A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL	
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Amendment 2	24 March 2015
Amendment 3	22 July 2015
Amendment 4	27 April 2016
Amendment 5	03 August 2017
Amendment 5.1	06 November 2017
Amendment 6	27 June 2018
Amendment 7	03 April 2020

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Version – Protocol Amendment 7

I have carefully read Protocol ACE-CL-003 entitled "A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, BV, and the institutional review board/independent ethics committee 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

SUMMARY OF AMENDMENT 7

Acerta Pharma, BV, amended this protocol (Protocol Amendment 7) to update text to be consistent with the updated Investigator Brochure, including adding rollover study language, updating reproductive toxicity language, updating risks and contraindications of each study drug, updating drug interaction language, and others. The amendment also clarified the discontinuation of acalabrutinib is based on minimal residual disease and clinical response and removed the restart of treatment for subjects in treatment-free follow-up. The protocol was also updated to add PK analysis (predose and 2 hours postdose) in Cohorts 3 and 4 in subjects who had not previously participated in PK analysis.

The substantive changes that were made as part of Protocol Amendment 7 are as follows:

Change	Rationale
Protocol Title Page Updated medical monitor.	Change in medical monitor.
Study Schema Updated criteria for acalabrutinib discontinuation for all cohorts. Removed restart of acalabrutinib for subjects on treatment-free follow-up.	To clarify criteria regarding discontinuation and restart of acalabrutinib.
Section 2.2.4 Clinical Trial Experience with Acalabrutinib and Dose Justification Updated Calquence® approval language. Added statement that Calquence® has been approved in the US and other markets for the treatment of adult patients with MCL who have received at least 1 prior therapy, CLL, and SLL.	To align with updated Calquence® approval language.
Section 2.2.4 Clinical Trial Experience with Acalabrutinib and Dose Justification Removed clinical trial data and referred the reader to the IB.	To refer the reader to the most recent information.
Section 3.1 Inclusion Criteria Updated guidelines for males for contraception and duration of contraception after the study.	To align with the current IB.
Section 5.1 Acalabrutinib Formulation, Packaging, and Storage Updated recommended storage conditions for acalabrutinib capsules.	To align with the current IB.
Section 5.2.1 Acalabrutinib Administration Added instructions for subjects at risk for TLS.	Updated safety to satisfy French Authority feedback on IB Version 8.1.
Section 6.1.1 Acalabrutinib Plus Obinutuzumab Added "In Cohorts 1 and 2, subjects who achieve a bone marrow MRD-negative CR have the option to discontinue acalabrutinib." Removed the restart of acalabrutinib.	Updated based on investigator feedback.
Section 6.1.2.1 Cohort 3 – Relapsed or Refractory CLL	Updated based on investigator feedback.

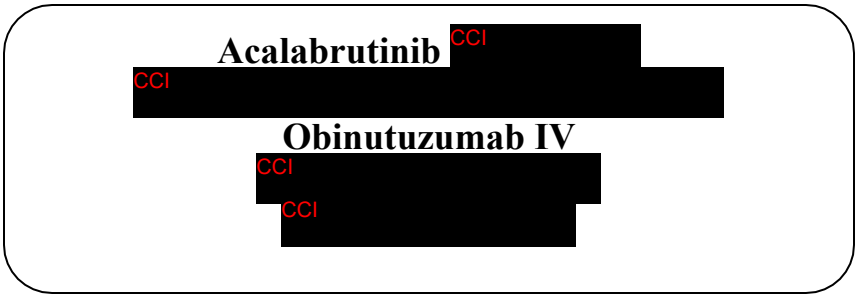
Change	Rationale
Section 6.1.2.2 Cohort 4 – Treatment-naive CLL Updated criteria for subjects who received at least 24 cycles of treatment. Removed restart of acalabrutinib.	
Section 6.3 Concomitant Medications Updated language with regards to antacids, H2-receptor antagonists, proton pump inhibitors, and CYP3A inhibitors and inducers.	To align with current IB.
Section 6.4.1 Risks Associated with Acalabrutinib Updated risks.	To align with current IB.
Section 6.4.2 Contraindications, Warnings, and Precautions For obinutuzumab and venetoclax: Updated to include contraindications, updated warnings and precautions.	To align with current prescribing information.
Section 6.4.2.5 Dietary Restrictions Removed restriction of grapefruit, grapefruit juice, Seville oranges, or Seville orange juice.	To align with current IB.
Section 6.4.3 Reproductive Toxicity Updated definitions of highly effective contraception.	To align with current IB.
Section 6.4.5 Hepatitis B Virus Reactivation Section 6.4.6 Progressive Multifocal Leukoencephalopathy Moved these sections from risks (Section 6.4.1) and updated the recommendations.	To align with current IB.
Section 6.4.7 Elevated Liver Function Tests Added section and referred to new appendix (Appendix 3).	To align with AstraZeneca SOPs.
Section 6.7 Duration of Therapy Updated discontinuation of therapy rules.	To align with other sections of the protocol.
Section 6.7 Duration of Therapy Added rollover study language.	To allow continued access to study drug.
Section 7.1.1 Obinutuzumab Removed information and referred to the GAZYVARO prescribing information.	To refer to the most recent prescribing information.
Section 8 Table 11 Schedule of Assessments: Cohorts 1 and 2 Section 8 Table 12 Schedule of Assessments: Cohorts 3 and 4 Updated ECG footnote to allow ECGs to be obtained as clinically indicated.	To allow for additional monitoring as clinically indicated.

Change	Rationale
Section 8 Table 11 Schedule of Assessments: Cohorts 1 and 2 Updated MRD evaluations from bone marrow to peripheral blood. Clarified that peripheral blood samples will be used to evaluate for MRD every 3 cycles (or at the discretion of the PI), in line with scheduled response assessments, per protocol.	To clarify the MRD evaluations.
Section 8 Table 12 Schedule of Assessments: Cohorts 3 and 4 Updated footnote "A" regarding acalabrutinib discontinuation.	To align with protocol updates.
Section 10.1 Reference Safety Information Added this section.	To refer to the current IB.
Section 10.2 Monitoring of Adverse Events Updated AE reporting language.	To align with updated reporting language.
Section 10.5.1 Second Primary Malignancies Added section to include guidance for reporting second primary malignancies.	Added to include reporting guidance of second primary malignancies.
Section 10.5.2 Adverse Events of Special Interest Added section to include reporting guidance for adverse events of special interest (ventricular arrhythmias) and guidance for treatment containing biologic products regarding suspected transmission of infectious agent.	Added to include adverse events of special interest "ventricular arrhythmias."
Section 13.3 Pharmacokinetics Added PK analysis in Cohorts 3 and 4 for subjects who had not previously participated in PK analysis at predose and 2 hours postdose, relative to acalabrutinib administration.	For collection of additional PK data.
Appendix 1 Known Strong In Vivo Inhibitors and Inducers of CYP3A Updated to current guidelines.	Updated to current guidelines.
Appendix 3 Actions Required in Cases of Increased in Liver Biochemistry and Evaluation of Hy's Law Added section for process to identify and report potential Hy's law and Hy's law cases.	For guidance to the investigator.

