria:
    - ANC $>1.5 \times 10^9$/L without need for exogenous growth factors (e.g., G-CSF)
    - Platelet count $\geq 100 \times 10^9$/L without need for exogenous growth factors
    - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

Patients who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to progressive CLL) will be considered as a CR with incomplete marrow recovery (CRi). These patients remain eligible for MRD assessments and will discontinue therapy if negative for residual disease (similar to management for patient achieving a CR)

8.5 PARTIAL RESPONSE

To satisfy criteria for a PR, all of the following criteria must be met:

- No evidence of new disease
- Change in disease status meeting ≥2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: 1) only lymphadenopathy is present at baseline; 2) only lymphadenopathy

and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:
    - In a patient with baseline lymphocytosis (ALC ≥4 x 10^9/L), a decrease in peripheral blood ALC by ≥50% from baseline or a decrease to <4 x 10^9/L
    - A decrease by ≥50% from the baseline in the SPD of the target nodal lesions
    - In a patient with enlargement of the liver or spleen at baseline, a decrease by ≥50% from baseline
    - A decrease by ≥50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- No target, splenic, liver, or non-target disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting 1 of the following criteria:
    - ANC >1.5 x 10^9/L or >50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)
    - Platelet count >100 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors
    - Hemoglobin >110 g/L (11.0 g/dL) or ≥50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

PR criteria met but without recovery of lymphocytosis = PR-L

8.6 STABLE DISEASE

To satisfy criteria for SD, the following criteria must be met:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD

8.7 DEFINITIVE DISEASE PROGRESSION

The occurrence of any of the following events indicates definitive PD:

- Evidence of any new disease:
    - A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD
    - New or recurrent splenomegaly, with a minimum LVD of 14 cm
    - New or recurrent hepatomegaly, with a minimum LVD of 20 cm
    - Unequivocal reappearance of an extra-nodal lesion that had resolved
    - A new unequivocal extra-nodal lesion of any size
    - *New non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL).

*Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of target lesions, spleen or liver, or non-target disease:
    - Increase from the nadir by ≥50% from the nadir in the SPD of target lesions
    - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm

- Splenic progression, defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
- Hepatic progression, defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)
- Unequivocal increase in the size of non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)
- Transformation to a more aggressive histology (e.g., Richter's syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression if the patient has no earlier objective documentation of CLL progression).

- Decrease in platelet count or hemoglobin that is attributable to CLL.
  - The current platelet count is $<100 \times 10^9$/L OR there has been a decrease by >50% from the highest on-study platelet count.
  - The current hemoglobin is <100 g/L (10.0 g/dL) OR there has been a decrease by >20 g/L (2 g/dL) from the highest on-study hemoglobin.

If there is uncertainty regarding whether there is true progression, the patient should continue study treatment and remain under close observation pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression; in such patients, both CLL- related and non-CLL-related causes for the constitutional symptoms should be considered.

Worsening of disease during temporary interruption of study treatment (e.g., for inter current illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the patient has experienced persistent definitive CLL progression, then the date of progression should be the time point at which progression was first objectively documented.

8.8 NON-EVALUABLE

In a patient who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images
- Images of the liver and spleen are missing at that time point (with the exception that absence of splenic images will not result in an NE designation in a patient known to have undergone splenectomy).

Note: A time-point will be considered to have a response of NE if any target lesion is missing. PD may be assigned at any time point regardless of the extent of missing target or non-target lesions. Missing non-target lesions will not impact the ability to assess for response or disease progression.

8.9 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of acalabrutinib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) may occur. The onset of isolated lymphocytosis usually occurs during the first few weeks of acalabrutinib therapy. Patients with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression

(i.e., disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy. Unless related to treatment interruption, new or increasing lymphocytosis after 6 months of starting treatment may be considered disease progression and should be confirmed as per the response criteria.

