CLINICAL RESEARCH PROJECT

Protocol #: 15-H-0016
Drug Name: ACP-196 (Acalabrutinib)
IND number: 118717
IND Sponsor: Acerta Pharma, BV

Title: A Phase II Study Using ACP-196 (Acalabrutinib) in Patients with Relapsed/Refractory and Treatment-naïve Deletion 17p CLL/SLL: Pharmacodynamic Assessment of BTK Inhibition and Antitumor Response.

Short Title: Acalabrutinib phase II study

Keywords: Acalabrutinib, BTK Inhibitor, Biologic Response Modifier Therapy, CLL, SLL

Principal Investigator:
PPD

Company Providing Investigational Drug: Acerta Pharma, BV

Subjects of Study:

Number	Sex	Age-range
48 evaluable subjects, max. 60 screened	M/F	> 18

Ionizing Radiation for Research:	Yes
Off-Site Project:	No
Multicenter trial:	No
DSMB Involvement:	Yes

PROTOCOL APPROVAL

Version M

I have carefully read Protocol 15-H-0016 entitled "A phase II study using ACP-196 (acalabrutinib) in patients with relapsed/refractory and treatment-naïve deletion 17p CLL/SLL: pharmacodynamic assessment of BTK inhibition and antitumor response". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Acerta Pharma, BV, and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) must approve any changes to the protocol in writing before implementation.

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

Principal Investigator's Signature Date

Print Name

Confidentiality Statement

This document contains proprietary and confidential information of Acerta Pharma, BV that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board/independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma, BV.

PRECIS

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are mature B-cell malignancies. Patients with relapsed disease and 17p deletion have a particularly aggressive disease course. Standard chemoimmunotherapy regimens for patients with relapsed/refractory disease (patients who have previously had treatment and need treatment again or patients who did not have a sufficient response to therapy) have resulted in few durable remissions.

B-cell receptor (BCR) activation is a key pathway engaged in the pathogenesis of CLL as well as in the interaction of CLL cells with the tumor microenvironment that is required for survival of CLL cells. The more aggressive forms of CLL, such as patients with relapsed/refractory disease, are characterized by stronger BCR activation. Disruption of tumor microenvironment interactions and inhibition of BCR signaling are promising therapeutic strategies in CLL. Bruton tyrosine kinase (BTK) is a key enzyme in BCR signaling. Ibrutinib is the first BTK inhibitor that has reached the clinic and is approved as therapy for relapsed/refractory CLL. The advent of kinase inhibitors such as ibrutinib has demonstrated significantly improved responses as second line therapies as well as improved responses in patients with 17p deletion compared to responses from standard chemoimmunotherapy regimens with long (more than 2 years) durable remissions in the majority of patients.

Acalabrutinib (ACP-196) is an orally available, new molecule that irreversibly inhibits BTK and shows encouraging activity and acceptable safety in nonclinical and clinical studies. Acalabrutinib has shown efficacy in 3 separate models of lymphoid malignancies. Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, CLL, and SLL. We believe that acalabrutinib, a more selective BTK inhibitor than ibrutinib, is designed to be more potent, more specific, and could overcome limitations currently seen with ibrutinib.

This study will investigate the safety and efficacy of acalabrutinib for patients with CLL/SLL who have relapsed/refractory disease or treatment-naïve deletion 17p. The primary endpoint is the response to acalabrutinib. Biological sampling from lymph nodes, bone marrow, and peripheral blood early during treatment will be used to investigate BTK inhibition in the bone marrow and lymph node compartments, the main sites for CLL progression in addition to the circulating tumor cells.

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1.1 Primary Objective

- To determine the response to acalabrutinib in subjects with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

1.2 Secondary Objectives

- Safety and tolerability of acalabrutinib
- Duration of response to acalabrutinib
    - Time to progression on acalabrutinib
    - Progression-free survival (PFS) and overall survival (OS) on acalabrutinib
- Explore the biologic effects of once-daily dosing as compared to twice-daily dosing of acalabrutinib on CLL tumor cells
- To measure BTK inhibition and on-target effects of single-agent acalabrutinib in CLL cells in lymph node, bone marrow, and blood of subjects with CLL or SLL

1.3 Exploratory Objective

- CCI

2.0 BACKGROUND AND SCIENTIFIC JUSTIFICATION

Chronic Lymphocytic Leukemia and/or Small Lymphocytic Lymphoma

The World Health Organization classification of hematopoietic neoplasias describes CLL as a leukemic, lymphocytic lymphoma, being only distinguishable from SLL by its leukemic appearance.[1] In the National Cancer Institute (NCI)-Working Group (WG) guidelines, the diagnosis of CLL requires the presence of at least 5 x 10^9 clonal B lymphocytes/L (5000/µL) in the peripheral blood. The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Clonal B lymphocytes in the peripheral blood should not exceed 5 x 10^9/L and the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy when possible.[2]

Chronic lymphocytic leukemia/SLL cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin (SIg), CD20, and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukemia cells is restricted to expression of either kappa or lambda Ig light chains.[2]

For the purposes of this study, the term “CLL” will encompass both CLL and SLL.

2.1 Pathophysiology

Chronic lymphocytic leukemia is characterized by a progressive accumulation of functionally incompetent lymphocytes. It is believed that antigenic stimulation, along with interactions of accessory cells, cytokines, and tumor microenvironment are promoting factors that stimulate proliferation of CLL cells and allows them to avoid apoptosis. These effects may differ in distinct CLL/SLL subgroups and thereby lead to the heterogeneity seen in clinical outcomes among individual cases.

Chronic lymphocytic leukemia cells cultured in vitro undergo apoptosis, but they can be rescued by coculturing with stromal cells or in presence of soluble factors.[3] The tumor-host interactions in vivo were recently better defined using gene expression profiling from tumor cells isolated concurrently from peripheral blood, bone marrow and lymph node.[4] This study identified the lymph node as a key site and B-cell receptor (BCR) signaling as a central pathway in CLL pathogenesis. Chronic lymphocytic leukemia

cells in the lymph node showed up-regulation of gene signatures, indicating BCR and nuclear factor-κB activation. Consistent with antigen-dependent BCR signaling and canonical nuclear factor-κB activation, phosphorylation of the spleen tyrosine kinase (Syk) and IκBα, was detected in lymph node derived cells. Expression of BCR target genes was stronger in clinically more aggressive CLL, indicating more effective BCR signaling in this subtype in vivo. Tumor proliferation, quantified by the expression of the E2F and c-MYC target genes and verified with Ki67 staining by flow cytometry, was highest in the lymph node and was correlated with clinical disease progression.[4] The BCR is a multimeric complex formed by the assembly of SIg homodimer and the noncovalently bound heterodimer Igα/Igβ (CD79a/CD79b). They operate through immunoreceptor tyrosine-based activation motifs (ITAM) by linking the antigen-binding Ig chains to intracellular tyrosine kinases of the Src-family. BCR signaling induces receptor oligomerization, Ig α and β phosphorylation and the recruitment and activation of the Syk.[5] The downstream signaling cascade depends on BTK and phosphoinositide 3-kinase (PI3K).[6] These data identify the disruption of tumor microenvironment interactions and the inhibition of BCR signaling as promising therapeutic strategies in CLL.

2.2 Epidemiology and Clinical Course of Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most common leukemia of adults in Western countries with an annual incidence of 2 to 4.5 per 100,000 in the general population. According to the NCI Surveillance Epidemiology and End Results (SEER) data, it is estimated that 14,990 men and women (8,870 men and 6,120 women) will be diagnosed with CLL. It affects males twice as frequently as females and is a disease of older individuals (median age 73.0 years for whites).[7] The highest rates of incidence are seen in Caucasians followed by African Americans. Lower rates of incidence are seen in Asian and Hispanic populations.

The complications of CLL usually arise from progressive disease. These complications are, but not limited to infection, hematologic abnormalities, immune phenomena, secondary cancers, and disease transformation. It has been estimated that up to 70% of patients with CLL will develop infections, and infections account for about 55% of deaths in patients with CLL. Hematologic abnormalities include autoimmune hemolytic anemia (AIHA) in approximately 37% of patients, pure red cell aplasia in 6% of patients, and immune mediated thrombocytopenia in 2 to 4% of patients.[8] Secondary cancers are noted in about 11% of cases such as acute myeloid leukemia and other solid malignancies. Finally, disease transformation into other forms or more aggressive lymphomas such as diffuse large B-cell lymphoma and Hodgkin's lymphoma occur in about 5% of cases.[9]

2.3 Diagnostic and Prognostic Categories of CLL/SLL

The diagnosis of CLL is based upon a complete blood count with differential, flow cytometry of the peripheral blood (to determine the immunophenotype of circulating lymphocytes), and examination of the peripheral smear. According to the 2008 update of the National Cancer Institute-sponsored Working Group (NCIWG) diagnosis and treatment of CLL[2], the following 2 criteria must be met:

- Absolute B lymphocyte count in the peripheral blood ≥5000/μL (5 x 10^9/L), with a preponderant population of morphologically mature-appearing small lymphocytes
- Demonstration of clonality of the circulating B lymphocytes by flow cytometry of the peripheral blood. A majority of the population should express the following pattern of monoclonal B-cell markers: extremely low levels of surface membrane immunoglobulins (SmIg) and either kappa or lambda (but not both) light chains; expression of B-cell associated antigens (CD19, CD20, and CD23); and expression of the T-cell associated antigen CD5.

The diagnostic criteria for SLL require the presence of lymphadenopathy and/or splenomegaly. B lymphocytes in the peripheral blood should not exceed 5 x 10^9/L and the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy when possible.

Two prognostic staging systems exist, known as the Rai and Binet staging systems. The Rai staging system (Table 1) is based upon the gradual and progressive increase in the body burden of leukemic lymphocytes, starting in the blood and bone marrow, progressively involving into lymph nodes followed by spleen and liver involvement. This will lead to eventual compromise of bone marrow function.

Table 1: Rai Staging System: [10]

Stage	Risk	Manifestations	Median survival (months)
0	Low	Blood and marrow lymphocytosis	120
I	Intermediate	Lymphocytosis and adenopathy	108
II	Intermediate	Lymphocytosis + organomegaly	94
III	High	Lymphocytosis + anemia (hemoglobin <11g/dL)	60
IV	High	Lymphocytosis + thrombocytopenia (platelets <100K/µL)	60

This system is of great value in stratifying patients with survival curves corresponding to the Rai low-risk, intermediate-risk, and high-risk groups, respectively. The Rai staging system was designed to provide prognostic information for patient care. However, some patients classified as having early-stage disease rapidly progress. For this reason, other prognostic markers such as immunoglobulin variable heavy chain (IGHV) genes, Zeta chain associated protein 70 (ZAP 70), and cluster of differentiation 38 (CD38) have been identified to further stratify the aggressive nature of a particular patient's disease status. IGHV genes are defined as mutated if there is a greater than 2 percent difference in nucleotide sequence compared with germline DNA.[11] The unmutated IGHV genes are associated with shorter OS and a higher risk of relapse following treatment, including hematopoietic cell transplantation.[12] ZAP 70 is a tyrosine kinase normally expressed by natural killer (NK) and T cells and is required for normal T-cell receptor signaling. ZAP 70 is not normally expressed in B lymphocytes but has been found in a subset of patients with CLL and appears to correlate with survival. Abnormal expression of ZAP 70 in CLL B cells is strongly associated with the presence of an unmutated IGHV, another poor prognostic factor.[13]

Chromosomal abnormalities also play an important role in prognostication. The first reports describing chromosomal aberrations in CLL cells date back to the late 1970s. The development of fluorescence in situ hybridization (FISH) in the late 1980s and early 1990s allowed for a more sensitive detection of chromosomal abnormalities. Dohner et al looked at genomic aberrations in CLL and found that the most common isolated chromosomal abnormality associated with B-CLL/SLL is deletion of 13q14, which is present in up to 64% of cases studied by FISH. This deletion is believed to be a primary event in CLL, as it is present in a majority of the tumor cells and is frequently the sole abnormality.[14] The prognosis of patients with 13q14 abnormalities appears to be significantly better, and is similar to that of patients with a normal karyotype.[14] In contrast, trisomy 12 is associated with an atypical morphology and immunophenotype, a high proliferation rate, and advanced clinical stage, and is thought to confer a worse prognosis. Trisomy 12 may be a secondary abnormality since it is typically identified in a minority of the tumor cells.[14] Other abnormalities that have been associated with a poor prognosis include deletions at 11q22-2, and deletions of the p53 locus on chromosome 17p13.[14] The properties of these cytogenetic markers are summarized in Table 2.

Table 2: Cytogenetic Abnormalities in CLL[14]

Chromosome	Median overall survival (months)	Median time to first treatment (months)
Deletion 17p13	32	9
Deletion 11q22-23	79	13
Trisomy 12	114	49
Normal	111	33
Deletion 13q14	133	92

The 17p deletion as a predictor of poor prognosis among patients requiring therapy and is seen in approximately 7 to 10% of patients. In a prospective study, Giesler et al used chromosome banding to detect abnormalities of chromosome.[17] This was associated with poor survival, and it was the only cytogenetic finding with independent prognostic value.[15] Deletions of 11q have been described in 17 to 20% of patients. 11q deletions are associated with extensive adenopathy, progressive disease and shorter survival in patients under the age of 55.[14] Chromosome 11q contains the ataxia telangiectasia mutated (ATM) gene and patients who have loss or mutation of both copies of this gene have an even worse OS associated with impaired cellular response to irradiation and cytotoxic drug exposure in vitro.[16] However this abnormality may be overcome with the use of fludarabine, cyclophosphamide, and rituximab (FCR).[17] The prognostic effect of 12q trisomy has been controversial in that some studies have demonstrated advanced disease and higher proliferative activity while others have demonstrated similar survival times to that of a normal karyotype.[18] The 13q abnormalities appear to be associated with a favorable outcome. Two studies using FISH found del(13q14) in 45 to 55% of patients.[14] These deletions are often associated with inactivation of the Rb gene.[19] The region of minimal deletion is suspected to harbor a CLL-associated tumor suppressor gene. Lack of Rb gene expression occurs in both the early and late stages of CLL.[19]

Other markers such as lymphocyte doubling time (LDT), bone marrow histologic pattern, and β2-microglobulin (B2M) are also useful as an adjunct to IGHV, ZAP 70, CD38, and FISH. The LDT can provide an estimation regarding the rate of disease progression. An actual or projected LDT in untreated patients <12 months predicts a progressive course and a longer LDT predicts an indolent course.[20] The pattern of lymphocyte infiltration in the bone marrow can suggest a progressive versus an indolent course. A diffuse pattern predicts a progressive course and a nondiffuse (interstitial and nodular) pattern predicts a more indolent course.[21] Finally, the B2M levels correlate with disease stage and tumor burden in patients with CLL. B2M may be regulated, at least in part, by exogenous cytokines. The source of these elevated cytokines in CLL is unclear, although IL-6, which inhibits apoptosis in CLL cells, may be released from vascular endothelium.[22]

2.4 Indications for Treatment of CLL

Newly diagnosed patients with asymptomatic early-stage disease (Rai 0, Binet A) should be monitored without therapy unless they have evidence of disease progression.[23] Patients with intermediate (stages I and II) and high risk (stages III and IV) according to the modified Rai classification or at Binet stage B or C usually benefit from the initiation of treatment.

According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL), active disease should meet one of the following criteria.[2]

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia

- Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or LDT of less than 6 months. Lymphocyte doubling time can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30,000/µL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
  a. Unintentional weight loss of 10% or more within the previous 6 months
  b. Significant fatigue (i.e., Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2; inability to work or perform usual activities)
  c. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection
  d. Night sweats for more than 1 month without evidence of infection

2.5 Treatment Options for CLL/SLL

2.5.1 Watchful Waiting

Immediate treatment is recommended in patients with advanced stage disease, high tumor burden, and severe disease-related "B" symptoms. Otherwise, a period of observation is recommended. Asymptomatic early-stage disease should be monitored until evidence of disease progression.[2] During the observation period, patients are periodically monitored with blood counts and assessed for evidence of progressive disease through physical examination and assessment of symptoms.

2.5.2 First-Line Chemotherapy/Immunotherapy/Chemoimmunotherapy

Monotherapy

Monotherapy with alkylating agents has served as initial front-line therapy for CLL. Chlorambucil has been considered the gold standard for CLL for several decades. This drug remains an appropriate option for unfit, elderly patients.[23] In addition, another agent known as bendamustine was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of CLL in 2008. Knauf et al[24] studied bendamustine compared with chlorambucil in previously untreated CLL patients. Complete response (CR) or partial response (PR) was achieved in 68% of the bendamustine-treated patients and 48% of the chlorambucil-treated patients.

Aside from alkylating agents, 3 purine analogs have been used as monotherapy in CLL. These purine analogs are fludarabine, pentostatin, and cladribine. Fludarabine is the best studied compound of the 3 in CLL. Fludarabine monotherapy produces superior overall response rates (ORR) compared with other treatment regimens containing alkylating agent.[25] Cladribine and pentostatin monotherapy also produce better ORR than chlorambucil, but are not as commonly used.