STUDY SCHEMA

PHASE 1B DOSE ESCALATION PORTION: OBINUTUZUMAB

- At least 6 subjects with relapsed/refractory chronic lymphocytic leukemia (CLL), then at least 6 subjects with treatment-naive CLL



PHASE 1B EXPANSION PORTION: COHORTS 1 AND 2

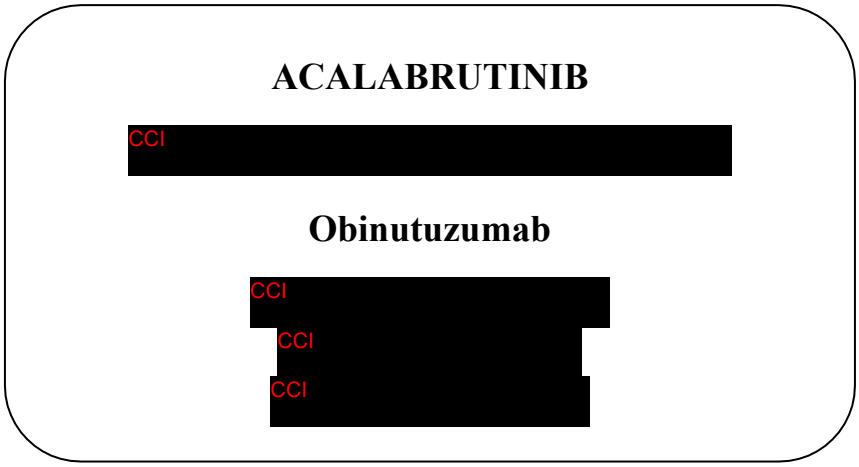
TWO PARALLEL COHORTS WILL BE TREATED IDENTICALLY

COHORT 1:

- Relapsed or refractory disease*

COHORT 2:

- No previous treatment
- 65 years or older OR refuse or are ineligible for approved chemotherapy and/or immunotherapy options



*Samples for pharmacokinetic analysis will be obtained from the first 8 subjects enrolled in the Phase 1b expansion of Cohort 1.

[#] Subjects who achieve bone marrow minimal residual disease (MRD)-negative complete response (CR) have the option to discontinue acalabrutinib.

STUDY SCHEMA (CONTINUED)

PHASE 1B: COHORTS 3 AND 4

Twelve subjects with relapsed/refractory CLL and 12 subjects with treatment-naive CLL

TWO PARALLEL COHORTS WILL BE TREATED

COHORT 3:
- Relapsed or refractory disease*

COHORT 4:
- No previous treatment*

ACALABRUTINIB

CCI

Rituximab

Rituximab

CCI

CCI

ACALABRUTINIB

CCI

Obinutuzumab

Obinutuzumab

CCI

Venetoclax

CCI

* Samples for pharmacokinetic analysis will be obtained from the first 8 subjects enrolled in each of Cohorts 3 and 4.

Discontinuation of acalabrutinib after CCI is possible by investigator decision based on minimal residual disease (MRD) and clinical response (refer to the Schedule of Assessments).

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Abbreviations and Definitions

Abbreviations and definitions of terms

ACD	acid citrate dextrose
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCL	B-cell lymphoma
B-PLL	B-cell prolymphocytic leukemia
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BID	twice daily
BR	bendamustine plus rituximab
BTK	Bruton tyrosine kinase
CBC	complete blood count
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIRS	Cumulative Illness Rating Score
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CR	complete response
CrCl	creatinine clearance
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CYP	cytochrome P450
DCO	data cutoff
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DSMC	Data Safety Monitoring Committee

Abbreviations and definitions of terms

EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediamine tetra-acetic acid
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCLLSG	German CLL Study Group
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's law
HR	hazard ratio
HR-QOL	health-related quality of life
IBM	ideal body mass
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGHV	immunoglobulin heavy-chain variable
IHC	immunohistochemistry
IMP	investigational medical product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
ITK	inducible T-cell kinase
IUD	intrauterine device

Abbreviations and definitions of terms

IV	Intravenous
IVIG	intravenous immunoglobulins
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
CCI	[redacted]
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute-sponsored Working Group
CCI	[redacted]
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PHL	potential Hy's law
PK	pharmacokinetic
PLCG2	phospholipase C gamma 2
PLL	prolymphocytic leukemia
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRL	partial remission (response) with lymphocytosis
QD	once daily
QTc	corrected QT interval
RSI	Reference Safety Information
SAE	serious adverse event
SD	stable disease
SFU	safety follow-up
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction

Abbreviations and definitions of terms

TLS	tumor lysis syndrome
TTNT	time-to-next treatment
ULN	upper limit of normal
US	United States

1 Study Objectives

1.1 Primary Objectives

Cohorts 1 and 2:

- To determine the overall response rate (ORR) at 12 months with the combination of acalabrutinib plus obinutuzumab in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL)
- To determine the ORR at 12 months with the combination of acalabrutinib plus obinutuzumab in subjects with treatment-naive CLL
- To establish the safety and feasibility of the combination of acalabrutinib plus obinutuzumab

Cohorts 3 and 4:

- To establish the safety of the combination of acalabrutinib plus rituximab plus venetoclax in subjects with relapsed or refractory CLL (Cohort 3)
- To establish the safety of the combination of acalabrutinib plus obinutuzumab plus venetoclax in subjects with treatment-naive CLL (Cohort 4)

1.2 Secondary Objectives

- To determine the complete response (CR) rate and minimal residual disease (MRD)-negative CR rate in subjects with previously untreated and relapsed and refractory CLL with these regimens (all cohorts)
- To evaluate the ORR of the combination therapy of acalabrutinib plus venetoclax plus an anti-CD20 antibody at Cycle 16 (Cohorts 3 and 4)
- To determine the time to response, duration of response (DOR), progression-free survival (PFS), time to CR, time-to-next treatment (TTNT), and overall survival (OS) with these regimens (all cohorts)
- To assess for serial development of resistance by baseline and longitudinal assessment of mutations of Bruton tyrosine kinase (BTK) and phospholipase C gamma 2 (PLCG2) at regular follow-up intervals and by examining diagnosis to relapse samples by whole exome sequencing (all cohorts)
- To determine trajectory of psychological and behavioral responses to acalabrutinib and covariation with response to therapy (all cohorts)
- To determine the pharmacokinetics (PK) of orally administered acalabrutinib (all cohorts) and venetoclax (Cohorts 3 and 4)

1.3 Exploratory Objectives

CCI [redacted]

CCI

[redacted]

2 Background and Rationale

2.1 Chronic Lymphocytic Leukemia Background

Chronic lymphocytic leukemia is the most prevalent form of adult leukemia. This disease has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a poor prognosis despite appropriate therapy (Byrd et al. 2004). While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias, and despite the relatively long-life expectancy for early stage disease, CLL remains an incurable disease. Patients diagnosed with or progressing to advanced disease have a mean survival of 18 months to 3 years. Unfortunately, these patients with advanced disease are also more refractory to conventional therapy.