9 STATISTICAL CONSIDERATIONS

9.1 DESIGN

This is a single-arm, single-center prospective study. The complete response rate will be estimated from forty enrolled subjects. An associated 95% two-sided confidence interval will be calculated using exact binomial methods. We anticipate a CR rate of 20%, which would result in a 95% two-sided confidence interval with a width of 26.6% (from 9.1% to 35.6%) for a sample size of 40 subjects. The maximum possible width of a 95% confidence interval using 40 subjects would be 32.4%.

9.2 PATIENT DISPOSITION

The disposition of patients includes the number and percentage of patients for the following categories: patients enrolled, patients treated (safety population), patients in the intent to treat population, and patients discontinued from the study. The reasons for study discontinuation will also be summarized in this table. Only one primary reason for study discontinuation will be reported in the summary. However, all reasons will be presented in the listing. A listing will present data concerning patient disposition.

9.3 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures.

9.4 EXTENT OF EXPOSURE

The dose (mg) of study drugs administered, the total number of doses of study drugs, and the duration of treatment (number of study cycles) will be summarized with descriptive statistics. The number and percentage of patients whose dose is modified at any time will be summarized by each type of modification by cycle and overall. The proportion of patients completing each cycle of treatment will be summarized.

9.5 EFFICACY ANALYSES

All patients included in the study should have a baseline tumor assessment within 60 days prior to Cycle 1/Day 1. Each patient will be assigned one of the following categories: 1) complete response or complete response with incomplete marrow recovery, 2) partial response or partial response with lymphocytosis, 3) stable disease, 4) progressive disease, 5) unknown (not assessable, insufficient data).

9.6 STATISTICAL ANALYSES

The treated population is defined as all enrolled subjects who received at least 1 dose of study drug. Efficacy and safety analysis will be based on this population.

The CR rate is defined as the proportion of patients with a best overall response of complete response with or without marrow recovery. Patients who do not have a tumor response assessment for any

reason will be considered non-responders and will be included in the denominator when calculating the CR rate.

The ORR is defined as the proportion of patients with a best overall response of partial response (PR) or complete response (CR). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the ORR.

Progression-free survival is defined as the time from treatment initiation until the date of first documentation of definitive disease progression or date of death from any cause, whichever occurs first. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress or are lost to follow-up will be censored at the day of their last tumor response assessment. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last tumor response assessment prior to initiation of new therapy.

The safety population includes all subjects who received at least 1 dose of study treatment. Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented by study drug actually received.

10 SAFETY REPORTING

10.1 DEFINITION OF ADVERSE EVENTS

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.
An adverse event includes the following:

- Signs or symptoms that were not present or observed in the patient prior to the AE reporting period and that emerge during the protocol-specified AE reporting period (i.e. TEAEs)
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as biopsy)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- 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 or diagnostic test results constitute AEs only if they induce clinical signs or symptoms, require treatment or further diagnostic tests, or lead to discontinuation or delay in treatment, or if it represents a clinically significant change from baseline as determined by the investigator
- Progressive disease will not be considered an adverse event.

Adverse events and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the severity of adverse events will be graded using the scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Hematologic toxicity will be graded by CLL criteria [37] and can be found in Appendix 2. For adverse events not covered by the NCI-CTCAE Version 5.0 grading system, the following definitions will be used:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

10.2 SERIOUS ADVERSE EVENTS (SAE)

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e. the AE actually causes or leads to death
- It is life threatening (i.e. the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- It requires or prolongs inpatient hospitalization, but not to include routine hospitalizations for neutropenic fevers that do not result in sepsis syndrome and/or ICU transfer
- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial

disruption of the patient's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.3 EXPECTEDNESS OF ADVERSE EVENTS

Expected adverse events are those that have been previously identified as resulting from administration of the agents. For the purposes of this study, an adverse event is considered expected when it appears in the investigational brochure, the package insert or is included in the informed consent form as a potential risk. An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the investigational brochure, the package insert, in published medical literature, in the protocol, or is not included in the informed consent form as a potential risk.