Immunotherapy

The advent of monoclonal antibodies demonstrated the first forms of targeted therapy for CLL and other malignancies. Rituximab was the first monoclonal antibody used as monotherapy in a consolidation setting

demonstrates improved PFS.[26] Del Poeta et al reported the estimated the PFS to be 73% at 5 years with rituximab consolidation. The combination of anti-CD20 monoclonal antibodies with chemotherapy (chemoimmunotherapy) for treatment-naïve patients have proven to be very efficacious therapies for CLL and will be discussed below.

Chemoimmunotherapy

Alkylating agents and purine analogs have different mechanisms of action and partially nonoverlapping toxicity profiles and these 2 modalities, when combined, achieve synergistic effects. With the advent of monoclonal antibodies, the addition of combination chemotherapy demonstrated improved responses. The combination of FCR resulted in an ORR of 95%, with CR in 72%, nodular partial response (nPR) in 10%, PR due to cytopenia in 7%, and PR due to residual disease in 6%. Six-year OS and failure-free survival were 77% and 51%, respectively. Median time to progression was 80 months.[27] Bendamustine has also been combined with rituximab (BR) for patients with untreated CLL. The ORR was 88% with a CR rate of 23% and a PR in 65%. After a median observation time of 27.0 months, median event-free survival (EFS) was 34 months, and 91% of patients were alive.[28]

The GCLLSG CLL10 trial looked at the comparison of FCR versus BR in untreated patients.[29] The ORR was identical in both arms with 97.8% (p=1.0). The CR rate with FCR was 47.4% compared to 38.1% with BR. Progression-free survival was 85.0% at 2 years in the FCR arm and 78.2% in the BR arm. Event-free survival was 82.6% at 2 years in the FCR arm and 75.7% in the BR arm. There was no difference in OS rate for the FCR versus BR arm (94.2% vs 95.8% at 2 years). Several other combinations have been investigated, such as cladribine with rituximab, methylprednisolone plus rituximab followed by alemtuzumab, fludarabine plus alemtuzumab, or fludarabine and cyclophosphamide and alemtuzumab. None of these regimens resulted in higher efficacy than FCR.[30]

Recently, Geode et al[31] studied a third-generation monoclonal antibody known as obinutuzumab in combination with chlorambucil for previously untreated patients with CLL. As compared with chlorambucil monotherapy and rituximab monotherapy, increased response rates and prolonged PFS were seen in the combination. The median PFS for combination obinutuzumab plus chlorambucil versus chlorambucil alone was 27 months and 11 months, respectively. Higher rates of CR were seen in the combination obinutuzumab plus chlorambucil than in the rituximab and obinutuzumab combination. The combination of obinutuzumab and chlorambucil was given FDA approval in 2013.

2.5.3 Complications of Chemoimmunotherapy

Chemoimmunotherapy in CLL, most notably the FCR regimen can lead to impressive response rates and to a median PFS up to 6 years.[27] However, late complications after fludarabine and alkylator therapy are often observed. Twenty percent of patients have a persistent cytopenia (platelet count of $<50x10^9$/L and/or neutrophil count $<10^9$/L). Intergroup study E2997 suggest a 5% incidence of myeloid neoplasia 6 years after fludarabine and cyclophosphamide therapy[24]; the adjusted incidence for myeloid neoplasia rate at 8 years was 8%. Survival in patients who do not achieve a CR and have disease progression after FCR is estimated to be less than 2 years.[27] These findings indicate that while FCR leads to a high response rate, it also leads to short- and long-term toxicities and likely a more difficult to treat disease at relapse as well.[27]

In the GCLLSG CLL 10 Trial[29] the toxicities of FCR and BR were compared. FCR-treated patients had significantly more frequent severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 to 5) adverse events (AEs) during the whole observation period (90.8% vs 78.5%). Severe hematotoxicity was especially more frequent in the FCR arm (90.0% vs 66.9%). The higher rate of severe neutropenia

(81.7% vs 56.8%) resulted in a significantly higher rate of severe infections (39.0% vs 25.4%) in the FCR arm. Treatment-related mortality occurred in 3.9% in the FCR arm and 2.1% in the BR arm.[29]

In general, the addition of monoclonal antibodies adds another infusion-related toxicity, that is, an allergic component, to the drug or a portion of the drug as in the case of rituximab and ofatumumab. Infusion-related reactions and neutropenia were more common with obinutuzumab-chlorambucil than with rituximab-chlorambucil, but the risk of infection was not increased.[31]

2.5.4 Relapsed or Refractory CLL

There is no generally agreed upon standard therapy regimen for CLL patients when they relapse. Treatment options include the front-line regimen described above. Treatments for relapsed patients need to be individualized. Considerations for choosing a certain regimen can be activity towards bulky disease, adverse FISH cytogenetics like 17p, physical fitness of patient, or toxicity profile.[25]

This section will include the most commonly used regimens for relapsed disease.

Repeat chemoimmunotherapy treatment options are usually used as second-line treatment. A phase 2 trial of FCR in 284 subjects with previously treated CLL (19% fludarabine refractory and 35% rituximab refractory) reported OR and CR rates of 74% and 30%, respectively. The estimated median PFS and OS were 21 and 47 months, respectively. On subgroup analysis, subjects with fludarabine-refractory disease, chromosome 17 abnormalities, or >3 prior treatments had shorter survival rates.[32] In addition, a multicenter phase II trial of BR in 78 subjects with relapsed or refractory CLL reported an ORR of 59% with a median duration of response of 15 months. After a median follow-up of 2 years, the median EFS and OS were 14.7 and 34 months, respectively.[33] Other options include the addition of rituximab plus high-dose methylprednisolone. A small series of 14 subjects with fludarabine-refractory CLL, 21% of whom had previously received rituximab, reported an ORR of 93% with a median time to progression of 15 months.[34] Other lymphoma regimens such as EPOCH, CHOP, and CVP with the addition of an anti-CD20 monoclonal antibody have also been used as therapy for relapsed/refractory disease. These regimens do not demonstrate any significant improvement in disease reduction or durable remissions.

Ofatumumab is a second generation anti-CD20 antibody used for relapsed/refractory disease. A phase 2 trial evaluated ofatumumab in 138 subjects with CLL who were either refractory to both fludarabine and alemtuzumab, or refractory to fludarabine, with lymphadenopathy greater than 5 cm. Subjects had received a median of 5 prior therapies. Overall response rates were 58% and 47% in the 2 subject groups, respectively. There were no CRs. Median OS was 13.7 and 15.4 months, respectively. The activity of ofatumumab appeared to be independent of whether the subjects had previously received the anti-CD20 antibody rituximab.[35] The US FDA granted accelerated approval to ofatumumab for the treatment of patients with CLL refractory to both fludarabine and alemtuzumab in 2009.

Alemtuzumab is an anti-CD52 monoclonal antibody and has been tested in a phase 3 trial with relapsed or refractory CLL (15% percent of whom had received prior fludarabine). These subjects were randomly assigned to treatment with either single-agent fludarabine or combination therapy with fludarabine plus alemtuzumab. Combination therapy resulted in a significantly longer median PFS (24 months vs 17 months).[36] Alemtuzumab has activity in cells lacking TP53 function. A retrospective analysis of 105 subjects with relapsed or refractory CLL treated with alemtuzumab included 35 subjects with 17p deletion. When compared with the entire study population, subjects with 17p deletion demonstrated a similar ORR (49% vs 43%), median PFS (7.1 vs 7.0 months), but shorter median OS (19.1 vs

32.8 months).[37] Alemtuzumab is not a commonly used treatment for many patients as there is a higher incidence of viral infections associated with treatment.

These relapsed/refractory regimens are not curative and generally only provide remission for a short period of time. In most cases, these regimens are used to bridge patients to the next treatment or aid in tumor reduction prior to stem cell transplant.

2.5.5 Stem Cell Transplantation

Patients with CLL are generally elderly, and due to the relatively benign course of the disease in the majority of patients, few are considered for aggressive treatments such as hematopoietic cell transplantation. Stem cell transplant remains as the only curative option for CLL. Prognostication and transplant-related mortality continue to improve, and this may potentially lead to more CLL patients being referred for stem cell transplant. Currently, this option is reserved to those patients with a good performance status and with high-risk prognostic factors, namely deletion 17p, and those patients who are refractory to prior therapies. Unfortunately, only a small subset of patients meets those criteria.

2.5.6 BCR Signaling Inhibitors (Single Agent)

There are several drugs in development for lymphoid malignancies that interfere with the BCR signaling. There are many new drugs in clinical trials that target BCR receptors signaling pathway. These drugs are grouped based on the kinase inhibition along the BCR signaling pathway. Many kinase inhibitors are currently being studied and are in development. This discussion will focus on Syk inhibitors, BTK inhibitors, and PI3K inhibitors which have thus had the most study and progress.

Fostamatinib, an oral Syk inhibitor, was tested in a phase 1/2 study. Friedberg et al found that 6 out of 11 (55%) subjects with CLL had a PR.[38] Common toxicities in these heavily pretreated subjects were diarrhea, fatigue, cytopenias, nausea, and hypertension. GS-9973 (entospletinib) is another Syk compound was shown to have favorable response in a single-arm, open-label phase 2 study involving subjects with relapsed or refractory hematologic malignancies.[39] This study enrolled 56 subjects: 32 subjects with CLL/SLL and 24 subjects with non-Hodgkin's lymphoma. Efficacy analysis was available for 22/54 subjects, which included 13 CLL/SLL subjects. At the week 8 evaluation, all subjects experienced reduced tumor bulk: 4 subjects achieved a decrease of >50% in their measurable lymph node disease; 8 had a <50% decrease. Thirty of 34 (88%) subjects experienced an AE. Reversible Grade 3 or 4 transaminase elevations occurred in 4 subjects. There were 2 mortalities in this trial; one from disease progression and another from pneumonia, which occurred at day 7 of the trial drug. Trials using combination of GS-9973 and idelalisib are ongoing and the results are pending. Other Syk inhibitors include PRT062627 or P505-15 showing promising results in cells line and mouse models. A dose-finding study using P505-15 in healthy volunteers has been completed and includes single and multiple dosing regimens.[40]

The kinase inhibitor ibrutinib targets BTK and has been shown to have activity in CLL. The first BTK inhibitor in clinical trials was ibrutinib, which received accelerated approval from the FDA in February 2014 for treatment of relapsed/ refractory CLL. The approval was based on favorable clinical response on 48 relapsed CLL subjects. The phase 1b/2 multicenter ibrutinib trial reported by Byrd et al. involved 85 relapsed CLL subjects in which 51 received 420 mg, and 34 received 840 mg of the drug.[41] The ORR was the same in the group that received 420 mg and the group that received 840 mg (71%), and an additional 20% and 15% of subjects in the respective groups had a partial response with lymphocytosis (PRL). The estimated PFS rate was 75% and the OS rate was 83% at 26 months. The most common side effects observed in the clinical study included thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, fever, constipation, peripheral edema,

arthralgia, nausea, stomatitis, sinusitis, and dizziness. Other BTK inhibitors in clinical trials include AVL-292 (phase 1b). Although ibrutinib demonstrated higher response rates than AVL, it was later found out that AVL may have underperformed due to differences in PK; higher doses were required to achieve improved responses.[42]

Idelalisib (CAL-101, GS-1101, Zydelig®) is a selective oral inhibitor of the p110δ isoform of PI3Kδ. Firocari et al reported on a phase 1 study that enrolled 54 subjects with heavily pretreated relapsed/refractory CLL treated with continuous once- or twice-daily doses ranging from 50 mg to 350 mg per dose. After a median of 9 months of drug exposure, an ORR of 39% was observed. Nodal response (50% reduction from baseline) was observed in a larger proportion of subjects (81%) who did not meet criteria for objective response. Median PFS was 17 months; it increased to 29 months for those receiving 150 mg twice daily or greater. Dose-limiting toxicities (DLTs) were not observed, and potentially treatment-related AEs (fatigue, rash, diarrhea, respiratory tract infections, and reversible increases in hepatic transaminases) resulted in discontinuation of treatment in only 7% of subjects. Because PI3Kδ influences clonal expansion and differentiation of suppressor T cells, some of these events, particularly diarrhea and/or colitis, may represent on-target toxicities of idelalisib.[43]

Long-term data regarding responses and toxicity are still maturing for kinase inhibitors. Thus far, they have shown dramatic responses in the short term but have failed to show deep remissions. Patterns of resistance are now emerging. With ibrutinib specifically, recent data have emerged regarding mutations that may indicate potential mechanisms of resistance.[44]

2.5.7 BCR Signaling Inhibitors (Combinations)

Kinase inhibitors have demonstrated very promising response rates and investigators have started using kinase inhibitors in combinations with chemotherapy, monoclonal antibodies, and other kinase inhibitors. The majority of these studies remain early in accrual and maturity.

Ibrutinib in combination with BR was administered to relapsed/refractory CLL subjects. Barrientos et al reported on 30 subjects with relapsed/refractory CLL/SLL who received up to 6 cycles of BR with a continuous fixed ibrutinib dose of 420 mg/day. With a median treatment duration of 16 months, the ORR was 93% (28/30 subjects, including 5 CRs and 3 nPRs), and 1 additional subject achieved a PRL. The most frequently reported treatment-emergent AEs were diarrhea (70%), nausea (66.7%), fatigue (46.7%), neutropenia (40%), and upper respiratory tract infection (36.7%). The most frequently reported treatment-emergent AEs Grade 3 or higher in severity were neutropenia (40.0%), maculopapular rash and fatigue (10.0% each), and thrombocytopenia, febrile neutropenia, and cellulitis (6.7% each). The estimated 12-month PFS was 90%. Moreover, responses appeared independent of high-risk features.[45]

Ibrutinib in combination with rituximab enrolled 40 subjects. At a median follow-up of 14 months, 32 of 40 subjects continued therapy without disease progression. Burger et al looked at 39 subjects who were evaluable for response assessment per 2008 IWCLL guidelines; 34 subjects (87%) achieved PR, and 3 subjects (8%) CRs, accounting for an ORR of 95%. One CR was negative for minimal residual disease by flow cytometry; the ORR in the 20 subjects with del17p or TP53 mutation was 90% (16 PR, 2 CR). Among the 8 subjects that came off of the study, 3 subjects died from unrelated infectious complications (2 cases of sepsis, 1 case of pneumonia), and 1 died from unrelated respiratory and cardiovascular failure. Two subjects came off of the study because of possibly ibrutinib-related toxicity (1 subdural hematoma, 1 Grade 3 mucositis), 1 subject had progressive disease, and 1 proceeded to stem cell transplantation. Treatment generally was well tolerated, with infectious complications (6 cases of pneumonia and 3 cases of upper respiratory infections) being the most common complication.[46]

Byrd et al reported on ibrutinib in combination with ofatumumab for treatment of relapsed CLL/SLL. For the 27 enrolled CLL/SLL subjects the ORR, as measured by IWCLL criteria and PFS is 100%, with a median follow-up of 9.8 months; 89% of CLL/SLL/prolymphocytic leukemia (PLL) subjects remained on study and only 1 subject discontinued treatment by proceeding to stem cell transplant. The majority of AEs were Grade 1 or 2 in severity, and no Grade 3 or 4 infusion reactions, neutropenia, or thrombocytopenia were observed.[47]

Idelalisib has also been studied in combination with rituximab versus rituximab plus placebo. Sharman et al demonstrated that the median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group (hazard ratio for progression or death in the idelalisib group, 0.15; $p<0.001$). Subjects receiving idelalisib versus those receiving placebo had improved ORR (81% vs 13%; odds ratio, 29.92; $p<0.001$) and OS at 12 months (92% vs 80%; hazard ratio for death, 0.28; $p=0.02$). Serious AEs occurred in 40% of the subjects receiving idelalisib and rituximab and in 35% of subjects receiving placebo and rituximab.[48]

2.5.8 Other Options

The intrinsic apoptotic pathway is often dysregulated in relapsed CLL/SLL due to a deficiency in pro-apoptotic proteins such as TP53 and overexpression of anti-apoptotic proteins such as Bcl-2. Venetoclax is a selective, potent, orally bioavailable, small-molecule Bcl-2 inhibitor that can trigger apoptosis. Seymour et al reported 56 subjects who were enrolled with a median time on study of 10.0 months. Venetoclax showed activity in subjects with relapsed/refractory CLL with a response rate of 84% for the study population, including 20% CR/CRi. Subjects with high-risk CLL showed similar efficacy with a response rate of 82% in del(17p) and 78% in F-refractory disease. The most common AEs (all grades, ≥25% of subjects) were diarrhea (46%), neutropenia (43%), fatigue (34%), upper respiratory tract infection (29%), and cough (25%). Grade 3/4 AEs occurring in ≥4 of 56 subjects were neutropenia (41%), tumor lysis syndrome (TLS) (11%), thrombocytopenia (10%), hyperglycemia (10%), anemia (7%), and febrile neutropenia (7%). This study continued enrollment using a revised dosing schedule designed to reduce the identified risk of TLS. A phase 2 monotherapy study in subjects with relapsed del(17p) CLL has commenced as well as combination studies with either rituximab or obinutuzumab in patients with relapsed CLL.[49]

2.6 Acalabrutinib (ACP-196)[50]

Calquence® (acalabrutinib) has been approved in the US and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, CLL, and SLL.