The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past (O'Brien et al. 1995), randomized trials have demonstrated a higher response rate and longer PFS with fludarabine (Rai et al. 2000, Johnson et al. 1996, Leporrier et al. 2001) and subsequently with fludarabine- and cyclophosphamide-based combinations (Catovsky et al. 2007, Eichhorst et al. 2006, Flinn et al. 2007). At the same time, the chimeric anti-CD20 monoclonal antibody rituximab was introduced for the treatment of CLL. At high doses (O'Brien et al. 2001) or with dose-intensive treatment (Byrd et al. 2001), single-agent rituximab has shown efficacy; however, CRs and extended remissions are very rare. The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine (Byrd et al. 2003), or fludarabine and cyclophosphamide (Wierda et al. 2005), which have produced high CR rates and extended PFS compared with historical controls. A large randomized clinical trial reported by the German CLL Study Group (GCLLSG) has shown a benefit of the addition of antibody therapy with rituximab to fludarabine and cyclophosphamide in the prolongation of PFS and OS in patients with untreated CLL (Hallek et al. 2010, Byrd et al. 2005). This encouraging progress in therapy and our understanding of the disease has resulted in significantly improved response rates and PFS. However, significant improvements in OS and ultimately cure, remain elusive goals.

While fludarabine-based chemoimmunotherapy is standard for younger patients, the therapy for older patients is less well defined. In the large Phase 2 and 3 trials outlined previously, median ages were typically in the early 60s, while the average age of patients diagnosed with CLL is 72, which calls into question whether these results are generalizable to the entire CLL population. In fact, the 1 randomized Phase 3 trial investigating primary CLL therapy in older patients

(Eichhorst et al. 2009) demonstrated that in patients ≥65 years old, fludarabine is not superior to chlorambucil. This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which not only demonstrated again that fludarabine is not superior to chlorambucil in older patients, but also showed that the addition of rituximab to chemotherapy was beneficial regardless of age (Woyach et al. 2013). Two studies have evaluated the combination of rituximab with chlorambucil, showing that this combination is safe and moderately effective (Foa et al. 2010, Hillmen et al. 2010).

The Type II glycoengineered CD20 monoclonal antibody obinutuzumab was introduced. In a Phase 1 trial of previously treated CLL as monotherapy, this antibody has a 62% response rate including 1 MRD-negative CR, suggesting that alone this antibody may be more active in CLL than rituximab (Morschhauser et al. 2009). The GCLLSG recently completed a Phase 3 trial of rituximab plus chlorambucil or obinutuzumab plus chlorambucil versus chlorambucil alone in patients with untreated CLL and significant comorbidities. In this population, obinutuzumab plus chlorambucil (but not rituximab plus chlorambucil) improved OS over chlorambucil alone (hazard ratio [HR]: 0.41, p=0.002), and obinutuzumab plus chlorambucil improved PFS over rituximab plus chlorambucil (median PFS: 26.7 months vs 14.9 months, p<0.001) (Goede et al. 2014). Based on these favorable data, the combination of obinutuzumab plus chlorambucil is Food and Drug Administration (FDA)-approved as frontline therapy for CLL patients.

Many older patients are also treated with the combination of bendamustine plus rituximab (BR). Although BR has not been compared directly with chlorambucil plus rituximab, results of a recent Phase 2 trial show an ORR of 88% with a median event-free survival of 33.9 months and 90.5% OS at 27 months. These results held for patients ≥70 years old and compare favorably with results published for chlorambucil plus rituximab (Fischer et al. 2012). While results with this regimen appear to be improved over historical controls, outcomes are not as good as those observed in younger patients with chemoimmunotherapy. Therefore, the optimal therapy for older patients remains an unmet need in clinical trials.

Additionally, most patients eventually relapse and are frequently refractory to existing agents. Patients who relapse after combined chemoimmunotherapy have a poor outcome with subsequent standard therapies. While options for these patients include alemtuzumab, bendamustine, high-dose corticosteroids, ofatumumab, and combination-based approaches, none of these therapies produces durable remissions that exceed that observed with first-line chemoimmunotherapy. Several of these therapies, including alemtuzumab and high-dose steroids, are also associated with significant toxicities and sustained immunosuppression (Bergmann et al. 2005, Bowen et al. 2007, Castro et al. 2008, Coiffier et al. 2008, Keating et al. 2002, Lozanski et al. 2004, Osuji et al. 2005, Thornton et al. 2003, Thornton et al. 1999, Tsimberidou et al. 2008).

A breakthrough in CLL treatment occurred with the approval of ibrutinib, an inhibitor of BTK, which is a key signaling pathway of the B-cell receptor (BCR). In an ongoing Phase 1b/2 study,

ibrutinib has shown extraordinary activity in patients with relapsed or refractory CLL. In patients with relapsed or refractory CLL and measurable lymphadenopathy, the rate of lymph node shrinkage >50% is 89%. With a median follow-up of 4 months, ORR was 48% due to asymptomatic lymphocytosis (Byrd et al. 2011), and with longer follow-up of 26 months in patients receiving the 420-mg dose, has improved to 71%, with an additional 20% of patients achieving a partial remission (response) with lymphocytosis (PRL) (Byrd et al. 2013). Lymphocytosis with ibrutinib is observed within 1 to 2 weeks of starting therapy, reaches a plateau within the first 2 to 3 cycles, and resolves over time; the duration does not appear to be related to the depth of response or response duration (Woyach et al. 2014). Response to ibrutinib occurs independently of high-risk genomic features including immunoglobulin heavy-chain variable (IGHV) mutational status and del(17p13.1). Responses to this drug have been durable as well, with an estimated 26-month PFS of 76% and OS of 83% for these relapsed and refractory patients (Byrd et al. 2013). This study also included a cohort of 31 previously untreated patients. With 16.6 months of follow-up, ORR is 71%, with an additional 10% of patients having persistent lymphocytosis; estimated 22-month PFS is 96% (Byrd et al. 2012).