10.4 ATTRIBUTION OF ADVERSE EVENTS

The investigator must attempt to determine if there exists reasonable possibility that an AE or SAE is related to the use of the investigational treatment. Attribution of adverse events should be described as treatment related or not related. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines when determining if an AE or SAE is treatment-related:

- Treatment-Related: There is a reasonable causal relationship between the investigational treatment and the adverse event. There is a plausible temporal relationship between the onset of the AE and administration of the investigational treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational treatment; and/or the AE abates or resolves upon discontinuation of the investigational treatment or dose reduction and, if applicable, reappears upon re-challenge.
- Not Treatment-Related: There is no reasonable causal relationship between the investigational treatment administered and the adverse event. Evidence exists that the AE has an etiology other than the investigational treatment (e.g. pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational treatment.

10.5 RECORDING/REPORTING ADVERSE EVENTS

AEs experienced by participants will be collected and reported from initiation of investigational treatment (to also include events preceding initiation of study treatment if an AE is at least possibly related to withholding medication prohibited by protocol, or a study procedure such as a biopsy), throughout the study, and within 30 days after the last dose of study medication. All SAEs regardless of grade, severe AEs (i.e. Grade ≥ 3), and events of death will be recorded, regardless of event attribution. Baseline disease-related signs and symptoms which are initially recorded as medical history, will subsequently be recorded as adverse events during the trial if they worsen in severity or increase in frequency. Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or serious adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study. Follow-up for SAEs should continue until resolution, stabilization, the subject has withdrawn consent or has been lost to follow-up.

- Further AE reporting procedures are as follows:
    - Serious adverse events must be reported to the Study Chair from the first dose of protocol-indicated treatment up to and including 30 days after administration of the last dose of investigational agent.
    - All AEs, regardless of grade, and events of death of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment.
    - Asymptomatic abnormal laboratory values of Grade 1 or Grade 2 that do not trigger dose interruption or modification of protocol-indicated treatment will be deemed not clinically significant and are not required to be individually noted or recorded within the study data.
    - Laboratory and vital sign abnormalities are to be recorded as AEs only if they are medically relevant as judged by the investigator (e.g. symptomatic, requiring corrective treatment, leading to discontinuation of protocol-indicated treatment, and/or fulfilling a seriousness criterion).
    - Since this is an investigator-initiated study, the principal investigator, also referred to as the study chair, is responsible for reporting SAEs to any regulatory agency and to the study chair's data safety monitoring committee (DSMC) and IRB.
    - Fatal and life-threatening SAEs must be reported within 24 hours of the study chair's observation or awareness of the event to the DSMC chairperson or designee
    - All other serious (non-fatal/non-life threatening) events must be reported within 4 calendar days of the study chair's observation or awareness of the event to the DSMC chairperson or designee.
    - The study team should report all SAEs and special situations for patients receiving acalabrutinib to Acerta-Pharma per contractual guidelines.
    - <u>The SAE report must include at minimum</u>:
        - **Event term(s)**
        - **Seriousness criteria**
        - **Intensity of the event(s):** Investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined using the NCI CTCAE version 5.0 as a guideline, whenever possible.
        - **Causality of the event(s)**: Investigator's determination of the relationship of the event(s) to study drug administration.
- **Deaths**

  All deaths that occur during the protocol-specified AE reporting period, regardless of attribution,

will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF.

- **Hospitalizations for Medical or Surgical Procedures**
  Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
    - Hospitalizations for the following reasons do not require reporting:
      - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions that have not worsened
      - Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
      - Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

- **Procedures for Reporting Drug Exposure During Pregnancy**
  Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or until 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab. Pregnancy should be confirmed with a serum pregnancy test. The patient should permanently discontinue protocol-indicated treatment. If a woman suspects that she is pregnant while participating in this study, she must inform the investigator immediately and study treatment should be withheld until pregnancy is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient should permanently discontinue protocol-indicated treatment.
  The investigator or medical designee should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. All pregnancies of patients taking acalabrutinib or partners of patients taking acalabrutinib as well as related outcomes should be reported to Acerta-Pharma per contractual guidelines. Any SAEs associated with the pregnancy (e.g. an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported using the SAE form. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage).