Mechanism of Action:

Acalabrutinib is a low molecular weight irreversible inhibitor of BTK, which binds covalently to a cysteine residue (Cys481) in the front position of the ATP-binding pocket of BTK. BTK inhibition blocks BCR signaling and induces apoptosis. Acalabrutinib and its major metabolite, ACP-5862, have limited off-target kinase activity. The lack of activity against Tec- and Src- family kinases, important for T cells, functioning NK cells and platelets, as well as against epidermal growth factor receptor (EGFR), important for epithelial cell function, may contribute to the safety and efficacy profile of acalabrutinib. Acalabrutinib has shown efficacy in 3 separate models of lymphoid malignancies: follicular cell line xenograft, primary CLL xenograft, and spontaneous canine lymphoma. Efficacy data have been evaluated in subjects with CLL, including subjects with relapsed/refractory CLL (N=134), treatment-naïve disease (N=99), subjects intolerant of ibrutinib (N=33), and subjects with Richter's or PLL transformation (N=29).

2.6.1 Distribution

Quantitative whole-body autoradiography was performed on 5 male and 5 female Sprague Dawley rats after a single oral administration of [14C]-acalabrutinib (4 mg/kg). Rats were sacrificed 0.25, 1, 24, 72, and 168 hours after compound administration and the concentration of radioactivity was measured in tissues by autoradiography/radioluminography. In the period of 0.25 to 24 hours after dosing, although the absolute radioactivity numbers went down rapidly, the relative concentrations of [14C]-acalabrutinib in various tissues at the individual time points remained similar. The highest radioactivity concentrations were present in the small intestinal wall, liver, kidney, blood, adrenal gland, stomach wall, spleen, lacrimal glands, and pancreas. Low or no radioactivity was observed in the brain, spinal cord, or lens of the eye. Overall, the in vivo retention studies showed that acalabrutinib is effectively excreted by rats and that no retention was observed 7 days after administration. The mean in vitro protein binding ratios of acalabrutinib at final concentrations of 1 and 10 µmol/L were 83.0% and 79.2% for fasted male mouse plasma, 86.6% and 93.4% for fasted male rat plasma, 73.8% and 68.3% for fasted male dog plasma, 88.5% and 86.0% for fasted male monkey plasma, and 97.5% and 91.9% for fasted male human plasma, respectively.

2.6.2 Metabolism and Clearance[50]

Metabolism

The biotransformation of acalabrutinib has been evaluated in rat and dog with characterization of metabolites in bile and urine following oral and intravenous (IV) administration. Parent drug GSH-conjugation and subsequent enzymatic degradation of the glutathione moiety to the glycine-cysteine (Gly-Cys) conjugates by removal of the glutamic acid and Cys conjugates by subsequent removal of the glycine were the major biotransformation pathways noted in rat bile and urine. GSH-conjugation in combination with oxidation of acalabrutinib was also observed. For all of the glutathione-type metabolites, the position of the GSH, Gly-Cys and Cys was indicated at the butynyl moiety. In the pooled 1- to 8-hour rat plasma samples, very low levels of parent drug and the parent-Cys conjugate were detected along with trace levels of the CysGly- and the oxidized GSH-conjugate. After IV administration of acalabrutinib to dogs, the metabolites detected in urine, bile, and plasma were qualitatively comparable to those observed in rats. In line with metabolism in the rat, GSH conjugation with subsequent metabolism of the glutathione moiety appeared to be the major metabolic pathway. In both rat and dog body fluids, minor polar metabolites were detected with unresolved structure elucidation.

To characterize the cytochrome P450 (CYP) isoforms responsible for the metabolism of acalabrutinib, CYP reaction phenotyping for acalabrutinib was examined in 2 different in vitro systems, human liver microsomes and recombinant CYP isoforms, Bactosomes™. Additional studies were performed in a human liver microsomal system with specific chemical inhibitors of individual CYP isoforms. Inhibition of acalabrutinib metabolism by specific CYP3A4/5 inhibitors (ketoconazole and troleandomycin) indicate that CYP3A4/5 is the predominant CYP isoform responsible for metabolism of acalabrutinib. Other specific chemical inhibitors for CYP1A2, CYP2E1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 had minimal effect on the metabolic consumption of acalabrutinib in human liver microsomes.

Collectively, these results suggest that the CYP-mediated metabolism of acalabrutinib is catalyzed primarily by CYP3A4/5.

In vitro metabolism studies evaluated the inhibition properties of acalabrutinib on the 7 major CYP isoforms. Acalabrutinib did not appreciably inhibit CYP1A2, CYP2B6, CYP2C19 (IC_{50} > 100 µM), or

CYP2C8 (IC_{50} = 37 μM), CYP2C9 (IC_{50} = 28 μM), or CYP3A4/5 with IC_{50} values that ranged from 57 μM (testosterone as substrate) to 69 μM (midazolam as substrate). Examination of time-dependent inhibition of CYP3A4/5 in human liver microsomes showed that acalabrutinib has the potential to serve as a time-dependent inhibitor of CYP3A4/5 isoforms with a shift in IC_{50} vales from 69 μM to 16 μM (midazolam as substrate) or 57 μM to 13 μM (testosterone as substrate) upon preincubation of acalabrutinib. In a similar manner, acalabrutinib has the potential to serve as a time-dependent inhibitor of CYP2C8 and CYP2C9 isoforms with a shift in IC_{50} values from 37 μM to 18 μM, and a shift in IC_{50} values from 28 μM to 14 μM, respectively. Furthermore, modeling of the direct CYP inhibition in vitro data (FDA 2012) suggests minimal potential for acalabrutinib to increase the area under the concentration-time curve (AUC) of a CYP3A4 substrate—an oral dose of 450 mg of acalabrutinib is projected to yield a R1 value = 1.07. In a similar manner, acalabrutinib is not expected to increase exposure of co-administered therapeutics that are substrates for other CYP isoforms.

The potential of acalabrutinib (up to 50 μM; a concentration 119-fold greater than an estimated human C_{max} for a dose of 100 mg; C_{max} = 420 nM) to induce CYP isoforms was evaluated in 3 cryopreserved preparations of cultured human hepatocytes from 3 donor livers. Hepatocytes were treated with varying concentrations of acalabrutinib (0.01, 0.05, 0.1, 0.5, 1, 5, 10, or 50 μM) or 1 of 3 known human CYP inducers, namely, omeprazole (50 μM), phenobarbital (750 μM), and rifampin (20 μM). Under the conditions of this study, where the positive controls caused anticipated and appropriate increases in CYP enzyme expression, treatment of all 3 cultured human hepatocytes with up to 50 μM acalabrutinib caused concentration-dependent increases (>2.0-fold and >20% of the positive control, up to 32.9-fold change) in CYP1A2 mRNA levels, and in at least 1 of the 3 hepatocyte preparations tested, treatment at 50 μM acalabrutinib increased (>2.0-fold and/or ≥20% of the positive control) CYP2B6 and 3A4 mRNA levels (up to 2.9- and 2.44-fold, respectively). At lower concentrations, acalabrutinib caused an approximately 2-fold induction of CYP1A2 mRNA at concentrations (1 μM) that are greater than 2-fold the estimated C_{max} of (420 nM) of acalabrutinib in humans after an oral dose of 100 mg. Furthermore, at an acalabrutinib concentration of 5 μM, the increase in CYP1A2 mRNA was less than 12% of the positive control, omeprazole. Therefore, acalabrutinib is not anticipated to be strong inducer of CYP1A2 in humans. In a similar manner, at concentrations (10 μM) that are >20-fold the estimated C_{max} of acalabrutinib (420 nM) in humans after an oral dose of 100 mg, no notable induction was observed of CYP2B6 and CYP3A4 (<2.0-fold and <20% of the positive control). Therefore, acalabrutinib is not anticipated to be a strong inducer of CYP isoforms in humans.

Excretion

Recovery of radioactivity from 6 individual human subjects who received an oral microtracer dose of [14C]-acalabrutinib was essentially complete within 96 hours post dose with total radioactivity recovery of 95.7% (4.5% coefficient of variation [CV]). Radioactivity excretion in feces was 77.5% to 86.9% of dose and excretion in urine was 10.3% to 14.7% of dose.

2.6.3 Clinical Experience in Chronic Lymphocytic Leukemia

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

2.6.4 Clinical and Scientific Justification for Protocol Design

The use of combined therapy with purine analogs and monoclonal antibodies as first-line CLL therapy has significantly improved patient outcomes. About 10% of CLL patients do not respond to first-line fludarabine-based therapies or have only short-lived responses. The advent of kinase inhibitors has

demonstrated significantly improved response to second-line therapies as compared to standard chemoimmunotherapy regimens.

Gene expression profiling has allowed for investigating the effect of the microenvironment on CLL cells in vivo.[52] BCR activation is a key pathway engaged in the tumor microenvironment and the more aggressive form of CLL is characterized by stronger BCR activation in vivo. These data identify the disruption of tumor microenvironment interactions and inhibition of BCR signaling as promising therapeutic strategies in CLL. BTK is a key enzyme in BCR signal transduction and mutational inactivation of BTK prevents B-cell maturation. Pharmacologic inhibition of BTK blocks BCR signaling.[53] Ibrutinib was the first BTK inhibitor to reach the clinic and was recently approved as second-line therapy for CLL.

This phase 2 study will investigate acalabrutinib, a novel BTK inhibitor, for patients with CLL/SLL. Patients with relapsed refractory disease will be enrolled.

The development of novel BTK inhibitors considering the success of ibrutinib is justified from the experience with second- and third-generation tyrosine kinase inhibitors for chronic myeloid leukemia. The availability of different inhibitors for the same target has been shown to benefit patients in terms of choosing between therapies with different side effects and probably also different efficacy profiles. Furthermore, acalabrutinib has been shown in nonclinical and patient studies to have a different PK profile with lower protein binding than ibrutinib, and a higher availability for BTK inhibition.[50] Also, acalabrutinib has shown a more narrow specificity for BTK inhibition than ibrutinib, which also targets tyrosine protein kinase (ITK) in T cells.[54] The specificity for BTK inhibition without ITK inhibition may be especially important as ibrutinib-mediated ITK inhibition has been shown to abrogate FcR-stimulated NK cell function.[55]

Thus, acalabrutinib, which does not inhibit ITK, may prove to show higher efficacy in combination approaches with monoclonal antibodies as in studies currently ongoing for ibrutinib. These differences are expected to give acalabrutinib a different profile in terms of both safety and efficacy compared to ibrutinib. These expected differences may thus turn out to be important for clinical use of BTK inhibitors in both single-agent therapy and for combination therapy where additive side effects due to off-target side effects of different kinase inhibitors could be significant.

Selection of the acalabrutinib treatment regimen (including starting dose, dose modifications, schedule, duration, and conditions of administration) for this study has been based primarily on safety, exposure, and activity profiles from animal studies in mice and dogs.[56,57] Phase 1 to 3 clinical studies involving CLL/SLL subjects with refractory/relapsed disease are currently ongoing. Pharmacodynamic results from Study ACE-CL-001 (described in Section 2.6.3) suggest BTK resynthesis occurs in malignant B cells within 24 hours. While all dosages evaluated in Study ACE-CL-001 showed full BTK occupancy 4 hours after dosing, the 100-mg twice daily dose cohort showed full target coverage over 24 hours (≥97% BTK occupancy at 4 and 24 hours). The 100-mg twice daily regimen is expected to provide acalabrutinib PK/pharmacodynamic correlation within 4 hours of dosing.

The following specific issues have been considered in the study design:

- The dose of acalabrutinib of 200 mg once daily is within the dose range (100 mg to 400 mg once daily and 100 mg to 200 mg twice daily) with no DLTs observed in any dose cohort in the phase 1 study. Full target inhibition and clinical responses have been seen in both 100 mg and 175 mg dose cohorts. A 200-mg daily dose therefore provides a safe dose that is expected to

be at least 2-fold above what is needed for full target inhibition and is the recommended dose for this phase 2 study.

- Due to the short half-life of acalabrutinib, testing 2 dosage regimens (twice daily vs once daily) and measuring the drug occupancy in different compartments (peripheral blood, bone marrow, and lymph nodes) will provide important information about mechanisms of action for a covalent inhibitor and guide future dosage regimens for both single-agent and combination trials. After the completion of 6 dosing cycles and associated procedures, subjects in the once-daily dosing cohort will be permitted to switch to twice-daily dosing at the investigator's discretion.
- Treatment until the occurrence of disease progression or unacceptable toxicity with a targeted agent is appropriate and follows the paradigm of imatinib administration for chronic myelogenous leukemia. This study design will provide further information regarding duration of response and drug safety during chronic administration. Recent in vitro studies show that acalabrutinib is only moderately cytotoxic, making it likely that continued dosing is required. Prolonged therapy thus offers study participants the potential for maximum benefit from treatment.
- Dose modifications described in the protocol are chosen to balance concerns for subject safety with the need to achieve antitumor activity.
- Studying previously treated CLL/SLL is justifiable as the side effect profile of the drug is favorable compared to chemoimmunotherapy. Given the experience with ibrutinib, the side effect profile would not be expected to be significantly different than that of ibrutinib. The vast majority of patients benefit from the treatment. If observed responses and side effect profile are beneficial, this study could serve as a platform to develop an early intervention study as well as further combination approaches with other kinase inhibitors.
- Enrolling subjects with relapsed disease into a trial of an agent with a different PK and specificity profile from ibrutinib that still targets the underlying pathogenic BCR pathway in CLL is reasonable.
- As acalabrutinib is able to mobilize CLL cells out of the lymph node, studying the tumor microenvironment of the lymph node prior to and during treatment will further our understanding of the role of signaling events in the lymph node for CLL/SLL pathogenesis. Obtaining blood, bone marrow, and lymph node biopsies before and during treatment is feasible, safe, and tolerable. Assessing the degree of BTK inhibition in different anatomic compartments and the resultant effect on tumor biology will help advance treatment options for these patients.
- In an effort to build quantitative understanding of the relationship between acalabrutinib and ACP-5862 concentration, BTK receptor occupancy, and biomarkers included in this study, sparse acalabrutinib plasma concentrations will be collected at time points through 4 hours post dose, to further understanding of the contribution of both acalabrutinib and the metabolite ACP-5862 to drug activity.

3.0 STUDY DESIGN

This is a phase 2 single center trial. It is an open-label study of acalabrutinib in subjects with CLL or SLL with a lead-in period for pharmacodynamic assessment. Subsequently, subjects will receive acalabrutinib continuously until disease progression or development of drug-related toxicity.

For pharmacodynamic assessment during the lead-in period, subjects will receive acalabrutinib for 3 days followed by study drug hold for a portion of the research sampling at different intervals from last dose. Study drug will be restarted after completion of research sampling.

Subjects will be enrolled onto 2 different study arms based on the presence or absence of superficial lymphadenopathy:

- Arm A will enroll approximately 32 subjects with superficial lymphadenopathy, who will undergo lymph node biopsy to assess pharmacodynamic endpoints
- Arm B will enroll approximately 16 subjects (with or without lymphadenopathy) who will undergo bone marrow biopsy to assess pharmacodynamic endpoints.

If Arm A completes accrual before Arm B, then all remaining subjects will be enrolled into Arm B.

In each Arm, subjects will be randomized to receive 1 of 2 dosing regimens: 1) acalabrutinib, 200 mg once daily; or 2) acalabrutinib, 100 mg twice daily. Thus, up to 24 subjects will receive acalabrutinib 200 mg once daily and up to 24 subjects will receive acalabrutinib 100 mg twice daily. Randomization will be provided by the Clinical Center Pharmacy, ID MRS section.

In Arm A (subjects willing and able to undergo superficial lymph node biopsies), tissue samples will be collected according to the following schedule:

- A1a) acalabrutinib, 200 mg once daily: lymph node biopsy (Day 3) 4 hours after the last dose;
- A1b) acalabrutinib, 200 mg once daily: lymph node biopsy (Day 4) 24 hours after the last dose.
- A2a) acalabrutinib, 100 mg q12 hours: lymph node biopsy (Day 4) 12 hours after the last dose;
- A2b) acalabrutinib, 100 mg q12 hours: lymph node biopsy (Day 5) 36 hours from last dose.