The randomized, open-label, Phase 3 RESONATE-2 trial evaluated the use of ibrutinib versus chlorambucil in 269 treatment-naive subjects with CLL or small lymphocytic lymphoma (SLL) age 65 years or older. The ORR was 82.4% versus 35.3% $p<0.0001$ ibrutinib versus chlorambucil. Ibrutinib significantly prolonged PFS as determined by an Independent Review Committee (IRC) reducing the risk of disease progression or death by 84% versus chlorambucil (HR: 0.161 [95% confidence interval [CI]: 0.091, 0.283]; median PFS not reached for ibrutinib versus 18.9 months [95% CI: 14.1, 22.0] for chlorambucil (Burger et al. 2015). These studies have led to the approval of this agent in both treatment-naive disease and for the treatment of relapsed CLL. These data with ibrutinib support the potential benefits of selective BTK inhibition in CLL.

While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases (e.g., epidermal growth factor receptor [EGFR]) (Honigberg et al. 2010), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5, which increases the possibility of drug-drug interactions. Finally, the inhibition of interleukin-2-inducible-T-cell-kinase (ITK) that is seen with ibrutinib has the potential to abrogate natural killer (NK) cell antibody-dependent cellular cytotoxicity (ADCC) (Kohrt et al. 2014), which makes combination with monoclonal antibodies less effective. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

Venetoclax, a B-cell lymphoma -2 (BCL-2) inhibitor, received accelerated approved in 2016 for the treatment of patients with CLL with 17p deletion who have received at least 1 prior therapy. The efficacy of venetoclax was established in an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least 1 prior therapy. In the

study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis fluorescence in situ hybridization (FISH) Probe Kit, which is FDA approved for selection of patients for venetoclax treatment. Patients received venetoclax via a CCI schedule starting at CCI Patients continued to receive CCI of venetoclax orally CCI The efficacy of venetoclax was evaluated by ORR as assessed by an IRC using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (Hallek et al. 2008). The median time on treatment at time of evaluation was 12.1 months (range: 0 to 21.5 months). Importantly, the efficacy results revealed an ORR of 80.2%, with a CR/CR with incomplete marrow recovery (Cri) rate of 7.5% (Stilgenbauer et al. 2015).

2.2 Acalabrutinib

2.2.1 Preclinical Data and Pharmacology

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

CCI For additional details, refer to the acalabrutinib Investigator Brochure.

2.2.2 Safety Pharmacology

CCI for detailed information on the safety pharmacology of acalabrutinib, refer to the acalabrutinib Investigator Brochure.

2.2.3 In Vivo Toxicology

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

2.2.4 Clinical Trial Experience with Acalabrutinib and Dose Justification

Calquence® has been approved in the United States (US) and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, CLL, and SLL.

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

CCI [redacted] Therefore, based on PK/PD, safety, and efficacy results of the Phase 1/2 study, acalabrutinib CCI [redacted] will be evaluated in this study. This regimen is expected to provide optimal target coverage with lower exposure levels (i.e., maximum observed drug concentration [C_{max}]) of acalabrutinib to avoid any potential off-target effects from acalabrutinib.

2.3 Obinutuzumab

Obinutuzumab is a humanized monoclonal antibody that has been glycoengineered to produce high affinity type II binding to CD20, which leads to increased ADCC relative to other CD20 antibodies as well as improved direct killing (Mossner et al. 2010). Obinutuzumab is currently FDA approved in combination with chlorambucil as initial therapy in CLL. In single-agent clinical trials with this agent, infusion reactions (mostly Grades 1 and 2) have been the most commonly observed adverse events (AEs). These reactions tend to occur only with the first infusion, and occasionally are associated with signs of tumor lysis syndrome (TLS). In combination with chlorambucil, Grades 3 and 4 thrombocytopenia and neutropenia have also been observed (in 12% and 34% of patients, respectively), and there have been documented cases of hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML) associated with this agent.

In combination with chemotherapy (fludarabine/chlorambucil or bendamustine), administration of obinutuzumab appears to be tolerable, and does not appear to induce added toxicity over that of chemotherapy itself (Brown et al. 2013).

As described in Section 2.1, a Phase 3 clinical trial by the GCLLSG (CLL 11) was completed comparing obinutuzumab in combination with chlorambucil to rituximab in combination with chlorambucil in terms of PFS and ORR in patients with CLL and comorbidities (Cumulative Illness Rating Score [CIRS] >6 or a creatinine clearance [CrCl] of 30 to 69 mL/minute). The median PFS, as confirmed by the IRC, was 26.7 months in the obinutuzumab plus chlorambucil arm as compared with 14.9 months with rituximab in combination with chlorambucil (HR=0.42;

95% CI: 0.33-0.54; p<0.0001) (GAZYVARO® Summary of Product Characteristics). Importantly, the combination of obinutuzumab and chlorambucil achieved a statistically significant improvement in the MRD-negative rate in the bone marrow of 19.5% of subjects, whereas only 2.6% of the subjects in the rituximab plus chlorambucil arm achieved MRD-negative status in the bone marrow (p<0.001) (Goede et al. 2014). This Phase 3 study has established the combination of obinutuzumab with chlorambucil as an acceptable standard of care in patients for whom fludarabine-based chemoimmunotherapy is not an acceptable option (National Comprehensive Cancer Network Guidelines version 2.2015). The most frequent Grade 3 or higher AEs with obinutuzumab in combination with chlorambucil are: neutropenia 35%, infusion related reaction 21%, thrombocytopenia 11%, and infections 2%.

2.4 Rituximab

Rituximab has been shown to be an effective treatment for CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab binds to CD20, a hydrophobic, transmembrane protein that is present on pre–B cells and mature B cells and in ≥90% of B-cell non-Hodgkin lymphomas (NHLs). Rituximab exerts its cytotoxic effects via complement-mediated B-cell lysis, ADCC, and induction of apoptosis (Cartron et al. 2004).

In the US, rituximab has been approved by the FDA for the treatment of CLL. The European Medicines Agency (EMA) granted an approval for the use of rituximab in combination with chemotherapy for previously untreated CLL. The FDA approved the use of rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated and previously treated CD20-positive CLL.

Rituximab is also being investigated in combination with venetoclax. The Murano Study (NCT02005471) is an open-label, multicenter, randomized, Phase 3 study to investigate the efficacy and safety of venetoclax in combination with rituximab compared with bendamustine in combination with rituximab in participants with relapsed or refractory CLL. The rationale for the combination of venetoclax with rituximab is partially based on the possible improved tolerability of rituximab in a generally older population (Eichhorst et al. 2016).