- **Data Safety Monitoring Committee and Institutional Review Board**
  Study Investigators will conduct continuous review of data and patient safety. The Investigator will submit quarterly progress reports of these data to the Data Safety Monitoring Committee for review. The review will include for each treatment arm/dose level: the number of patients enrolled, withdrawals, significant toxicities, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with a Progress Report to the Data Safety Monitoring Committee (DSMC) for review. Actual review dates will be assigned when the 1st patient is accrued.

- Any serious adverse event that is serious, related AND unexpected must be reported within 5 calendar days to both the DSMC Safety Coordinator and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.
- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review at the quarterly meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The Data Safety Monitoring Committee provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk and complexity of the trial, and is assigned by the Protocol Review Committee at the time of their initial review and approval. The Data and Safety Monitoring Committee will monitor all adverse event rates utilizing a cumulative spreadsheet listing of all events submitted along with progress reports by the PI. All serious adverse events that have occurred in the prior 3 months will be reviewed at the regular quarterly meeting of the DSMC in order to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to current or future subjects.

- **Food and Drug Administration (FDA)**
  In this trial, unexpected adverse events believed to be related to investigational therapy will be reported to the FDA via MedWatch (using the online form currently available at https://www.accessdata.fda.gov/scripts/medwatch/), by telephone 1-800-FDA-1088, or by fax 1-800-FDA-0178 (using the form currently available at http://www.fda.gov/medwatch/report/hcp.htm).

- **Additional Reporting Requirements for IND**
  Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines: The Study chair is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed to be possibly, probably or definitely related to the investigational agents. An unexpected AE is one that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event.

11 CLINICAL DATA COLLECTION

11.1 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation. Acerta-Pharma / Astra Zeneca will be notified of any amendments to the protocol.

All amendments require review and approval of the Principal Investigator. The written amendment must be submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB.

The amendment will be submitted formally to the FDA or other regulatory authorities by the investigator as applicable, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

11.2 FINANCIAL DISCLOSURES AND ETHICAL CONSIDERATIONS

All investigators will be required to have a signed up-to-date curriculum vitae (CV), current within two years, a current copy of their medical license, and a completed FDA form 1572.

This study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

11.3 IRB AND REGULATORY APPROVAL

The study protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures, information about payments and compensation available to the patients and documentation evidencing the PI's qualifications must be submitted to the IRB for ethical review and approval prior to the study start and in accordance with institutional guidelines.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB study review. The PI must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB. Sites must follow institutional IRB guidelines for submission requirements.

If applicable, the PI will notify the IRB within 90 days of the end of the study, or if the study terminates early, the PI must notify the IRB within 15 days of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC).

11.4 INFORMED CONSENT

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements.
Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.
If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study must be obtained.

11.5 CONFIDENTIALITY

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization. In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period. In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept

on file by the Sponsor. Patients will be informed of their rights within the ICF.

11.6 STUDY DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate. Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, EKG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Site Study File/SSF or ISF) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The IRB shall maintain adequate documentation / records of IRB activities for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other study-related records for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

11.7 DATA COLLECTION AND SAFETY

The study CRF is the primary data collection instrument for the study. An electronic case report form will be utilized for the collection of all data and all data will be entered using the English language and should be kept current to enable the monitor to review the patients' status throughout the course of the study.
In order to maintain confidentiality, only study number, patient number, initials, and date of birth will identify the patient in the CRF. If the patient's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

11.8 PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential.

A clinical study report will be prepared upon completion of the study. The PI will disclose the study results, in the form of a clinical study report synopsis, to the applicable regulatory authorities within one year of the end of the study.