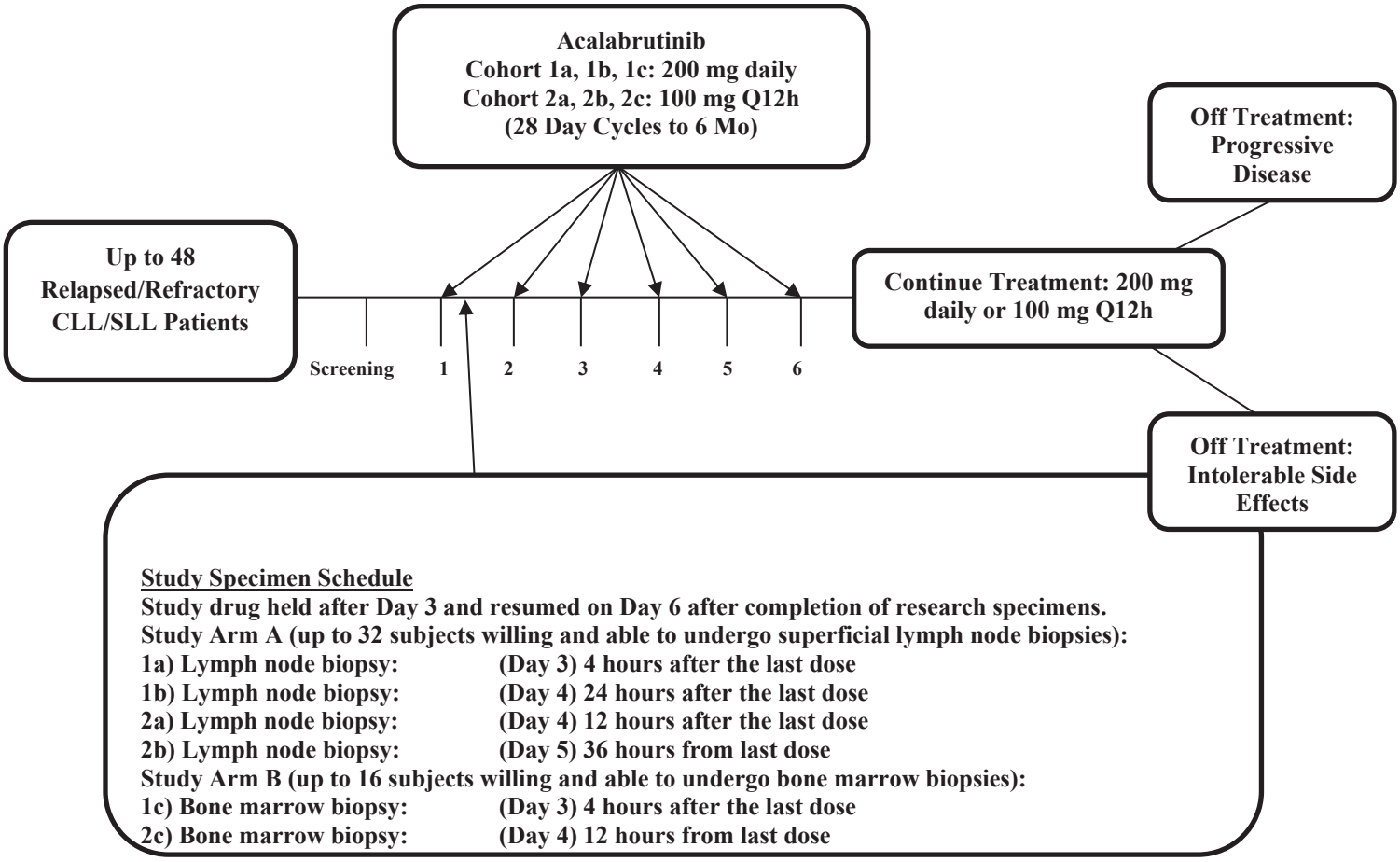
In Arm B (subjects willing and able to undergo bone marrow biopsies), tissue samples will be collected according to the following schedule:

- B1c) acalabrutinib, 200 mg daily: bone marrow biopsy (Day 3) 4 hours after the last dose;
- B2c) acalabrutinib, 100 mg q12 hours: bone marrow biopsy (Day 4) 12 hours from last dose.

For all 6 cohorts, peripheral blood samples will be collected at the time that biopsies are done, i.e., on day 3 4 hours post dose (peak level), on day 4 (trough level), and on day 5 (trough level plus 24 hours off drug).

On day 6, after all sampling is complete, subjects resume continuous treatment until disease progression or limiting side effects.

Subjects in once-daily cohorts will be permitted, at the investigator's discretion, to transition to twice-daily dosing after 6 cycles of acalabrutinib.


Acalabrutinib
Cohort 1a, 1b, 1c: 200 mg daily
Cohort 2a, 2b, 2c: 100 mg Q12h
(28 Day Cycles to 6 Mo)
Off Treatment: Progressive Disease
Up to 48 Relapsed/Refractory CLL/SLL Patients
Continue Treatment: 200 mg daily or 100 mg Q12h
Screening
1
2
3
4
5
6
Off Treatment: Intolerable Side Effects
Study Specimen Schedule
Study drug held after Day 3 and resumed on Day 6 after completion of research specimens.
Study Arm A (up to 32 subjects willing and able to undergo superficial lymph node biopsies):
1a) Lymph node biopsy: (Day 3) 4 hours after the last dose
1b) Lymph node biopsy: (Day 4) 24 hours after the last dose
2a) Lymph node biopsy: (Day 4) 12 hours after the last dose
2b) Lymph node biopsy: (Day 5) 36 hours from last dose
Study Arm B (up to 16 subjects willing and able to undergo bone marrow biopsies):
1c) Bone marrow biopsy: (Day 3) 4 hours after the last dose
2c) Bone marrow biopsy: (Day 4) 12 hours from last dose

Cohort	A1a (lymph node)	A1b (lymph node)	A2a (lymph node)	A2b (lymph node)	B1c (bone marrow)	B2c (bone marrow)
Drug dose	200 mg once daily	200 mg once daily	100 mg twice daily	100 mg twice daily	200 mg once daily	100 mg twice daily
At baseline	Bone marrow biopsy, lymph node biopsy	Bone marrow biopsy, lymph node biopsy	Bone marrow biopsy, lymph node biopsy	Bone marrow biopsy, lymph node biopsy	Bone marrow biopsy	Bone marrow biopsy
Cycle 1, Day 3	Lymph node biopsy 4 hrs post dose				Bone marrow biopsy 4 hrs post dose	
Cycle 1, Day 4		Lymph node biopsy 24 hrs post dose	Lymph node biopsy 12 hrs post dose			Bone marrow biopsy 12 hrs post dose
Cycle 1, Day 5				Lymph node biopsy 36 hrs post dose		
End of cycle 6	Bone marrow biopsy. Lymph node biopsy when indicated.	Bone marrow biopsy. Lymph node biopsy when indicated.	Bone marrow biopsy. Lymph node biopsy when indicated.	Bone marrow biopsy. Lymph node biopsy when indicated.	Bone marrow biopsy.	Bone marrow biopsy.
At 12 months from start of drug	Bone marrow biopsy.	Bone marrow biopsy.	Bone marrow biopsy.	Bone marrow biopsy.	Bone marrow biopsy.	Bone marrow biopsy.
After 12 months	Bone marrow biopsy and/or lymph node biopsy when indicated.	Bone marrow biopsy and/or lymph node biopsy when indicated.	Bone marrow biopsy and/or lymph node biopsy when indicated.	Bone marrow biopsy and/or lymph node biopsy when indicated.	Bone marrow biopsy and/or lymph node biopsy when indicated.	Bone marrow biopsy and/or lymph node biopsy when indicated.

Indicated means: a lymph node biopsy may be requested for work-up of persistent disease. A bone marrow biopsy may be requested to confirm complete response by International Workshop on Chronic Lymphocytic Leukemia criteria.
In subjects with progressive disease bone marrow and/or lymph node biopsy may be done as part of the work-up as clinically indicated.

4.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

4.1 Inclusion Criteria

1. Men and women 18 years of age and older with histologically confirmed disease as defined by the following:
    - CLL: clonal B-lymphocytosis ≥5,000 cells/μL or SLL: lymphadenopathy with the tissue morphology of CLL but that are not leukemic, <5,000 cells/μL.
    - Immunophenotypic profile or immunohistochemistry read by an expert pathologist as consistent with CLL. This will include CD5, CD19, and CD20 expression by the CLL cells typically also with CD23 expression, but CD23 negative cases may be included if there is no t11;14 translocation present.
2. Active disease as defined by at least one of the following (IWCLL consensus criteria):
    - Weight loss ≥10% within the previous 6 months
    - Extreme fatigue
    - Fevers of greater than 100.5ºF for ≥2 weeks without evidence of infection
    - Night sweats for more than 1 month without evidence of infection
    - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
    - Massive or progressive splenomegaly
    - Massive nodes or clusters or progressive lymphadenopathy
    - Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months

- Compensated autoimmune hemolysis

3. Relapsed/refractory CLL/SLL, or treatment-naïve subjects with deletion 17p, TP53 mutations, or NOTCH-1 mutation.
4. ECOG performance status of ≤2
5. Absolute neutrophil count (ANC) >500/µL, platelets >30,000/µL
6. Female subjects who are sexually active and able to bear children must agree to use highly effective methods of contraception during the study and for 2 days after the last dose of study drug.
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty and serial biopsies
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

4.2 Exclusion Criteria

1. Radiotherapy, radioimmunotherapy, biological therapy, chemotherapy, or investigational products in the 4 weeks prior to study drug administration
2. Richter's transformation
3. Autoimmune hemolytic anemia or thrombocytopenia requiring steroid therapy
4. Steroids ≥20 mg prednisone or equivalent for more than 3 days within the last 3 months.
5. Impaired hepatic function: total bilirubin ≥1.5 x upper limit of normal (ULN) (unless due to Gilbert's syndrome), aspartate amino transferase (AST)/alanine aminotransferase (ALT) ≥2.5 x institutional ULN, unless due to infiltration of the liver
6. Impaired renal function: estimated glomerular filtration rate (eGFR) ≤50 as determined by CKD-EPI equation
7. Life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib oral (PO), or put the study outcomes at undue risk
8. Concomitant immunotherapy, chemotherapy, radiotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), or experimental therapy
9. Active hepatitis B or hepatitis C infection
10. HIV infection
11. Female subjects: current pregnancy or unwilling to utilize effective contraceptive methods or refrain from pregnancy if of childbearing potential or currently breastfeeding
12. Psychiatric illness/social situations that would limit the subject's ability to tolerate and/or comply with study requirements.
13. Unable to understand the investigational nature of the study or give informed consent.
14. Individuals <18 years old
15. Known hypersensitivity to any component of acalabrutinib
16. Any prior therapy with other BTK inhibitors
17. Requires systemic anticoagulation with coumadin (warfarin)
18. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years or which will not limit survival to <2 years.
19. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
20. Grade ≥2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation
21. History of stroke or intracranial hemorrhage within 6 months before signing the treatment consent form
22. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of signing the treatment

consent form, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or left ventricular ejection fraction (LVEF) ≤40%

23. Requires treatment with strong or moderate CY3A4/5 inhibitors (unless no alternative is available)

5.0 TREATMENT PLAN

5.1 Drug Administration

Acalabrutinib is an orally administered product. Acalabrutinib will be administered with or without food. Acalabrutinib administration will take place in the outpatient facility of the PPD clinical center or at the subject's home. The drug dose is 200 mg PO daily (Cohort 1a, 1b, 1c) or 100 mg q12 hours (Cohorts 2a, 2b, 2c). Subjects in the once-daily dosing cohorts will be permitted, at the investigator's discretion, to transition to twice-daily dosing after completing 6 cycles of acalabrutinib. Use of proton pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib has the potential to decrease acalabrutinib exposure. If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib). Avoid co-administration with proton pump inhibitors. Subjects will take study drug at approximately the same times each day.

5.2 Therapy Schedule

All cycles will be 28 (±5) days long.

5.3 Prophylactic Medications

- Allopurinol 300 mg PO once daily at the discretion of the Principle Investigator (PI) (Cycle 1 only)
- Bactrim DS PO once daily 3 times per week (or alternative agent in case of sulfa allergy) at the discretion of the PI
- Acyclovir 800 mg PO twice daily at the discretion of the PI

5.4 Holding and Dose Adjustments of Study Drug Administration in the Case of Treatment-Related Toxicity:

5.4.1 Neutropenia

- Grade 4 ANC (<500/μL) for >7 days deemed related to study drug

Occurrence	Action
1st – 2nd	Hold acalabrutinib until recovery to Grade 1 or baseline; may restart at original dose level: Filgrastim or Peg-filgrastim at the discretion of the PI
3rd	Hold acalabrutinib until recovery to Grade 1 or baseline; restart at 1 dose level lower (100 mg once daily)
4th	Discontinue acalabrutinib

5.4.2 Thrombocytopenia

- Grade 4 platelets (<75% decrease from baseline) deemed related to study drug

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

5.4.3 Nonhematologic Toxicities

- Grade 3 nonhematological toxicity deemed related to study drug (despite optimal supportive care)

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

- Subjects experiencing a second occurrence of Grade 3 diarrhea, constitutional symptoms, readily reversible metabolic events, or infection may be restarted at the same dose when the toxicity resolves to Grade 1 or baseline.

Other Grade 1-2 nonhematologic toxicities thought related to drug do not necessitate holding of acalabrutinib, as long as the AE is not a toxicity as detailed in Section 5.5 are encountered. Supportive measures as appropriate should be taken to minimize side effects. An interruption of study drug administration is permissible.

5.5 Holding of Study Drug Administration

5.5.1 Surgical Procedures

BTK inhibition might affect platelet aggregation, therefore:

Consider the benefit-risk of withholding acalabrutinib for 3 days presurgery and postsurgery depending upon the type of surgery and the risk of bleeding.

5.5.2 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with acalabrutinib. Therefore, subjects with a history of hepatitis B virus (HBV) infection (HBV core antibody positive) will be referred to a physician with expertise in managing hepatitis B for antiviral prophylaxis. Subjects who receive HBV prophylaxis are eligible for participation in the study. After the start of study drug, subjects should be monitored every 3 months with a quantitative polymerase chain reaction (PCR) test for HBV DNA. Monitoring every 3 months should continue until 12 months after last dose of acalabrutinib.

Any subject with a rising viral load (above lower limit of detection: approximately 10 IU/mL) should discontinue study treatment and pre-emptively be treated with a nucleoside analog (i.e., lamivudine) for at least 12 months after the last treatment cycle of therapy or be referred to a specialist such as a gastroenterologist for management. This may not be relevant in all participating countries. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels), (see Section 11.2.2).

Subjects who are anti-HBc positive should have a quantitative PCR test every 3 months during treatment and every 3 months thereafter for 12 months after the last dose of any study drug. Subjects who are

receiving antiviral prophylaxis should have a quantitative PCR monthly for the first 3 months and then every 3 months thereafter for 12 months after last dose of any study drug.

The household members of subjects who develop HBV reactivation will be counseled and advised to be screened for HBV with their primary care doctors.

5.5.3 Progressive Multifocal Leukoencephalopathy

If progressive multifocal leukoencephalopathy (PML) is suspected, hold further treatment with acalabrutinib treatment until a diagnosis of PML is excluded. If a diagnosis of PML is confirmed, permanently discontinue acalabrutinib.

5.5.4 Permanent Discontinuation of Study Drug Administration in Case of Treatment-related Adverse Events

- Serious or life-threatening cardiac arrhythmias (Grade 3 or 4)
- Severe infection (requiring vasopressor support >24 hours, or intubation)
- Hepatitis B viral load above the lower limit of detection
- Confirmed diagnosis of PML
- Any Grade 4 toxicity excluding readily reversible metabolic or laboratory abnormalities or hematologic toxicities
- Progressive disease as defined in Section 7.3
- Pregnancy or unwillingness to use highly effective method of contraception

Subjects who will not be able to receive further study drug administration will be followed for safety and after resolution of the event will continue to be followed at regular intervals and will undergo reassessment of disease as outlined in Sections 6.0 and 7.0.

5.6 Supportive Care (Noninvestigational)

- **Growth Factors:** Filgrastim or pegfilgrastim may be used at the PI's discretion in subjects with neutropenia.
- **Blood Products:** Subjects will be transfused with packed red blood cells and platelets as clinically indicated. All required blood products will be irradiated prior to transfusion.
- **Anti-infective Agents:** Anti-infective agents will be used as indicated for treatment of intercurrent infections.
- **Pneumocystis pneumonia (PCP) prophylaxis**: PCP prophylaxis is not mandatory but will be offered. Typically, prophylaxis will be with TMP/SMX. Subjects who are allergic to sulfa drugs may be given an alternative agent, at the discretion of the PI.

5.7 Permitted and Nonpermitted Concomitant Medications (Investigator's Brochure)

Subjects may continue most medications they were prescribed prior to study enrollment for co-morbid conditions. We ask subjects to report all medications and over the counter drugs they are taking.

5.7.1 Guideline for Use of CYP Inhibiting and Inducing Drugs

Avoid co-administration of strong CYP3A inhibitors with acalabrutinib (see APPENDIX B). Alternatively, if the inhibitor will be used short-term, interrupt acalabrutinib. When acalabrutinib is administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily. Avoid co-administration of strong CYP3A inducers with acalabrutinib (see APPENDIX B). If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.

5.7.2 Concomitant Use of QT Prolonging Agents

No compound induced changes in the mean, diastolic or systolic arterial blood pressure, heart rate and the length of the heart rate corrected QT interval (QTc) could be detected during 24-hour recording patterns in healthy subjects administered acalabrutinib in therapeutic (100 mg) or supratherapeutic (400 mg) doses. (HV-005). Acalabrutinib may be given with other medications that may cause prolonged QTc.