Results from the Phase 1b M13-365 study showed combining venetoclax with rituximab led to objective responses in 86% of patients with relapsed/refractory CLL. The most frequently reported grade 3/4 AEs were neutropenia (53%), thrombocytopenia (16%), anemia (14%), febrile neutropenia (12%), and leukopenia (12%). Nonhematologic toxicities were common but generally mild, the most common being gastrointestinal (GI) toxicity.

2.5 Venetoclax

Venetoclax is a BCL-2 inhibitor indicated for the treatment of patients with CLL with 17p deletion, as detected by an FDA-approved test, who have received at least 1 prior therapy. Venetoclax is currently FDA approved for use as a single-agent therapy.

The safety of single agent venetoclax at the CCI recommended CCI following a dose ramp-up schedule is based on pooled data of 240 patients with previously treated CLL from 2 Phase 2 trials and 1 Phase 1 trial. The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Serious adverse reactions were reported in 43.8% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and TLS.

2.6 Combination Therapy with a BTK Inhibitor Plus CD20 Monoclonal Antibody

The combination of a BTK inhibitor with a CD20 monoclonal antibody is appealing because the rapid clearing of peripheral lymphocytosis that is seen with antibodies is expected to increase the rapidity of response with BTK inhibitors. Additionally, in the laboratory BTK inhibition antagonizes the tumor microenvironment (Herman et al. 2011), which may increase the bone marrow clearance, which is limited with rituximab.

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

One, a Phase 1b/2 study of ibrutinib CCI administered continuously until time of relapse and ofatumumab has enrolled 3 time-sequential cohorts. In the first cohort of 27 patients, ibrutinib begins on CCI and continues until disease progression, while ofatumumab begins at CCI All 27 patients completed the first month of therapy without a dose-limiting toxicity (DLT). Of the 24 patients with CLL, all attained a partial response (PR) (100%) with 23 remaining on treatment and 1 proceeding to a nonmyeloablative stem cell transplant. Infusion toxicities with ofatumumab were more modest than expected. Cohorts administering ofatumumab either concurrently or prior to ibrutinib have also been completed where feasibility was confirmed, but either early toxicity (concurrent schedule) or early progression (ofatumumab first arm) has resulted in choosing the run-in arm with ibrutinib for CCI followed by addition of ofatumumab for future study.

In another Phase 2 trial performed at MD Anderson Cancer Center, which enrolled only patients with high-risk disease, rituximab and ibrutinib were administered concurrently beginning in CCI with CCI rituximab and then CCI administration for a total of

CCI In this trial, toxicities were modest, and responses were again seen at an earlier time point than expected from single-agent therapy (Burger et al. 2012).

A third study, a Phase 3 trial of BR versus ibrutinib versus ibrutinib plus rituximab is currently accruing patients (A041202). Overall, experience with different administration sequences suggests that a run-in with BTK inhibitor for the CCI followed by initiation of antibody beginning CCI may be better tolerated, and in vivo pharmacodynamic studies support target modulation that would enhance tumor apoptosis.

While combinations of ibrutinib with CD20 monoclonal antibodies are currently being pursued, laboratory data suggests that ibrutinib may not be the best BTK inhibitor for this. Our group has determined that besides inhibition of BTK, the homology between BTK and ITK leads to this drug functioning as an irreversible ITK inhibitor in vitro and in vivo in patients receiving this therapy (Dubovsky et al. 2013). While inhibiting ITK in T-cells may have benefit to diminish Th2 immune suppression, it has been shown in vitro to negatively impact NK-cell ADCC, thereby reducing the benefit of adding antibodies (Kluter et al. 2010). In addition, loss of ITK has been associated with fatal Epstein-Barr Virus (EBV) lymphoproliferative disorders, which have rarely been observed in patients receiving ibrutinib (Huck et al. 2009, Linka et al. 2012, Mansouri et al. 2012).

2.7 Combination Treatment with a BTK Inhibitor Plus BCL-2 Inhibitor

Ibrutinib induces remissions in the majority of treated patients, but CR is uncommon even after prolonged administration. Early genetic studies have demonstrated that BCL-2 over-expression rescues BTK deficient XID murine B-cells from spontaneous apoptosis (Woodland et al. 1996). As such, combination therapy is being investigated clinically to determine whether the responses can be deepened.

A Phase 2 trial (NCT02756897) of venetoclax and ibrutinib in patients with relapsed/refractory CLL is underway at MD Anderson Cancer Center assessing the rate of CR or PR; or CRi. Treatment-naive patients with high-risk disease (e.g., 17p deletion, mutated TP53) are also eligible.

A Phase 1b/2 study (NCT02427451) of obinutuzumab, ibrutinib, and venetoclax in relapsed/refractory CLL is also underway at The Ohio State University. Obinutuzumab, ibrutinib, and venetoclax were started CCI Responses were assessed according to IWCLL 2008 criteria, including bone marrow biopsy with 4-color immunophenotyping of marrow and peripheral blood for MRD, after Cycles 8 and 14. The Phase 1b portion of the study established venetoclax CCI as the recommended Phase 2 dose in this combination with no observed DLTs. Accrual to Phase 2 relapsed/refractory (n=25) and treatment-naive (n=25) CLL cohorts continues (Jones et al. 2016). A prospective, open-label, multicenter Phase 2 trial (NCT02758665) of ibrutinib plus venetoclax plus

obinutuzumab in physically fit (CIRS ≤6 and normal CrCl) and unfit (CIRS >6 and CrCl ≥50 mL/min) patients with previously untreated CLL with TP53 deletion (17p-) and/or mutation is also underway (ClinicalTrials.gov, U.S. National Institutes of Health 2017).

2.8 Justification for a Trial Combining Acalabrutinib with Obinutuzumab/Rituximab with Venetoclax

BTK inhibition is currently transforming the treatment of CLL. While patients appear to be having durable responses, very few responses are CR, which suggests that drug discontinuation will not be an option. The combination of BTK inhibition with CD20 antibody therapy is appealing to both expedite and potentially deepen these remissions. Of the CD20 antibodies available, obinutuzumab in combination with chemotherapy may be the most effective in the treatment of CLL and has shown the potential to induce complete and even MRD-negative responses (Goede et al. 2014). Rituximab has been shown to be better tolerated in older patients than obinutuzumab and has likewise demonstrated the potential for complete and MRD-negative responses in combination with venetoclax (Eichhorst et al. 2016). While ibrutinib is a BTK inhibitor with robust efficacy and safety data, the effect of ibrutinib on ITK has important implications for combining ibrutinib with CD20 antibodies, and justifies exploration of more selective BTK inhibitors, such as acalabrutinib, to optimize the addition of CD20 monoclonal antibodies to BTK inhibitor therapy. This Phase 1b trial therefore seeks to optimize the clinical efficacy and rates of MRD negativity of BTK inhibitor plus CD20 antibody therapy and venetoclax by exploring these combination therapies. With the approval of venetoclax and its possible synergistic effect with BTK inhibition and an anti-CD20 antibody, this study will further assess the safety of the combination with acalabrutinib, rituximab, and venetoclax in relapsed/refractory CLL subjects and acalabrutinib, obinutuzumab, and venetoclax in treatment-naive CLL subjects.