12 PLANNED CORRELATIVE ANALYSES

At URMC, study labs (peripheral blood) will be collected immediately before initiation of the first dose of rituximab (50 mg IV), at 1 hour and at completion of the infusion. Peripheral blood will also be sampled immediately before and 2 hours after the subcutaneous administration 50 mg of rituximab on days 3, 8, and 15 of cycle 1, on day 1 of cycles 2-6 of rituximab, at 4 weeks after the administration of the last dose of rituximab, and then every 3 months until 24 months after initiation of therapy. After collection, these samples will be processed and analyzed in the laboratory of Dr. Clive Zent at the University of Rochester.

Acalabrutinib and HFLD SQ rituximab correlative studies specimen requirements						
	Cycle 1 D1	**Cycle 1 D3 or 4 or 5**	**Cycle 1 D8**	**Cycle 1 D15**	**Cycle 2-6 D1**	**Cycle 9-24 D1**
5 ml yellow top tube (serum)	X*	X#	X#	X#	X	X***
10 ml purple top tube (CLL cells)	X*	X#	X#	X#	X##	
10 ml purple top tube (lymphocytes)	X**				X***	X***

* Before start of RTX infusion and then at 1 hour and at completion of infusion. All samples need to be labeled with the amount /dose of rituximab administered and the time of sample collection. Document any interruptions in infusion

** before start of rituximab infusion

*** before rituximab on D1 of cycles 3, 6, 9, 12, 16, 18, 22, 25 (+/- 4 weeks)

before and 2 hours after rituximab injection

before rituximab injection - need to collect 2 tubes (only applies to Cycle 2 D1)

Window for each sample is +/- 15 minutes.

At the post cycle 12 and/or cycle 24 response assessment, peripheral blood and bone marrow samples will be analyzed for minimal residual disease in the laboratory of Dr. Richard Burack at the University of Rochester. Minimal residual disease in peripheral blood and bone marrow will be evaluated by 6-color flow cytometry in attempt to quantify each patient's depth of remission.

Minimal residual disease processing/transport

Peripheral blood:

1. Whole blood will be collected in 2 BD CPT tubes [e.g. BD Vacutainer CPT Mononuclear Cell Preparation Tube - Sodium Heparin (16x125mm/8mL)]
2. Centrifuge at 1800xg for 30 minutes in a swing bucket centrifuge (not a fixed angle) within 24 hours of collection
3. If shipping, place in absorbent sleeve (e.g. Absorb Aqui-pak), then in insulated sealable pouch with ambient cold pack (e.g. Koolit gel pack)
4. Send in rigid package, compliant for shipping biological class B materials. Label package as "Acalabrutinib rituximab Study"

Bone marrow:

1. Bone marrow will be collected in Sodium Heparin (green top). An aliquot of an original specimen is acceptable.
2. If shipping, place in absorbent sleeve (e.g. Absorb Aqui-pak), then in insulated sealable pouch with ambient cold pack (e.g. Koolit gel pack)
3. Send in rigid package, compliant for shipping biological class B materials. Label package as “Acalabrutinib rituximab Study”

Ship to:

Phil Rock, Tissue Bank
University of Rochester Medical Center
601 Elmwood Ave. Hematopathology – Room#2.3655A
Rochester NY 14642
Phone: 585-275-3713
Fax: 585-276-2390
Email: Philip_rock@urmc.rochester.edu

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Appendix 1. Known Strong in Vivo Inhibitors or Inducers of CYP3A

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

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
d. 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 13 November 2018:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 2. Grading scale for hematologic toxicity in CLL studies

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

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is <20 x109/L (20 000/uL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 109/L [20 000/uL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions.

§If the absolute neutrophil count (ANC) reaches < 1 X 109/L (1000/_L), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 X 109/L (1000/uL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

Appendix 3. Highly effective methods of contraception

Intrauterine Device Methods	Hormonal Methods
Copper T	Any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents) such as:
Levonorgestrel-releasing intrauterine system	Medroxyprogesterone injections Etonogestrel implants Hormone shot or injection Normal and low dose combined oral pills Norrelgestomin EE transdermal system