5.7.3 Concomitant Use of Antiplatelet Agents and Anticoagulants

Due to potential bleeding complications associated with other BTK inhibitors, subjects who require anticoagulation with warfarin will not be allowed to start treatment with acalabrutinib unless the anticoagulation drug has been changed. With other forms of anticoagulation acalabrutinib should be monitored carefully and subjects should be observed closely for signs and symptoms of bleeding.

5.8 Special Instructions for Subjects

5.8.1 Immunizations

Live vaccines are contraindicated in this subject population. Subjects who would like to receive other routine nonattenuated vaccinations will be allowed to do so. Subjects will be advised not to receive live viral vaccines. The ability to generate an immune response to any vaccine following administration of acalabrutinib has not been studied.

5.8.2 Birth Control

Female subjects with reproductive potential who are sexually active must use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib. Examples of highly effective methods of contraception are listed in Section 11.8.

5.8.3 Calcium Carbonate

Subjects should be instructed to 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. Use of omeprazole or esomeprazole or any other long-acting proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in acalabrutinib exposure.

6.0 CLINICAL MONITORING

Samples will be ordered and tracked through the PPD . Should a PPD screen not be available, the PPD will be completed and will accompany the specimen and be filed in the medical record.

All evaluations under Section 6.0 where research blood is required for tumor mutations, blood may be redrawn and sent to the testing company if there are problems with the sample.

Subjects with a history of HBV infection should be monitored as described in Section 5.5.2.

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

Cases of PML have been reported in patients treated with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbance, visual disturbance, sensory deficits, weakness, and coordination and gait difficulties. If PML is suspected, hold further treatment with

acalabrutinib until a diagnosis of PML is excluded. A diagnostic evaluation may include, but is not limited to:

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

If PML is confirmed, permanently discontinue acalabrutinib.

Subjects should be monitored for increases in liver biochemistry indicating potential Hy's law (PHL) or Hy's law (HL). The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study. See APPENDIX C for the process to be followed in identifying and reporting cases of PHL and HL.

6.1 Screening Visit

Written informed consent will be obtained from all subjects by the investigator or his/her designee before any protocol specific procedures are carried out.

Screening Visit will include the following:

- Complete medical history
- Physical examination
- Concomitant medication review
- ECOG performance evaluation
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and lactate dehydrogenase (LDH)
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- Coagulation panel (PT, PTT)
- C-reactive protein (CRP)
- Iron studies (ferritin, transferrin, iron)
- Folate, Vitamin B12
- Beta-2 microglobulin
- Haptoglobin
- Direct antiglobulin test (DAT)

The following results from other PP IRB approved protocols that subjects may have participated in or outside results may be used as part of the screening laboratory tests for this study:

- Flow cytometry panel for CLL (may be done on blood and/or bone marrow and/or lymph node) or immunohistochemistry of lymph node or bone marrow demonstrating CLL/SLL. Results obtained within the past 12 months prior to signing the treatment consent form are acceptable.
- In treatment-naïve subjects, interphase FISH cytogenetics for deletion 17p13 within 3 months of signing the treatment consent form
- Viral serologies for hepatitis B and C, HIV 1/2 within 1 month of signing treatment consent form. For individuals with a positive hepatitis B core antibody, HBV DNA PCR will be performed to screen for subclinical infection within 3 months of signing the treatment consent form.
- For females of childbearing potential, 2 negative pregnancy tests sensitive to 50 mIU/mL. (Negative tests to be completed 2-4 weeks apart.)

- Complete staging computed tomography (CT) of the neck, chest, abdomen and pelvis within 3 months prior to signing treatment consent. Intravenous and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- Electrocardiogram (ECG) within 3 months prior to signing treatment consent

6.2 Baseline Testing

Screening results may be used as baseline. Baseline tests will be obtained within 1 month prior to starting study drug, unless noted otherwise:

- CCI

Laboratory results from other PPD IRB approved protocols that subjects may have participated in or outside reports may be accepted:

- For females of childbearing potential, pregnancy test sensitive to 50 mIU/mL or less
- IGHV mutation analysis where possible (as this test does not change with time, any prior report is acceptable)
- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13 within 3 months prior to starting study drug
- Bone marrow aspirate and biopsy within 3 months of starting treatment
- CCI
- Lymph node biopsy within 3 months of signing treatment consent form (per investigator discretion)

6.3 On Therapy Evaluations

6.3.1 Day 1 (C1/D1) Through Day 5 (C1D5)

Adverse events will be continually monitored. Assessments for PML will be completed as clinically indicated throughout the study.

Day 1 (C1/D1): To be drawn before the first dose (may be drawn up to 3 days before the first dose):

- For females of childbearing potential, pregnancy test sensitive to 50 mIU/mL or less
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- Beta-2 microglobulin
- CRP
- Coagulation panel (PT, PTT)
- Serum free light chains, quantitative immunoglobulins
- Serum protein electrophoresis with immunofixation
- Lymphocyte phenotyping (T, B, NK)
- CCI

Day 3 (C1/D3): To be drawn before study drug intake

- Complete blood count with differential

Day 3 (C1/D3): To be drawn 4 hours after study drug intake (± 2 hours)

- Complete blood count with differential
- CCI
- Subjects in cohort A1a will have a lymph node biopsy 4 hours after study drug intake (± 2 hours).*
- Subjects in cohort B1c will have a bone marrow (BM) biopsy 4 hours after study drug intake (± 2 hours).*

Day 4 (C1/D4):

- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- Beta-2 microglobulin
- CRP
- CCI
- Subjects in cohort A1b (24 hours (± 2 hours) post dose) and A2a (12 hours (± 2 hours) post dose) will have a lymph node biopsy for research.*
- Subjects in cohort B2c (12 hours ± 2 hours) will have BM biopsy for research.*

Day 5 (C1/D5):

- Complete blood count with differential
- LDH
- Beta-2 microglobulin
- CCI
- Subjects in cohort A2b (36 hours ±2 hours post dose) will have a lymph node biopsy for research.*

*All attempts will be made to obtain research lymph node biopsies and bone marrow biopsies within the given time frame. However, due to unanticipated factors in the clinical center work flow (emergency procedures in interventional radiology, staffing issues in procedure unit) we will allow specimens to be obtained outside the specified window.

6.3.2 On Therapy Evaluations Through 6 Cycles of Treatment

Evaluations will be completed at the PP at Cycle 1 Day 14 (± 3 days) and then for Cycle 1 through Cycle 5 (Day 28 ± 5 days). A cycle is defined as 4 weeks (28 days). The following assessments will be completed:

- Interval history and physical examination
- Concomitant medication review
- ECOG performance status evaluation
- Adverse events
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)

- CRP
- HBV DNA quantitative PCR (subjects with history of HBV infection only, every 3 months)
- HCV RNA quantitative PCR at Cycle 6 (subjects with a history of hepatitis C only)
- Beta-2 microglobulin
- Repeat pregnancy test if applicable in women of child bearing potential (except day 14).
- CCI

Additional blood draws, procedures, or imaging are (Day 28 ± 5-day window):

- C2/D28: Lymphocyte phenotyping (T, B, NK)
- C2/D28: Complete staging CT of the neck, chest, abdomen and pelvis will be obtained. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- C3/D28: Serum free light chains

6.3.3 Post 6 Cycles of Therapy (Day 28 ± 15-day window unless otherwise noted)

- Interval history and physical examination
- Concomitant medication review
- ECOG performance status evaluation
- Adverse Events
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- Coagulation panel (PT, PTT)
- Serum free light chains, quantitative immunoglobulins
- Serum protein electrophoresis with immunofixation
- CRP
- HBV DNA Quantitative PCR* (subjects with history of HBV infection only)
- Beta-2 microglobulin
- Haptoglobin
- DAT
- Lymphocyte phenotyping (T, B, NK)
- Repeat pregnancy test (women of child bearing potential)
- Peripheral blood flow cytometry panel for CLL may be obtained
- Staging CT of the neck, chest, abdomen and pelvis. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- Bone marrow biopsy and aspirate. Bone marrow flow cytometry panel for CLL may be performed.
- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13 may be obtained.
- CCI
- Lymph node biopsy may be obtained within 4 months of the "post 6 cycles of therapy" visit at the discretion of the PI; if lymph node biopsy performed, then lymph node flow cytometry panel for CLL may be obtained.

- CCI [redacted]

*Every 3 months, HBV DNA quantitative PCR testing should be performed locally as needed for subjects with a history of HBV infection.

6.3.4 Assessments Every 3 Months (± 15-day window) While on Therapy

- Interval history and physical examination
- Adverse events
- Concomitant medication review
- ECOG performance status evaluation
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic Panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- CRP
- Coagulation panel (PT/PTT) if clinically indicated
- HBV DNA quantitative PCR (subjects with history of HBV infection only)
- HCV RNA quantitative PCR (only for subjects with a history of hepatitis C infection with positive results at Cycle 6)
- Beta-2 microglobulin
- Repeat pregnancy test if applicable (women of child bearing potential)
- Reticulocyte count
- Serum-free light chains, quantitative immunoglobulins
- Haptoglobin
- DAT
- CCI [redacted]
- Lymphocyte phenotyping (T, B, NK) may be collected.
- Epstein-Barr virus (EBV)/cytomegalovirus (CMV) PCR may be obtained.

6.3.5 Additional Studies at 12 and 24 Months and Yearly Thereafter (± 30-day window unless otherwise noted)

- Lymphocyte phenotyping (T, B, NK)
- Staging CT of the neck, chest, abdomen and pelvis. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13 may be obtained.
- HBV DNA quantitative PCR (subjects with history of HBV infection only)
- Peripheral blood flow cytometry panel for CLL may be done.
- Bone marrow biopsy and aspirate should be performed 3 months ± 15-days after the subject meets CT and hematologic criteria for CR.
- When a bone marrow biopsy and aspirate is performed, a flow cytometry panel for CLL may be obtained.
- Lymph node biopsy may be obtained within 4 months of the 12, 24 or yearly visit at the discretion of the PI.

- When a lymph node biopsy is performed a flow cytometry panel for CLL may be obtained.
- CCI
- CCI

6.3.6 CCI

6.3.7 Assessments at Time of Progressive Disease or Suspicion of Progressive Disease

- Interval history and physical examination
- Adverse events
- Concomitant medication review
- ECOG performance status evaluation
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- CRP
- Coagulation panel (PT/PTT) if clinically indicated
- HBV DNA quantitative PCR (subjects with history of HBV infection only)
- Beta-2 microglobulin
- Serum-free light chains, quantitative immunoglobulins
- Lymphocyte phenotyping (T, B, NK) - yearly
- Staging CT of the neck, chest, abdomen and pelvis. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- PET scan as clinically indicated
- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13 may be obtained.
- Peripheral blood flow cytometry panel for CLL may be obtained.
- Bone marrow biopsy and aspirate, bone marrow flow cytometry panel for CLL may be obtained.
- Lymph node biopsy (if accessible), flow cytometry panel for CLL may be obtained.
- CCI
- CCI

6.3.8 Safety Follow-up 30 (+7) Days After the Last Dose of Study Drug (for Subjects Who Remain on Study)

- Interval history and physical examination
- Adverse events

- Concomitant medication review
- ECOG performance status evaluation
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- CRP
- Coagulation panel (PT/PTT) if clinically indicated
- HBV DNA quantitative PCR (subjects with history of HBV infection only)
- Beta-2 microglobulin
- Serum free light chains, quantitative immunoglobulins
- Lymphocyte phenotyping (T, B, NK) - yearly
- Staging CT of the neck, chest, abdomen, and pelvis, as clinically indicated. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function.
- PET scan as clinically indicated
- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13 may be obtained.
- Peripheral blood flow cytometry panel for CLL may be obtained.
- Bone marrow biopsy and aspirate, bone marrow flow cytometry panel for CLL may be obtained.
- Lymph node biopsy (if accessible), flow cytometry panel for CLL may be obtained.
- CCI
- CCI

6.3.9 Discontinuation Follow-Up

The following will be completed every 6 months (± 30-day window) for subjects who discontinue study drug for reasons other than progression or start of an alternate anticancer therapy. Assessment conducted will be based on investigator discretion and disease status.

- If progressive disease is suspected, see Section 6.3.7
- Interval history and physical examination
- ECOG performance status evaluation
- Complete blood count with differential
- Acute Care Panel (Na, K, Cl, CO_2, creatinine, glucose, and urea nitrogen)
- Mineral panel (phosphorus, magnesium, albumin, and calcium)
- Total protein, uric acid, and LDH
- Hepatic panel (alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Coagulation panel (PT/PTT) if clinically indicated
- CRP
- HBV DNA quantitative PCR (subjects with history of HBV infection only)
- Beta-2 microglobulin
- Serum free light chains, quantitative immunoglobulins
- Lymphocyte phenotyping (T, B, NK)
- Staging CT of the neck, chest, abdomen and pelvis. IV and PO contrast will be used unless the subject has a contrast allergy or impaired renal function as clinically indicated.
- PET scan as clinically indicated

- Interphase FISH cytogenetics for deletion 13q14, trisomy 12, deletion 11q22-23, and deletion 17p13
- Peripheral blood flow cytometry panel for CLL
- Bone marrow biopsy and aspirate, bone marrow flow cytometry panel for CLL
- Lymph node biopsy (if accessible), flow cytometry panel for CLL
- CCI

7.0 CRITERIA FOR RESPONSE

Responses for spleen and lymphadenopathy will be primarily assessed using CT scans. In the absence of a CT scan, assessment by physical exam may be substituted.

Response assessments will be made by IWCLL 2008 guidelines[2] incorporating the 2012 and 2013 clarifications for subjects treated with kinase inhibitors.[59] Response includes CR, PR, and PRL (Table 3).

Table 3: Criteria for Response

Response	CR	PR[F]	PRL[F]	PD[G]
Group A				
Lymphadenopathy[A]	None >1.5cm	Decrease ≥50%	Decrease ≥50%	Increase ≥50% or any new lesion >1.5 cm
Splenomegaly/hepatomegaly[B]	None	Decrease ≥50%	Decrease ≥50%	Increase ≥50% or new splenomegaly or hepatomegaly
Blood lymphocytes[C]	<4000/µL	Decrease ≥50%	Increase or <50% decrease	Increase ≥50% and ≥5,000/µL B lymphocytes
Bone marrow[D]	Normocellular, <30% lymphocytes, no B-lymphoid nodules.	Not applicable	Not applicable	Not applicable
Group B[E]				
Platelet count	>100,000/µL	>100,000/µL or increase ≥50%	>100,000/µL or increase ≥50%	Decrease ≥50% secondary to CLL
Hemoglobin	>11.0g/dL	>11.0 g/dL or increase ≥50%	>11.0 g/dL or increase ≥50%	Decrease ≥50% secondary to CLL
Neutrophils	>1,500/µL	>1,500/µL or increase ≥50%	> 1,500/µL or increase ≥50%	Not applicable

CR = complete response; CRi = CR with incomplete blood count recovery CT = computed tomography; PD = progressive disease; PR = partial response; PRL = partial response with lymphocytosis

[A] Sum of the products of up to 6 lymph nodes as evaluated by CT scans. In the absence of a CT scan assessment by physical exam may be substituted.

[B] Splenomegaly assessed by CT scan. In the absence of a CT scan assessment by physical exam may be substituted. New splenomegaly or hepatomegaly is assessed by physical exam.

[C] Subjects with treatment-related lymphocytosis remain on study unless associated with other signs of progressive disease. Treatment-related lymphocytosis may occur at the start of treatment or at any time when resuming treatment after a dose interruption.

[D] Complete response requires confirmation with bone marrow biopsy. In the absence of a confirmatory bone marrow biopsy the response can be classified as CRu. In case of a hypocellular marrow the response can be classified as CRi.

[E] PR or PRL, at least 1 Group B criterion has to be met. CR, all criteria in A and B must be met. In subjects meeting Group A criteria for CR but not Group B, the response can be classified as CRi.

[F] PR and PRL criteria refer to changes from baseline.

[G] PD criteria refer to changes from baseline in subjects who never responded and to changes from best response (nadir) in subjects who responded.

7.1 Complete Response (CR)

- Is defined as meeting all criteria in A and B.
- Meet all criteria in A and B but bone marrow confirmation is pending: unconfirmed complete response (CRu).
- Meet all criteria in A but bone marrow is hypocellular, or criteria in B are not met: complete response with incomplete blood count recovery (CRi).

7.2 Partial Response (PR)

- Is defined by 2 criteria in Group A if abnormal before therapy and at least 1 Group B criterion.
- In subjects with just 1 involved Group A site (e.g., lymphadenopathy in a subject with SLL), the response is PR when the criterion for that site is met.
- If criteria for PR, except for a decrease in the number of blood lymphocytes by 50% or more from the value before therapy, are met, then assessment will be PRL.
- SLL subjects need to have both ALC >50% and ALC >5K to be PRL.