3 Patient Eligibility Criteria

3.1 Inclusion Criteria

1. Subjects with a diagnosis of intermediate or high risk CLL (or variant immunophenotype), SLL, or B-cell prolymphocytic leukemia (B-PLL) by IWCLL 2008 criteria (Hallek et al. 2008) who have:
   - Cohorts 1 and 3: Previously received at least 1 therapy for their disease (Cohort 3 enrollment limited to CLL).
   - Cohort 2: Previously untreated disease and ≥65 years old OR under 65 years old and refuse or are ineligible for chemoimmunotherapy.
   - Cohort 4: Previously untreated disease; Cohort 4 enrollment limited to CLL.

2. Subjects in Cohorts 1 and 3 may have received previous ibrutinib (or another BTK inhibitor) as long as discontinuation was for a reason other than on-treatment disease progression.
3. All subjects must satisfy one of the following criteria for active disease requiring therapy:
   - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to AIHA or thrombocytopenia)
   - Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
   - Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
   - Constitutional symptoms, which include any of the following:
     - Unintentional weight loss of 10% or more within 6 months
     - Significant fatigue limiting activity
     - Fevers ≥100.5°F for 2 weeks or more without evidence of infection
     - Night sweats >1 month without evidence of infection
4. This criterion was removed with Amendment 5.
5. Subjects with a history of Richter's syndrome are eligible if they now have evidence of CLL only, with <10% large cells in the bone marrow.
6. Subjects must have adequate organ function, defined as creatinine ≤2.5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x ULN, and bilirubin ≤2.5 x ULN. For Cohorts 3 and 4, subjects must have creatinine clearance ≥50 mL/min using modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of mass):
7. IBM (kg) = [(height cm – 154) ● 0.9] + (50 if male, 45.5 if female).
8. Platelets ≥50 x 10^9/L. In subjects with CLL involvement of the marrow, ≥30 x 10^9/L for Cohorts 1 and 2. For Cohorts 3 and 4, subjects must have hemoglobin >9 g/dL.
9. Absolute neutrophil count (ANC) ≥750/mm^3. In subjects with CLL involvement of the marrow, ANC ≥500/mm^3. For Cohorts 3 and 4, subjects must have ANC ≥1000/mm^3.
10. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
11. Subject must not have secondary cancers that result in a life expectancy of <2 years or that would confound assessment of toxicity in this study.
12. Subjects must be ≥18 years of age.
13. Subject must provide written informed consent. A signed copy of the consent form will be retained in the subject's chart.

14. Subject must be able to receive outpatient treatment and follow-up at the treating institution.

15. Subject must have completed all CLL therapies ≥4 weeks prior to first study dose. Palliative steroids are allowed but must be at a dose equivalent of ≤20 mg prednisone daily for at least 1 week prior to treatment initiation.

16. Women who are sexually active and can bear children must agree to use highly effective forms of contraception while on the study and for 2 days after the last dose of acalabrutinib, 30 days after the last dose of venetoclax, 12 months the last dose of rituximab, or 18 months after the last dose of obinutuzumab, whichever is the longest period following the subject's study drug discontinuation. Men who are sexually active and able to have children must agree to use highly effective methods of contraception during the study and use a barrier method (condom; even if the subject had a vasectomy) for 2 days after the last dose of acalabrutinib, 18 months after the last dose of obinutuzumab, or 12 months after the last dose of rituximab, or 30 days after the last dose of venetoclax, whichever is longer. Highly effective forms of contraception are defined in Section 6.4.3. Additionally, men must agree to refrain from sperm donation during the study and for 18 months after the last dose of obinutuzumab, or 12 months after the last dose of rituximab, or 30 days after the last dose of venetoclax, whichever is longer.

17. Subjects must be able to swallow whole capsules.

18. Inclusion of women and minorities: Subjects of both genders and all racial/ethnic groups are eligible for the study if they meet eligibility criteria outlined. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared with another. The small number of subjects in a Phase 1b trial precludes any analysis of data to compare subject subgroups based on gender or race/ethnicity.

3.2 Exclusion Criteria

1. For Cohorts 2 and 4, received previous therapy for CLL. Treatment of autoimmune complications of CLL with steroids or rituximab is allowed, however, CD20 must have returned on 10% of the CLL cells if rituximab was recently administered. Palliative steroids are acceptable at doses ≤20 mg prednisone equivalent daily.

2. Any life-threatening illness, medical condition, or organ dysfunction, which in the investigator's opinion, could compromise the subjects' safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.

3. Female subjects who are pregnant or breastfeeding.

4. Subjects with active cardiovascular disease not medically controlled or those who have had myocardial infarction in the past 6 months, or corrected QT interval (QTc) ≥480 ms.

5. Malabsorption syndrome, disease significantly affecting GI function, or resection of the stomach or small bowel or gastric bypass, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

6. Grade ≥2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
7. Major surgery within 4 weeks before first dose of study drug.
8. History of a bleeding diathesis (e.g., hemophilia, Von Willebrand disease).
9. Uncontrolled AIHA or idiopathic thrombocytopenia purpura.
10. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
11. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 28 days of first dose of study drug.
12. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
13. Subjects with active infections requiring intravenous (IV) antibiotic/antiviral therapy are not eligible for entry onto the study until resolution of the infection. Subjects on prophylactic antibiotics or antivirals are acceptable.
14. Subjects with history of or ongoing drug-induced pneumonitis.
15. Subjects with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
16. Serologic status reflecting active hepatitis B or C infection.
    a. Subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HBsAg) negative will need to have a negative hepatitis B DNA result by polymerase chain reaction (PCR) before randomization. Those who are HBsAg-positive and/or hepatitis B PCR positive will be excluded.
    b. Subjects receiving prophylactic intravenous immunoglobulin (IVIG) may have positive hepatitis serologies. Subjects who are on IVIG who have positive hepatitis serologies must have a negative hepatitis B DNA to be eligible.
    c. Subjects with a history of HBV infection but negative HBV serologies at screening must also have a negative HBV PCR to be eligible.
    d. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA during screening. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR positive will be excluded. No further testing beyond screening is necessary if PCR results are negative. However, in the setting of rising transaminase and/or bilirubin levels, HCV PCR testing should be performed when clinically indicated.
17. Subjects with substance abuse or other medical or psychiatric conditions that, in the opinion of the investigator, would confound study interpretation or affect the subject's ability to tolerate or complete the study.