7.3 Progressive Disease (PD)

Progressive disease is defined by at least one of the following criteria when occurring in the absence of a confounding process (e.g., infection), and that is maintained or continues to progress over a period of at least 3 months:

- Progressive lymphocytosis ≥50% from nadir, confirmed due to expansion of CLL cells by flow cytometry (≥5,000 B lymphocytes/µL)
- or an increase ≥50% in the sum of the products of at least 2 lymph nodes with at least 1 lymph node >1.5 cm in greatest diameter
- or the appearance of a new pathologic lymph node >1.5 cm in greatest diameter
- or new onset splenomegaly or hepatomegaly on physical exam, or other new CLL organ infiltrates
- or an increase ≥50% in splenomegaly or hepatomegaly
- or the progression or development of cytopenia (excluding autoimmune cytopenia), as documented by a decrease of hemoglobin levels by >2 g/dL, or by a decrease of platelet counts by >50%, if a marrow biopsy supports a disease-related etiology.

Other criteria for PD include:

- Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

A rise of the lymphocyte count at the beginning of therapy or resumption of therapy after a period of drug hold in absence of other indications of progressive disease will not be considered as evidence of progressive disease because this type of agent does typically lead to a mobilization of tumor cells into the peripheral blood.

8.0 ANCILLARY LABORATORY RESEARCH STUDIES

8.1 Collection of Samples

Blood samples: A volume not to exceed 550 mL of peripheral blood will be requested during the initial 8-week period. CCI

Lymphapheresis: CCI Lymphapheresis may also be collected in subjects with lymphocytosis that persists at 6 months, 12 months, yearly thereafter, and at progression of disease.

Bone marrow biopsies and aspirate: CCI

Lymph node biopsies: An excisional or core lymph node biopsies may be obtained pretreatment and at a timepoint during cycle 1.

CCI

PBMC sample: At a single on-treatment visit, six 10-mL NaHep tubes of peripheral blood may be collected (see Section 6.3.6).

CCI

CCI

8.2 Intended Use

These specimens will not be used for diagnostic purposes.

The translational and correlative endpoints of the study require analysis of tumor samples from blood, bone marrow, and lymph node for occupancy of BTK and impact of kinase inhibition on the tumor cells.

The assessment of BTK inhibition as a pharmacodynamic endpoint and the ability of acalabrutinib to occupy and inactivate BTK will be conducted at Acerta Pharma, BV.

CCI

CCI

- CCI

8.3 Storage, Tracking and Disposition of Samples and Data

Storage: All samples at PPD will be stored in the laboratory of PPD. Samples collected will be de-identified prior to storage in the laboratory of the Principal Investigator following current PPD Policy. Efforts to ensure protection of subject information include:

- Each sample is assigned a unique number.
- Vials holding subject samples are labeled with the sequential laboratory accession ID number that does not contain any personal identifier information.
- An electronic database is used to store subject information related to the coded samples.
- The laboratory is located in a controlled access building and laboratory doors are kept locked. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing subject information are kept in the locked laboratory or other controlled access locations.

Tracking: Samples will be ordered and tracked through the PPD. Should a PPD not be available, the PPD will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside PP without IRB notification and an executed MTA or CTA.

End of study procedures: Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

Loss or destruction of samples: Should we become aware that a major breech in our plan for tracking and storage of samples has occurred, the IRB will be notified.

8.4 CCI

CCI

CCI

CCI

- CCI

CCI

9.0 BIOSTATISTICAL CONSIDERATIONS

9.1 Primary Endpoint: Response to Acalabrutinib

The best response to treatment will be determined according to IWCLL 2008 criteria incorporating 2012 and 2013 clarifications pertaining to subjects treated with kinase inhibitors. Response includes CR, PR, and PRL.

9.2 Secondary Endpoints

- Safety and tolerability of once daily and twice-daily dosing of acalabrutinib
- Response and duration of response
    - Time to progression on acalabrutinib
    - Progression-free survival and OS on acalabrutinib
- Degree of inhibition of BTK assessed using a specific probe assay in tumor samples collected on acalabrutinib (blood, bone marrow, and lymph node), and after 2 and 6 months of continued dosing (blood and bone marrow).
- On-treatment effects on tumor biology of CLL cells in blood, bone marrow, and lymph nodes including proliferation (Ki67), activation (flow cytometric markers such as CD38, CD69, CD86), and gene expression.
- Clonal dynamics on treatment assessed using FISH cytogenetics and gene sequencing for somatic mutations.

- Shifts in cellular and humoral immunity on treatment (e.g., immunoglobulin levels, changes in T-cell subsets).

9.3 Exploratory Endpoint

- CCI

9.4 Sample Size

The study will enroll 44 subjects evaluable for response to complete the primary endpoint. Subjects receiving at least 6 months of therapy for whom CR assessment as detailed in Section 7.0 will be considered evaluable for response. The subjects in 2 different dosing cohorts are pooled to evaluate the primary endpoint of response: Cohort 1. acalabrutinib 200 mg once daily; and Cohort 2. acalabrutinib 100 mg twice daily. Each dosing cohort will include 22 subjects. To account for subjects discontinuing participation before having completed 6 months on treatment, we will enroll up to 4 additional subjects. Thus, up to 48 subjects may be started on study drug. To account for screening failures, up to 12 additional subjects may be screened for protocol. Up to 60 subjects will sign the screening consent and up to 48 will sign the standard consent to start treatment, with the intention of accruing 44 evaluable subjects.

CCI

For pharmacodynamics studies, we aim to have at least 6 subjects donating paired tumor samples pretreatment and on-treatment in each cohort for a total of 36 subjects.

9.5 Statistical Methods

The planned analyses will include descriptive statistics on the proportions of ORs. The response probabilities will be estimated using the sample proportions and their inferences including confidence intervals and hypotheses testing will be evaluated using Binomial distributions, and, if appropriate, normal approximations. The duration of response, OS, and the PFS time will be analyzed using appropriate nonparametric tools in survival analysis such as Kaplan-Meier estimates taking consideration of random censoring.

In addition, methods based on survival analysis, cumulative incidence rates, and other competing risk models will be used to evaluate the treatment effects. Graphical tools will be used to display the appropriate estimates (i.e., estimated proportions and Kaplan-Meier curves) and their corresponding 95% confidence intervals. Methods based on multiple regression, analysis of variance, logistic regression and nonparametric regression will also be employed if deemed appropriate.

Response rate and survival will also be reported on an intention-to-treat basis.

As a secondary analysis, the efficacy and safety profiles of 2 dosing cohorts will be compared. The effect on the possible dosing reduction due to AEs will be examined and adjusted. Appropriate methods will be used to examine missing patterns and handle the missing data in the analysis as deemed appropriate.

CCI

9.6 Study Stopping Rules

The study will be monitored to ensure that the occurrence of a specified set of treatment-related serious AEs that occur during the treatment period does not substantially exceed an anticipated rate. The following specified treatment-related serious AEs determined to be probably or definitely related to therapy will be considered for early stopping of the study

1. AEs resulting in death
2. Severe infection requiring vasopressor >24 hours or intubation
3. Any Grade 4 toxicity **excluding**
    - Readily reversible metabolic or laboratory abnormalities
    - Hematologic toxicities

We anticipate the rate of these specified treatment-related serious AEs within the 6 month period (completion of primary endpoint) to be 15% or less. Since the 2 dosing cohorts do not differ in total dose, we will monitor the treatment-related serious AEs in the 2 dosing cohorts together. Following Geller et al. (2003), our stopping rule is determined by a Bayesian approach. The stopping boundary for an experiment is reached if the Bayesian posterior probability that the true probability of developing one or more of the specified treatment-related serious AEs exceeds this benchmark rate of 15% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives prior parameters alpha = 1.35, beta = 7.65. Hence when we make decisions about stopping the study, the data from the study will dominate over the prior opinion. We begin monitoring the treatment-related serious AEs when 3 subjects are evaluable for treatment-related serious AEs within the 6 months.

Number of subjects in the experiment	Stop if the number of subjects who have developed any of the specified treatment-related serious adverse events reaches:
≤ 5	3
≤ 10	4
≤ 15	5
≤ 20	6
≤ 26	7
≤ 31	8
≤ 36	9
≤ 42	10
≤ 47	11
≤ 48	12

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 48 independent Bernoulli trials, each had a probability p for having treatment-related serious AEs and q=1-p for not having treatment-related serious AEs and compared the treatment-related serious AEs outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies (i.e., "number of stopped studies"/100,000) which were stopped using the above stopping rule. The following table summarizes the proportions of stopped studies under a number of scenarios for p:

Probability of TRSAE = p	0.10	0.15	0.20	0.25	0.30
Proportion of Stopped Studies	3.8%	18.8%	47.2%	75.5%	91.8%
Average number of subjects	46.7	42.8	35.4	26.7	19.4
Average number TRSAEs	4.7	6.4	7.1	6.7	5.8

TRSAE = treatment-related serious adverse event

These results suggest that our stopping rule has a low probability stopping a study when the proportion of treatment-related serious AEs is below the benchmark value of 15%, and the probability of stopping a study is high when the true proportion of treatment-related serious AEs exceeds this benchmark value. Based on these results, we believe that our Bayesian stopping rule has satisfactory statistical properties.

9.7 Stopping Rule for Mortality

In addition, we have a stopping rule for treatment-related mortality (TRM; death that are probably or definitely related to the protocol regimen). We anticipate the TRM rate within 1 year to be 5% or less. Using the same Bayesian approach, the stopping boundary is reached if the Bayesian posterior probability that the true probability of developing TRM's exceeds 5% is at least 90%. We take our prior distribution to be a beta distribution with parameters $(\alpha, \beta) = (0.45, 8.55)$. This indicates that the relative weight we place on our prior opinion is approximately 20% of the weight we will place on the results of the new study. The following table summarizes the threshold numbers for stopping the study based on above Bayesian approach.

Number of subjects in the experiment	**Stop if the number of subjects who have TRMs reaches:**
≤ 2	2
≤ 20	3
≤ 33	4
< 47	5
48	6

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 48 independent Bernoulli trials, each had a probability p for having TRM and q=1-p for not having TRM and compared the TRM outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies (i.e., "number of stopped studies"/100,000) which were stopped using the

above stopping rule. The following table summarizes the proportions of stopped studies under a number of scenarios for p:

Probability of TRM = p	0.03	0.05	0.07	0.10	0.15	0.20
Proportion of Stopped Studies	3.5%	14%	30.8%	58.6%	88.3%	97.9%
Average number of subjects	47.1	44.6	40.7	33.4	22.7	16
Average number TRMs	1.4	2.2	2.9	3.4	3.4	3.2

These results suggest that our stopping rule has a low probability stopping a study when the proportion of TRM is below the benchmark value of 5%, and the probability of stopping a study is high when the true proportion of TRM exceeds this benchmark value. Based on these results, we believe that our Bayesian stopping rule has satisfactory statistical properties.

9.8 Off Study Criteria (for Subject Participation)

Subject choice: Subjects may be removed from the study at their request. The risks of withdrawing will be discussed, as will alternative treatment options. Subjects who opt to withdraw from the protocol will be strongly encouraged to continue to have laboratory tests (complete blood count, chemistries) monitored for 1 month after study withdrawal for their safety.

PI Decision: Subjects will be taken off study for:

- Initiation of nonprotocol treatment
- Significant PD or a concomitant condition that would make the subject ineligible for further protocol participation. Subjects who meet criteria of PD and are continuing to gain clinical benefit from therapy may be able to temporarily remain on acalabrutinib after discussion with the medical monitor.
- Reactivation of HBV infection
- Pregnancy or initiation of breast feeding
- Subject becomes significantly noncompliant with study drug administration, study procedures, or study requirements, which might increase risk or substantially compromise the interpretation of study results.

Completion of the study: Subjects will be followed indefinitely until an off-study criterion is met or the study is closed to further follow-up care.

Subjects who discontinue study drug for reasons other than disease progression or start of alternative anticancer therapy will be followed approximately every 6 months (± 30 days) until disease progression or start of alternative anticancer therapy, whichever comes first.

Subjects or the partner of a subject who becomes pregnant will be followed for the duration of the pregnancy and birth of the offspring.

Once protocol participation is complete, the subject will be referred back to his or her referring physician, consented to the PPD for consideration for standard therapy or evaluated for eligibility for another PPD protocol, depending on what is considered to be in the best interest of the subject.

Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per Section 10.2. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

10.0 DATA AND SAFETY MONITORING

Principal Investigator: Accrual, efficacy and safety data will be monitored by the Principal Investigator: PPD

PPD **IRB:** Prior to implementation of this study, the protocol and the proposed subject consent and assent forms will be reviewed and approved by the properly constituted Institutional Review Board (IRB) operating according to 45 CFR 46. This committee will approve all amendments to the protocol or informed consent and conduct continuing annual review so long as the protocol is open to accrual or sample and/or data analysis continues. Accrual and safety data will also be monitored and reviewed annually by the IRB.

Quality assurance and control monitoring will be consistent with the PPD Quality Assurance and Quality Control Policy.

PPD **DSMB:** The PPD Data Safety and Monitoring Board (DSMB) will review the protocol, progress report, accrual, efficacy and safety data at 6- or 12-month intervals as scheduled. All AEs and serious adverse events (SAEs) observed during the clinical trial and for which there is a relationship with the use of acalabrutinib or the conduct of the study will be reported to the DSMB at the regularly scheduled DSMB meeting. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

Acerta Pharma, BV (Sponsor): An annual progress report, any amendments to the protocol, and any change in the status of the protocol will be forwarded to:

PPD

In addition, regular communication with the Sponsor occurs to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths).

10.1 Assessment of Safety

10.1.1 Definitions

Please refer to PPD for current definitions.

10.1.2 Severity

Definitions found in the CTCAE v4.03 will be used for grading the severity (intensity) of nonhematologic AEs:

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

The grading scale for hematologic toxicity in subjects with CLL is in the table below.

Grading Scale for Hematologic Toxicity in CLL[2]

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

ANC = absolute neutrophil count; CLL = chronic lymphocytic leukemia; G-CSF = granulocyte colony-stimulating factor; WBC = white blood cell

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

10.1.3 Pregnancy

Subjects will be advised to immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 2 days after the last dose of study drug. Any female subjects receiving acalabrutinib who become pregnant must immediately discontinue study drug. The investigator will counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

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

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

Monitoring of the pregnancy should continue until conclusion of the pregnancy at which point the Pregnancy Report Form Part II must be completed and submitted to Acerta Pharma, BV Drug Safety. If a viable baby is born, then at 2 months postpartum the Pregnancy Report Form Part III must be completed and submitted.

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

10.1.4 Adverse Event and Serious Adverse Event Causality Assessments

The relationship of AEs and SAEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

The following descriptions below help to guide the assessment of causality:

No = There is no reasonable possibility that the event may have been caused by study drug. The AE:

- May be judged to be due to extraneous causes such as disease or environment or toxic factors
- May be judged to be due to the subject's clinical state or other therapy being administered
- Is not biologically plausible
- Does not reappear or worsen when study drug is re-administered
- Does not follow a temporal sequence from administration of study drug

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

- Follows a temporal sequence from administration of study drug
- Is a known response to the study drug based on clinical or preclinical data
- Could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- Disappears or decreases upon cessation or reduction of dose of study drug
- Reappears or worsens when study drug is re-administered

10.1.5 Adverse Events of Special Interest

The following are adverse events of special interest (AESIs) and must be reported to the sponsor expeditiously (see Section 10.2 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

10.1.6 Second Primary Malignancies

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

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

10.2 Documenting and Reporting of Adverse and Serious Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record and eCRF, with the exception of laboratory values that are not associated with clinical symptoms. Those will only be captured in the subject's medical records.

Reporting serious, unexpected adverse reactions (SUSARs) to IRB:

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current acalabrutinib Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma, BV Drug Safety/Designee will forward a formal notification describing the SUSAR to all investigators. The investigators should follow the local institutional requirements of reporting SUSARs to IRB.

Reference Safety Information (RSI):

For the purpose of reporting adverse events (AEs) and serious adverse events (SAEs), the acalabrutinib Investigator Brochure contains the Reference Safety Information (RSI) for acalabrutinib.

10.3 PPD IRB and CD Reporting

10.3.1 Serious Events

Expedited Reporting:

Events requiring expedited reporting will be submitted to the IRB per PPD

Reports to the IRB at the time of Continuing Review:

The investigator or designee will refer to PPD to determine IRB reporting requirements.

Reports to the CD:

The investigator or designee will refer to PPD guidelines to determine CD reporting requirements and timelines.

10.3.2 Reporting Period for AEs

After the signing of the informed consent form (ICF) and prior to the first dose of study drug, all SAEs must be reported. After the first dose of study drug, all AEs/SAEs, irrespective of attribution of causality must be reported.

All AEs must be reported until 30 days after the last dose of study drug or the start of new anticancer therapy (whichever comes first). After this period, investigators should report any SAEs and other AEs of concern that are believed to be related to prior treatment with study drug.

All SAEs which occur during the reporting period should be followed to resolution or until the investigator assessed the subject as stable or until the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health of the investigator does not expect any further improvement or worsening of the event.

10.3.3 Reporting Requirements for SAEs

PPD **IRB:** Please see Section 10.3.1 above.

Acerta Pharma, BV:

- The SAE should be reported within 24 hours of discovery of the event or information via electronic data capture (EDC) on the AE/SAE eCRF.
- If after hours, or if the EDC is not available, fax an SAE Reporting Form within 24 hours of the discovery of the event or information to fax number or email below and then enter the SAE on the AE/SAE eCRF when EDC is available (Note: All SAEs must be reported via EDC even if initial notification to Acerta Pharma, BV is via fax or email on the SAE Reporting Form).

Acerta Pharma, BV Drug Safety Contact Information	
PPD	

- Drug Safety queries will be issued in EDC and the site is expected to address queries within a reasonable time period (e.g., 24-48 hours).

The following may not be reported to the IRB immediately:

- A standard procedure for protocol therapy administration

- The administration of blood or platelet transfusion
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, C or biomarker blood sampling)
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an AE
- A procedure planned before entry into the study

10.4 Data Management

Authorized study site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided by the sponsor. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. Data will be abstracted from Clinical Center progress notes as well as from progress notes forwarded from the subjects' home physician that have been uploaded into the electronic medical record. Laboratory data from PP and from referring home physicians will be entered into the system.

We will maintain the confidentiality of identifiable private information collected in this Clinical Trial and protect the privacy of the individual human subjects. All human subjects' personally identifiable information (PII) as defined in accordance with the Health Insurance Portability and Accountability Act (HIPAA), eligibility and consent verification will be recorded in PPD and a database provided by Acerta Pharma, BV. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with PP information security standards. Neither individual personal identifiers nor the key linking coded data to individuals will be released to Acerta Pharma, BV without prior IRB approval and an executed PPD or MTA. The PPD may provide clinical specimens and data (blood, bone marrow, lymph node, serum or plasma) for the analysis of BTK inhibition in tumor samples, as well as tumor samples or derivatives thereof (cells, DNA, RNA, protein) to Acerta Pharma, BV under this study. Identifiable data will not be sent outside PPD without prior IRB approval or appropriate conditions for disclosure outlined in the executed PPD or MTA.

End of study procedures: Data will be stored in locked cabinets and in a password protected database until it is no longer of scientific value.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Publication policy: Given the research mandate of PPD, subject data including the results of testing and responses to treatment will be entered into an PP -authorized and controlled research database. Any future research use will occur only after appropriate human subject protection institutional approval such as prospective PP IRB review and approval or an exemption from the PPD

10.5 Protocol Monitoring

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

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

11.0 HUMAN SUBJECT PROTECTION

The investigator(s) accept their responsibilities for protecting the rights and welfare of human research subjects and will permit, with reasonable advance notice and at reasonable times, the designated research monitors to monitor the conduct of the research, as well as to audit source documents to the extent necessary to verify compliance with FDA Good Clinical Practice and the approved protocol.

11.1 Rationale for Subject Selection

11.1.1 Predicted distribution by gender, age and race:

Chronic lymphocytic leukemia is a rare neoplasm that comprises a substantial proportion of all leukemia in middle-aged persons and is the most common type among elderly persons in Western populations. Epidemiologic studies suggest that distribution by gender will be 66% males and 33% females.[13] This trend appears to be lost with age. Chronic lymphocytic leukemia is more common in Caucasian and African-American populations but rare in Hispanics and very rare in the Asian population. This study will be open to all subjects who fit the inclusion criteria and provide informed consent to protocol participation. We would predict that distribution should be comparable to that seen on the PPD screening protocol as follows:

- by gender: 33% females; 66% males
- by age: ages 23-79, median 60
- by race: 2% Asian, 11% Black, 8% Hispanic, 79% White

11.1.2 Special Populations

Justification for exclusion of children: Chronic lymphocytic leukemia is uncommon in patients less than 45 years of age and is virtually unknown in patients less than 20 years of age. At the time of diagnosis, more than 95% of patients are 45 years old and above.[7] Chronic lymphocytic leukemia may also be, biologically, a different disease in children. Ibrutinib has not been studied in human subjects under 18 years of age. For these reasons, individuals <18 years old have been excluded from protocol participation.

Justification for exclusion of pregnant women: There are no clinical studies that were done on pregnant women, and it is unknown whether acalabrutinib or its metabolites are excreted in human milk. In addition, it is highly unlikely that a woman of premenopausal age will present with CLL or SLL at the Clinical Center. CLL/SLL is a malignancy of B cells that predominantly affects the elderly population. Diagnosis is typically made in adults over the age of 50 and more than half of the people with CLL/SLL are over the age of 70.

Justification for exclusion of subjects with impaired hepatic or renal function: In dedicated hepatic impairment studies (ACE-HI-001 and ACE-HI-102), subjects with normal liver function (N=6), acalabrutinib exposure (AUC) was increased by ~~2~~1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild

(Child-Pugh A; N=6), moderate (Child-Pugh B; N=6), and severe (Child-Pugh C; N=8) hepatic impairment, respectively. To minimize risks, subjects enrolled in this study must have AST and ALT levels <2.5 x the institutional ULN.

Acalabrutinib has not been formally studied in subjects with renal impairment. To minimize risks, subjects enrolled in this study must have an eGFR >50.

Justification for exclusion of cognitively impaired subjects: Cognitively impaired and institutionalized persons will not participate in this study. Subjects must be able to provide informed consent and understand and comply with the treatment plan and follow-up.

Recruitment: The study will be listed on the clinicaltrials.gov. If recruitment goals are not met, a recruitment plan will be developed by the PPD.

Payment for participation: $0 – Subjects will not be compensated for their participation in this study. There is no payment for the blood samples obtained for research.

Reimbursement for protocol participation travel, food, and lodging will be consistent with PP guidelines.

For travel from home: Travel from home for the first PPD visit will not be reimbursable. If the subject consents to protocol participation travel home following the first visit will be reimbursable. Subjects will be reimbursed 100% of government rate for travel once the subject has been determined eligible to participate and signs consent.

Local travel (car/taxi/shuttle/train/bus): Subjects will be reimbursed for local train/bus and/or shuttle costs consistent with PPD guidelines. Car mileage will be reimbursed $0.41/mile when the distance from home is greater than 30 miles. Reimbursement for mileage less than 30 miles from home is not provided. Subjects will not be reimbursed for rental car cost beyond the car mileage rate. Taxi will be paid only when medically necessary and authorized by the PI.

Meals: Subjects will not be reimbursed for meals.

Lodging: Will be consistent with PPD guidelines.

PPD

11.2 Serious Risks Associated with Acalabrutinib Treatment

The acalabrutinib Investigator Brochure contains the Reference Safety Information for acalabrutinib.

11.2.1 Hemorrhage

Serious hemorrhagic events occurred in clinical trials been reported by subjects treated with acalabrutinib.

The mechanism for hemorrhage is not well understood. Subjects receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding acalabrutinib for at least 3 days presurgery and postsurgery. Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

11.2.2 Infections

Serious infections (bacterial, viral, and fungal) , including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus reactivation, aspergillosis, and PML have occurred.

Consider prophylaxis in patients who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

Hepatitis B Virus Reactivation

Cases of HBV reactivation have occurred in clinical studies with acalabrutinib. Subjects who are HBV core antibody-positive or have a known history of HBV infection should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring should continue every 3 months until 12 months after last dose of acalabrutinib.

Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

Progressive Multifocal Leukoencephalopathy

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

If PML is suspected, hold further treatment with acalabrutinib treatment until PML is excluded.

A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation
- Brain MRI
- PCR analysis for John Cunningham virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

11.2.3 Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in Section 6.0 and as medically appropriate. Please refer to Section 5.4 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.

11.2.4 Second Primary Malignancies

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

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

11.2.5 Atrial Fibrillation

Atrial fibrillation or flutter has occurred in clinical studies with acalabrutinib particularly in subjects with cardiac risk factors including hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as appropriate. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

11.3 Potential for Drug-Drug Interactions

Based on available nonclinical and clinical data, acalabrutinib is metabolized by CYP3A, GSTM1/M2 and amide hydrolysis. CYP3A-mediated oxidation appears to be the major route of metabolism in humans. Nonclinical CYP interaction studies data indicate that acalabrutinib is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

Agents That May Increase Acalabrutinib Plasma Concentrations (CYP Isoform Inhibitors)

Acalabrutinib may be metabolized by CYP3A4. Therefore, any medications that are strong inhibitors of CYP3A4 should be avoided.

Agents That May Decrease Acalabrutinib Plasma Concentrations (CYP Isoform Inducers)

Acalabrutinib may be metabolized by CYP3A4. Therefore, any medications that are strong inducers of CYP3A4 should be avoided.

Acalabrutinib absorption may be lower in individuals being treated with proton pump inhibitors, histamine 2 (H2) receptor antagonists, or antacids.

11.4 Contraindications

Acalabrutinib is contraindicated in subjects with clinically significant hypersensitivity to any of the compound's structural components.

11.5 Overdose Instructions

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

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

For overdoses associated with a SAE, the standard reporting timelines apply.

For any subject experiencing an acalabrutinib overdose (as defined above), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of

acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

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

11.6 Risks Related to Blood Draws

No major risks are involved with blood draws. Minor complications including bleeding, pain, bruising, inflammation, and hematoma formation at the site of blood draws. Vasovagal reactions or infections may rarely occur.

11.7 Risks Related to CT Scan

Computed tomography, sometimes called CT scan, uses special x-ray equipment to obtain image data from different angles around the body and then uses computer processing of the information to show a cross-section of body tissues and organs. Oral and/or IV contrast agents will be used and are usually well tolerated. However, some subjects will experience allergic reactions to IV contrast. To lower the risk of allergic reactions, low allergenic contrast agents are administered at PP clinical center. In addition, subjects will be advised that approximately 2 to 7% of subjects who receive contrast agents will experience a temporary reduction in kidney function lasting up to 2 weeks following infusion and that in rare instances, permanent renal damage can result from the use of the IV contrasting agent. Therefore, in subjects with impaired kidney function, we will not use IV contrast.

The amount of radiation subjects will receive from the research scans in this study is 7.0 rem for the first year, which is above the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the PPD. After the first year, subjects will receive 3.5 rem of radiation annually. All female subjects will receive pregnancy testing prior to radiation exposure.

11.8 Risks Related to Pregnancy and Nursing Mothers

There are no clinical studies in pregnant women, and it is unknown whether acalabrutinib or its metabolites are excreted in human milk. Therefore, women of childbearing potential who are sexually active must use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib.

Women will be considered of nonreproductive potential if they are either:

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

OR

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

OR

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

Examples of highly effective methods of contraception are defined below‡:

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

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

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

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 10.1.3).

Developmental and reproductive toxicology studies in rats have not identified acalabrutinib-related toxicities for fertility, reproductive success, embryofetal development or embryofetal survival. In rabbits, at dose levels which resulted in maternal toxicities skeletal variations were associated with reductions in fetal weights. In rat reproductive study, dystocia (prolonged/difficult labor) was observed.

11.9 Risks Related to Bone Marrow Biopsy

The anesthetic can cause some temporary stinging and burning. A pulling sensation and discomfort may be felt as the marrow is withdrawn, and sometimes, very infrequently a nerve may be injured during the procedure causing pain. Although rare, there is a potential for bleeding at the site and local infection. Bleeding can be stopped by applying local pressure, and infection can be treated with antibiotics.

Another risk associated with this procedure is allergic reactions.

11.10 Risks Related to Lymph Node Biopsy

Lymph nodes are part of the immune system. They are found in the neck, behind the ears, in the armpits, and in the groin. A lymph node biopsy removes lymph node tissue to be looked at under a microscope for signs of cancer. There are several ways to do a lymph node biopsy.

- A fine or core needle aspiration biopsy puts a thin needle into the lymph node and removes cells to look at. Subjects will feel only a quick sting from the local anesthesia used to numb the

skin and may feel some pressure from the biopsy needle. After a core needle biopsy, the site may be tender for 2 to 3 days.

- An open biopsy makes a cut in the skin and removes the lymph node. General anesthesia may be required. For 1 to 2 days, subjects may feel tired and have a mild sore throat from the tube that was used to help them breathe during the biopsy. Throat lozenges and gargling with warm salt water will be recommended. After the open biopsy, the biopsy site may feel tender, firm, swollen, and/or bruised. Subjects may be advised not do any heavy lifting or other activities that stretch or pull the muscles around the area. Subjects will be instructed on wound care and timing of suture removal.

Another risk associated with this procedure is allergic reactions.

11.11 Risks Related to Transfusions

Some risks with the transfusion with blood and /or blood products include fever or allergic reactions. These risks are uncommon and are usually mild, but on rare occasions may be severe or life threatening. Extremely rare risks include infections with viruses, such as hepatitis or HIV or serious incompatibility reactions.

11.12 Risks in Relation to Benefit

The benefits to the adult subject could be a reduction or a disappearance of the CLL/SLL resulting in an improved quality of life, a decreased susceptibility to infections, and foremost a significant improvement in survival time. Potentially, treatment with other therapies could also be avoided or postponed.

11.13 Informed Consent Processes and Procedures

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the subject and a signed informed consent document will be obtained prior to entry onto this study.

At any time during participation in the protocol, should new information become available relating to risks, AEs, or toxicities, this information will be provided orally or in writing to all enrolled or prospective subject participants. Documentation will be provided to the IRB and if necessary, the informed consent amended to reflect relevant information.

Note: Effective January 21, 2019, a witness to the signature of the written long form research consent at an PP site (whether initially approved by an IRB before or after January 21, 2019) is no longer a requirement.

11.14 Conflict of Interest

Acerta Pharma, BV is providing the acalabrutinib for this study to PP without charge. No PP investigator involved in this study receives any payment or other benefits from Acerta Pharma, BV. The PI assures that each associate investigator received a copy of the PP 's Guide to preventing conflict of interest. No members of the research team reported a potential conflict of interest.

11.15 Technical Transfer Agreements

The protocol has the following associated PPD :

- Between PPD , and Acerta Pharma, BV

The protocol is associated with the following MTA:

- Between PPD and PPD will

provide de-identified RNA and DNA samples collected under this protocol for sequencing and analysis.

12.0 PHARMACEUTICALS

12.1 Acalabrutinib[50]

Background Information: Note for more detailed and comprehensive background information please refer to the acalabrutinib IB.

Investigational Product Name and Description: Acalabrutinib is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)-imidazo[1,5-α]pyrazin-1-yl)-N-(pyridin-2-yl)-benzamide. Acalabrutinib is a more selective and irreversible small-molecule inhibitor of BTK than ibrutinib, currently under investigation. When formulated, the investigational product is acalabrutinib capsule. Molecular weight: 465.5 g/mole. Acalabrutinib is a white to yellow solid.

BTK in lymphoma and B-cell malignancies: The role of BTK in BCR signaling is well established by the existence of the human genetic immunodeficiency disease X-linked agammaglobulinemia (XLA), and the mouse genetic immunodeficiency disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and NK cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B cells.

Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies. First, expression of a functional BCR is maintained throughout lymphoma progression even as the nonexpressed immunoglobulin heavy chain (IgH) is involved in oncogenic translocations and despite prolonged treatment of tumor cells with anti-idiotype therapy. In addition, selective knockdown of BCR components by RNA interference results in apoptosis in multiple B cell lymphoma cell lines4. The inhibitor ibrutinib in these same studies also promoted apoptosis in these cells.

Ibrutinib (Imbruvica®), a first-generation oral, small-molecule BTK inhibitor has been developed for the treatment of patients with B-cell malignancies and was recently approved in the US for treatment of MCL. While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. For example, ibrutinib inhibits EGFR, while acalabrutinib does not. In addition, ibrutinib is a substrate for CYP3A4/5 and CYP2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

Acalabrutinib is a selective BTK inhibitor with greater selectivity and better physiochemical properties than the BTK inhibitors currently in development. Acerta Pharma, BV is developing acalabrutinib for the treatment of patients with B-cell malignancies. Calquence® has been approved in the US and other markets for the treatment of adult patients with MCL who have received at least one prior therapy, CLL, and SLL.

Toxicology:
Acalabrutinib has been evaluated in Good Laboratory Practice (GLP) repeat-dose general toxicity studies with dosing durations up to 6 months in rats and 9 months in dogs. In vitro and in vivo safety pharmacology and toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. Results from acalabrutinib general toxicity studies show that dose levels ≤100 mg/kg/day are well tolerated in mice and rats, and dose levels ≤30 mg/kg/day are well tolerated in dogs.

In addition, developmental and reproductive toxicity has been evaluated in studies of acalabrutinib in rats and rabbits. No effects of acalabrutinib on fertility, in male rats at exposures 18-times, or in female rats at exposures 16-times the acalabrutinib exposure in patients at the recommended dose of 100 mg twice daily, embryofetal development (EFD) or survival were observed. In an EFD study in rabbits, oral administration of acalabrutinib during the period of organogenesis, at an exposures 4-times the AUC in patients at 100 mg twice daily, produced maternal toxicity and resulted in decreased fetal body weights and delayed skeletal ossification. Acalabrutinib produced no maternal toxicity and no evidence of teratogenicity or fetal development, growth, or survival at an exposure approximately equivalent to the human exposure at the recommended dose. In a prenatal and postnatal development study in rats, oral administration of acalabrutinib from gestation day 6 through lactation day 12, was associated with dystocia (prolonged/difficult labor) at exposures ≥ 4-times the clinical exposure at the recommended dose of 100 mg twice daily.