18. Subjects cannot concurrently participate in another therapeutic clinical trial.
19. Subject who have received a live virus vaccination within 1 month of starting study drug.

4 Registration of Patients

4.1 Informed Consent

The subject must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required. Written informed consent will be obtained by a co-investigator or a specific designee previously approved by The Ohio State University Institutional Review Board (IRB), using forms approved by the IRB.

4.2 Registration Procedure

The study will be conducted at 1 site in the US. The principal investigator/scientific protocol chairman will serve as the liaison with Acerta and will coordinate protocol management. Subjects will undergo an initial assessment to determine eligibility and to determine baseline disease status prior to study enrollment. Subjects will be registered through the database of The Ohio State University Clinical Trials Office and provide written informed consent. All subjects for whom questions arise relative to eligibility for the study should be discussed with the medical monitor prior to entry onto the study.

To ensure timely communication of treatment tolerance, the progress of each subject will be discussed with the principal investigator on a monthly basis, or as needed, with any AEs being promptly communicated to the principal investigator by the treating physician or designee to ensure safe treatment of other subjects in the study.

5 Study Drugs and Administration Guidelines

5.1 Acalabrutinib Formulation, Packaging, and Storage

Acalabrutinib drug substance and drug product are manufactured according to cGMP and will be provided to the investigational site by Acerta Pharma, BV, or a designee in hard gelatin capsules intended for oral administration. Each capsule contains CCI [redacted]

Acalabrutinib will be provided in white, high-density polyethylene bottles.

Labels for study drug bottles will meet all applicable requirements of the US FDA, Annex 13 of cGMP (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable. Each bottle is closed with a white, continuous-thread, child-resistant, polypropylene screw cap.

Bottles containing acalabrutinib will be shipped and stored at room temperature (approximately 15°C to 30°C). The recommended storage condition for acalabrutinib capsules is below 30°C.

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

5.2 Drug Preparation and Administration

5.2.1 Acalabrutinib Administration

Acalabrutinib is intended to be administered orally [redacted] The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Acalabrutinib can be taken with or without food. For Cohorts 3 and 4, venetoclax should be given first, followed at least 30 minutes later by acalabrutinib. Anti-CD20 antibody (i.e., rituximab or obinutuzumab) should be administered last, at least 1 hour after acalabrutinib.

In this study, acalabrutinib is to be administered [redacted] Note: Any subjects enrolled on the prior versions of the protocol were switched from acalabrutinib [redacted] as of Protocol Amendment 4.

It is recommended that acalabrutinib be taken as close to the scheduled time as possible (preferably within ±1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been greater than 3 hours, the dose should not be taken, and the subject should take the next dose at the next scheduled time.

Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses. Compliance will be assessed at every visit. Subjects will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 15.7. Returned capsules must not be redispensed to the same subject or to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

For subjects considered at risk for TLS, administer appropriate hydration and allopurinol or rasburicase per institutional standards prior to initiating treatment.

5.3 Dose Delays

Any clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the medical monitor.

- **Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms.**

Transient worsening of disease during temporary interruption of study therapy (e.g., for intercurrent illness, drug-related toxicity, or surgery) may also not indicate definitive disease progression. In these instances, relevant clinical, laboratory, and/or radiographic assessment should be attempted to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the time point at which progression was first objectively documented.

Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor. For full study treatment discontinuation criteria, refer to Section 11.

5.3.1 Obinutuzumab Administration

Obinutuzumab will be obtained commercially as a standard therapy for CLL. Complete details on recommended premedications are provided in the prescribing information.

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose. Obinutuzumab will be administered in a single day, with the exception of the first administration when subjects will receive their first dose of obinutuzumab over [redacted]. For subjects treated at [redacted] obinutuzumab), [redacted] will be given on [redacted] and [redacted] on [redacted]

Table 1: Dose of Obinutuzumab to be Administered During [redacted], Each of [redacted] Duration

Day of Treatment Cycle	Dose of Obinutuzumab	Rate of Infusion (in the absence of infusion reactions/ hypersensitivity during previous infusions)
[redacted]		

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

Obinutuzumab should be administered via IV infusion through a dedicated line. Do not administer as an IV push or bolus. Administration of obinutuzumab should occur at least 1 hour after the acalabrutinib dose on days of concomitant dosing.

5.3.2 Venetoclax Administration

Venetoclax will either be obtained commercially, if available, or be supplied by Acerta. Preparation and administration are per prescribing information.

Assess subject-specific factors for level of risk of TLS and provide prophylactic hydration and antihyperuricemics to subjects prior to first dose of venetoclax to reduce risk of TLS (see Dosage and Administration and Warnings and Precautions in the venetoclax prescribing information).

Administer the venetoclax dose according to a [redacted] to the recommended [redacted] as shown in Table 2. The [redacted] dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS. Venetoclax should be given first, followed at least 30 minutes later by acalabrutinib.

Instruct subjects to take venetoclax tablets with a meal and water at approximately the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Table 2: Dosing Schedule for CCI Phase of Venetoclax Dosing

Week	Venetoclax CCI Dose
CCI	

5.3.3 Rituximab Administration

Rituximab will be obtained commercially as a standard therapy for CLL. Preparation and administration are per prescribing information. Complete details on recommended premedications are provided in the prescribing information.

The rituximab regimen will be CCI Administration of rituximab should occur CCI the acalabrutinib dose on days of concomitant dosing.

5.3.4 Drug Supply Records

Accurate accounting of all study medication must be maintained. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

6 Treatment Plan

6.1 Overview

6.1.1 Acalabrutinib Plus Obinutuzumab

In the Phase 1b dose-escalation portion of the study, 2 cohorts (Cohort 1, relapsed/refractory and Cohort 2, treatment-naive) will be evaluated with slightly staggered enrollment. First, 6 subjects with relapsed/refractory CLL will be enrolled into Cohort 1. Once the safety has been evaluated, the relapsed/refractory cohort will be expanded to 26 subjects and enrollment of 6 treatment-naive subjects can begin in Cohort 2. Once safety is established for Cohort 2, then the cohort will be expanded to 19 subjects (Phase 1b expansion portion).