Please refer to acalabrutinib IB for additional details.

Pharmacokinetics:
Acalabrutinib has a short PK half-life with a long-lasting pharmacodynamic effect due to covalent binding to BTK. In a first-in-human study in healthy subjects, acalabrutinib plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts (2.5 mg twice daily to 100 mg once daily), and mean half-life ranged from 0.97 to 2.1 hours. Acalabrutinib has an absolute oral bioavailability of 25%, is best taken with water, can be taken with or without food, and does not accumulate in plasma upon repeat-dose administration. Based on population PK analysis, acalabrutinib PK was linear over the 75 to 250 mg dose range. Variability in exposure to acalabrutinib is mainly due to a combination of gastric pH-dependent absorption and predominantly cytochrome P450 (CYP)3A-mediated metabolism.

Clinical Studies:
For information on acalabrutinib clinical experience, please refer to the acalabrutinib IB.

Indication:
Acalabrutinib is a low molecular weight irreversible inhibitor of BTK, which binds covalently to a cysteine residue (Cys481) in the front position of the ATP-binding pocket of BTK. Acerta Pharma, BV is developing acalabrutinib for the treatment of patients with cancer. Calquence® has been approved in the US and other markets for the treatment of adult patients with MCL who have received at least one prior therapy, CLL, and SLL (see Section 2.6).

Formulation, Packaging, and Storage:
Acalabrutinib will be provided in white, high-density polyethylene bottles with induction-sealed liner. Each bottle contains 30 capsules (100 mg of acalabrutinib per capsule). Investigational product should be kept in a secure place under appropriate storage conditions as stated on clinical study label.

Dosage and Administration:
Investigators are prohibited from supplying acalabrutinib to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as sub-investigators on FDA Form 1572. The investigator must ensure that subjects receive acalabrutinib only from personnel who fully understand the procedures for administering the drug.

At any given monthly visit, only enough acalabrutinib for 1 cycle should be dispensed. In cases where there are subject scheduling conflicts, additional doses of acalabrutinib may be given to accommodate visits

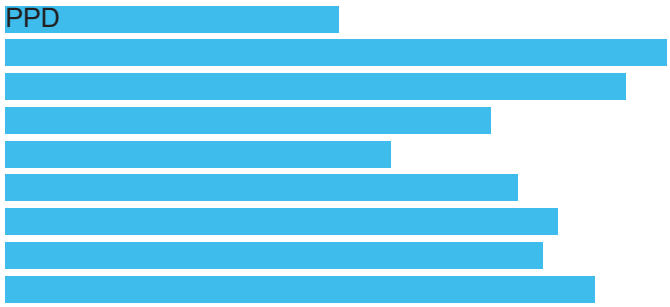
within the 5-day window. At the post 6-month assessment and every additional clinic visit a 3-month supply of study drug will be given. Extra doses of acalabrutinib may be given to accommodate visits within the ±15-day window and must be given from the same batch.

The dose for this study is based on the phase 1 experience with acalabrutinib in CLL described in Section 2.6.4. Acalabrutinib 100 mg twice daily or 200 mg once daily is intended to be administered orally with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Each dose of acalabrutinib should be taken at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time for subjects taking acalabrutinib once daily and up to 3 hours after the scheduled time for subjects taking acalabrutinib twice daily. All subjects should return to the normal schedule the following day. If it has been greater than the allowed time, the dose should not be taken, and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Supply:
The drug product acalabrutinib is manufactured by Acerta Pharma, BV.

Shipping:



Accountability Procedures:
Drug accountability records will be maintained for all clinical supplies. Any empty and partially used vials and clinical trial supplies will be destroyed locally according to the institution's standard operating procedures for drug destruction. The pharmacy will maintain detailed documentation of the number and identification of vials which are destroyed, and copies of these documents will be provided to the sponsor and Acerta Pharma, BV. Disposition of all unused boxes of study drug will be carried out according to instructions provided by the sponsor and/or Acerta Pharma, BV at the end of the study after drug accountability is performed by the study monitor.

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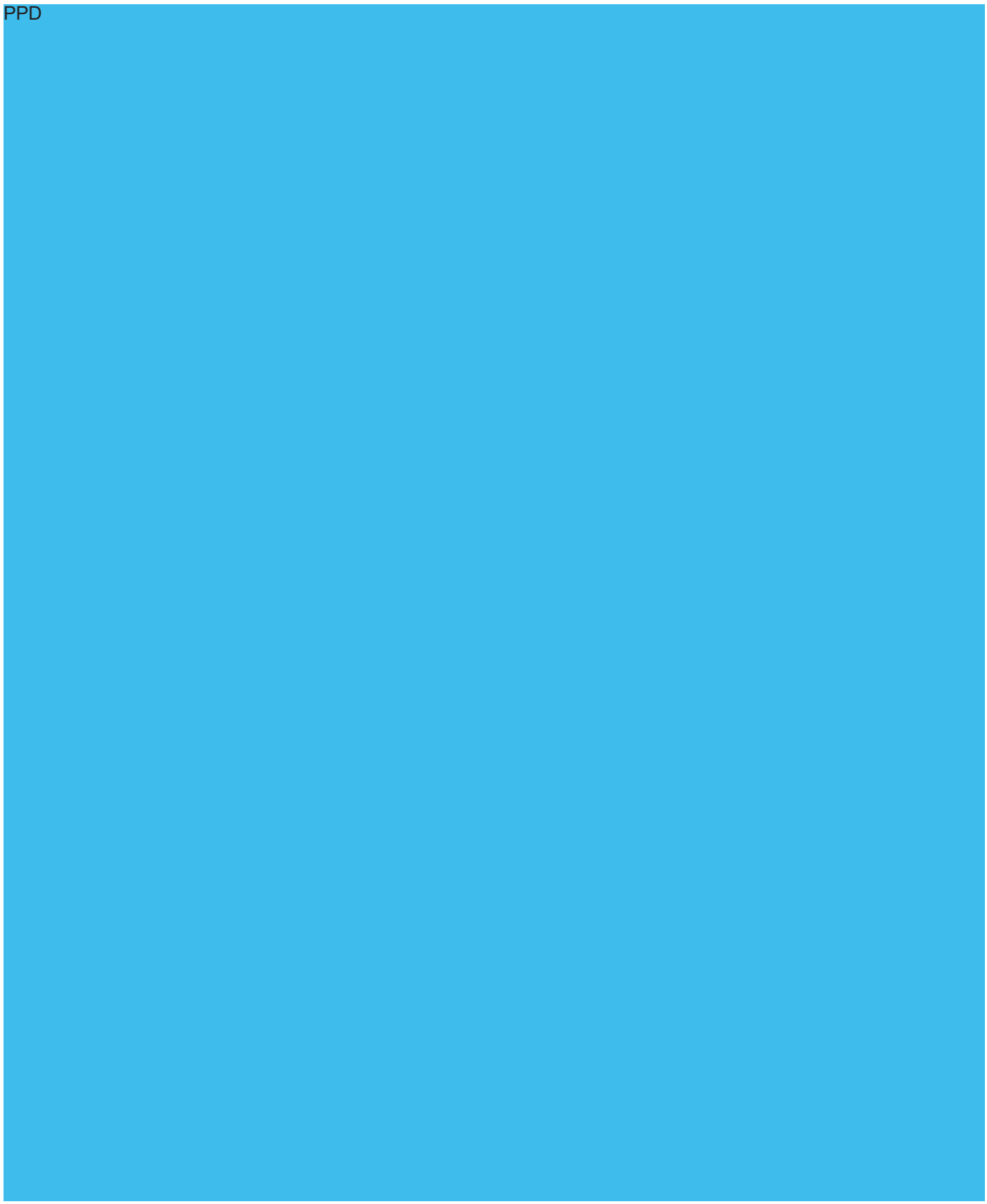
APPENDIX A

PPD

PPD



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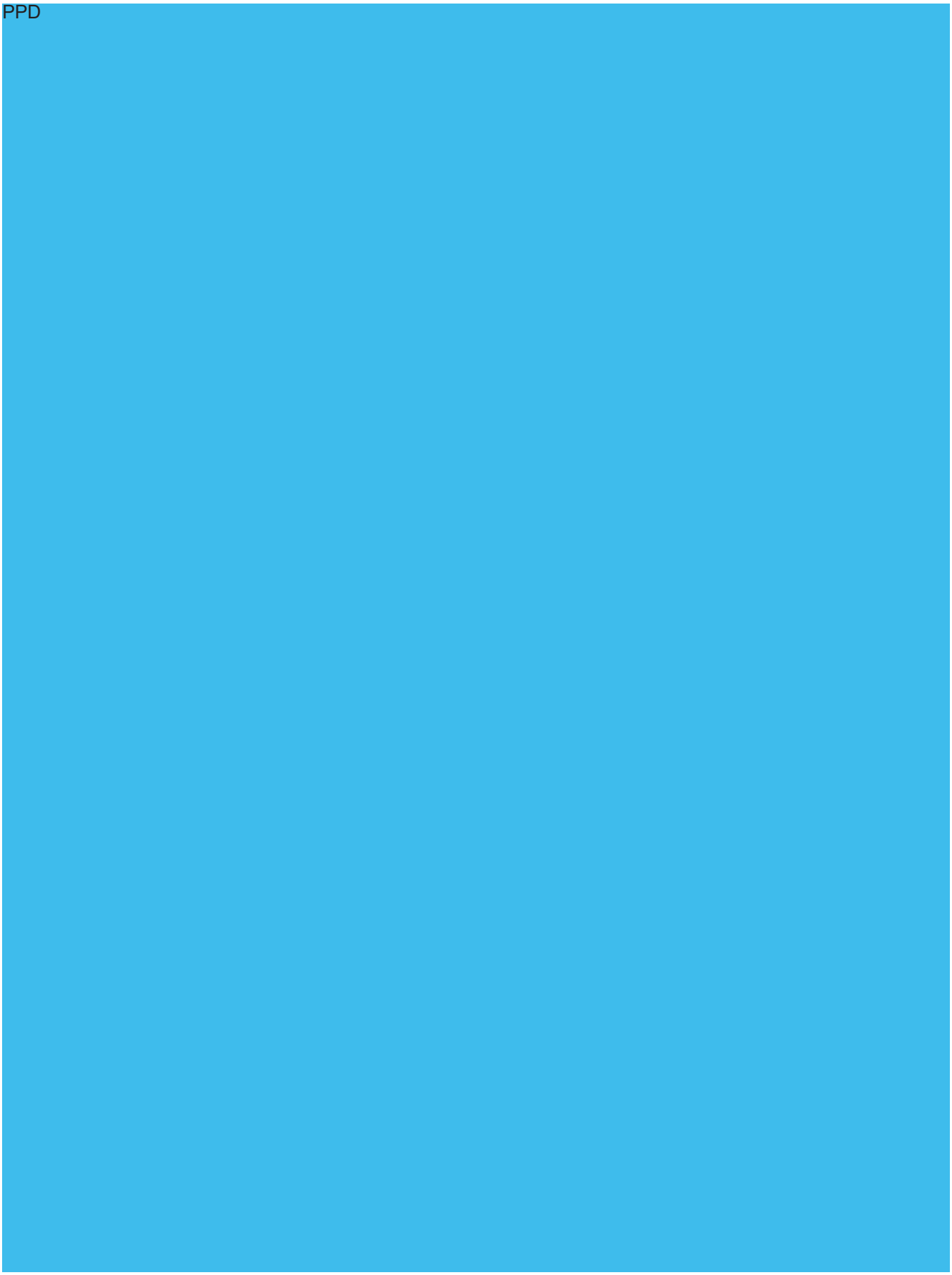
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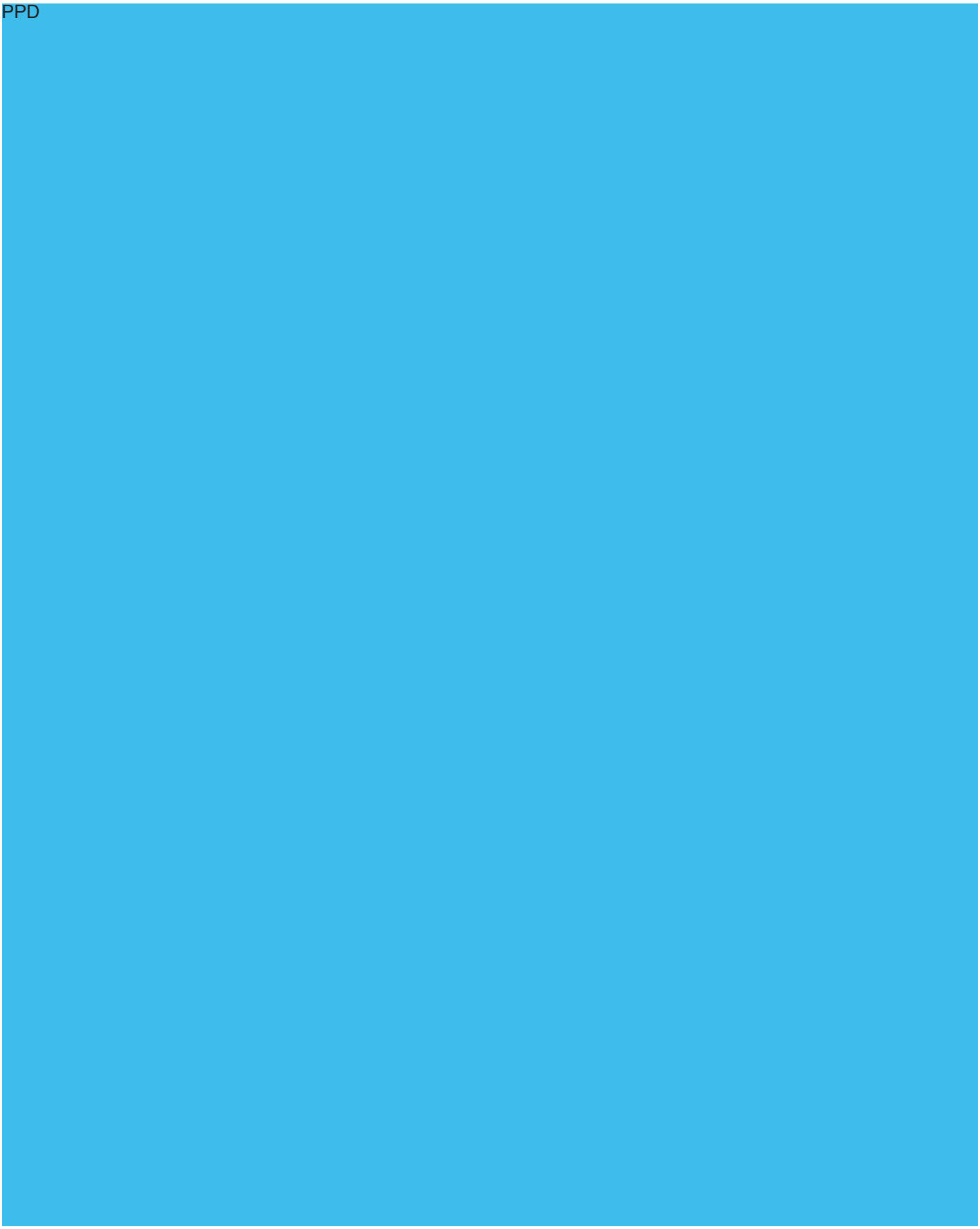
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APPENDIX B

EXAMPLES OF CO-ADMINISTERED DRUGS THAT NEED ADDITIONAL CONSIDERATION

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

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

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

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

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

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

P-gp Inhibitors	BCRP inhibitors	Narrow therapeutic index P-gp substrates
amiodarone	curcumin	digoxin
carvedilol	cyclosporine A	everolimus
clarithromycin	eltrombopag	sirolimus
dronedarone		
itraconazole		
lapatinib		
lopinavir and ritonavir		
propafenone		
quinidine		
ranolazine		
ritonavir		
saquinavir and ritonavir		
telaprevir		
tipranavir and ritonavir		
verapamil		

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

Bile acid sequestrants	Proton pump inhibitors	H2-receptor antagonists
cholestyramine	dexlansoprazole	cimetidine
colestipol	esomeprazole	famotidine
colesevelam	lansoprazole	nizatidine
	omeprazole	ranitidine
	rabeprazole	
	pantoprazole	

Source: FDA Established Pharmacologic Class Text Phrase. Web link accessed 18 July 2018: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm428333.pdf

APPENDIX C

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

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥3 x ULN
- AST ≥3 x ULN

- Total bilirubin ≥2 x ULN

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

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

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

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

- If the answer is **No:**

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

- If the answer is **Yes**:

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

- If there is no significant change, no action is required

- If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE

LABORATORY TESTS

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

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

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

Reference

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