Each cycle will be CCI

Acalabrutinib will be administered starting CCI and will be administered CCI until disease progression.

Obinutuzumab will be given in the standard dosing fashion starting on [redacted] On [redacted] subjects will receive [redacted] IV. On [redacted] subjects will receive [redacted] On [redacted] subjects will receive [redacted] IV. On [redacted] subjects will receive [redacted] of each cycle. For subjects treated at [redacted] will be given on [redacted] and [redacted] on [redacted] On [redacted] subjects will receive [redacted] IV and during [redacted] subjects will receive [redacted] on [redacted] of each cycle.

It is acceptable for cycles to begin [redacted] of a new cycle. For example, if the treatment due date is a [redacted] New cycles can be started up to [redacted] the protocol-defined date for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled). Documentation to justify a delay or advance of a cycle should be provided.

In Cohorts 1 and 2, subjects who achieve a bone marrow MRD-negative CR have the option to discontinue acalabrutinib.

6.1.2 Acalabrutinib Plus Venetoclax plus Rituximab or Obinutuzumab

In the acalabrutinib plus venetoclax plus rituximab or obinutuzumab Phase 1b portion of the study, 12 subjects with relapsed/refractory CLL and 12 subjects with treatment-naive CLL will be enrolled into Cohorts 3 and 4, respectively. Subjects in Cohort 3 will be treated with acalabrutinib, rituximab, and venetoclax. Subjects in Cohort 4 will be treated with acalabrutinib, obinutuzumab, and venetoclax. Based on the safety observed with the combination of ibrutinib, venetoclax, and obinutuzumab in an ongoing study (Jones et al. 2016), safety will be reviewed for the first 3 subjects who complete Cycle 3 in each cohort. The review will be repeated for additional subjects if needed. Unless a safety concern is identified (e.g., dose delays [redacted] enrollment in Cohorts 3 and 4 will continue during the safety review until the desired number of subjects is reached. There are no DLTs defined for this portion of the study. See Section 5 for study drugs and administration guidelines.

6.1.2.1 Cohort 3 – Relapsed or Refractory CLL

Acalabrutinib will be administered starting [redacted] until disease progression. Subjects who received at least [redacted] of treatment and achieved CR, CRi, and/or MRD negativity may have therapy discontinued at investigator discretion.

Rituximab will be given at a starting dose of [redacted] followed by [redacted]

Venetoclax will be given in the standard dosing fashion starting on [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] Beginning with [redacted] subjects will receive [redacted] orally [redacted] until the completion of [redacted] (Table 2).

Each cycle will be [redacted]

It is acceptable for cycles to begin [redacted] of a new cycle. For example, if the treatment due date is a [redacted] New cycles can be started up to [redacted] the protocol-defined date for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled). Documentation to justify a delay or advance of a cycle should be provided.

6.1.2.2 Cohort 4 – Treatment-naive CLL

Acalabrutinib will be administered starting [redacted] until disease progression. Subjects who received at least [redacted] of treatment and achieved CR, CRi, and/or MRD negativity may have therapy discontinued at investigator discretion.

Obinutuzumab will be given in the standard dosing fashion starting on [redacted] On [redacted] subjects will receive [redacted] IV. On [redacted] subjects will receive [redacted] On [redacted] subjects will receive [redacted] IV. On [redacted] subjects will receive [redacted] of each cycle. There will be a total of [redacted] obinutuzumab infusions through the end of [redacted] For subjects treated at [redacted] will be given on [redacted] and [redacted] on [redacted] On [redacted] subjects will receive [redacted] IV and during [redacted] subjects will receive [redacted] on [redacted] of each cycle.

Venetoclax will be given in the standard dosing fashion starting on [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] On [redacted] subjects will receive [redacted] orally [redacted] for [redacted] Beginning with [redacted] subjects will receive [redacted] orally [redacted] until the completion of [redacted] (see Table 2).

Each cycle will be [redacted]

It is acceptable for cycles to begin [redacted] of a new cycle. For example, if the treatment due date is a [redacted] New cycles can be started up to [redacted] the protocol-defined date for

major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled). Documentation to justify a delay or advance of a cycle should be provided.

6.2 Premedications

6.2.1 Premedication for Acalabrutinib

No premedication is required for acalabrutinib administration.

6.2.2 Premedication for Obinutuzumab

Thirty to 60 minutes prior to the first dose of obinutuzumab, subjects may receive:

- Acetaminophen 650 mg orally
- Diphenhydramine 50 mg IV; this may be reduced or discontinued by the treating physician if it is not tolerated due to side effects.
- Dexamethasone 20 mg IV

Premedication may continue for all subsequent doses of obinutuzumab at the discretion of the investigator, but diphenhydramine and dexamethasone may be discontinued in subjects who do not experience an infusion reaction after 2 doses. Refer to the prescribing information.

6.2.3 Premedication for Venetoclax

Venetoclax can cause rapid reduction in tumors and thus poses a risk for TLS in the initial [redacted] phase. Changes in blood chemistries consistent with TLS requiring prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Perform tumor burden assessments, including radiographic evaluation (e.g., computed tomography [CT] scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all subjects and correct pre-existing abnormalities prior to initiation of treatment with venetoclax. A repeat CT scan may be performed at Cycle 2, Day 21 (±3 days) in subjects at high risk of TLS, at investigator's discretion. Reduced renal function (CrCl <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases [see VENCLEXTA™ prescribing information: Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].

Table 3 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment based on tumor burden determination from clinical trial data. All subject co-morbidities should be considered before final determination of prophylaxis and monitoring schedule.

Table 3: Recommended Tumor Lysis Syndrome Prophylaxis for Venetoclax Based on Tumor Burden from Clinical Trial Data

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Antihyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x 10^9/L	Oral (1.5 to 2 L)	Allopurinol[b]	Outpatient • Predose, 6 to 8 hours, 24 hours at first dose of CCI and CCI • Predose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x 10^9/L	Oral (1.5 to 2 L) and consider additional intravenous	Allopurinol	Outpatient • Predose, 6 to 8 hours, 24 hours at first dose of CCI and CCI • Predose at subsequent ramp-up doses • Consider hospitalization for subjects with CrCl <80 mL/min at first dose of CCI and CCI see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x 10^9/L AND any LN ≥5 cm	Oral (1.5 to 2 L) and intravenous (150 to 200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of CCI and CCI • Predose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Predose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node; TLS = tumor lysis syndrome
[a] Administer intravenous hydration for any subject who cannot tolerate oral hydration.
[b] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[c] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine), review in real time.
[d] For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

6.2.4 Premedication for Rituximab

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

6.3 Concomitant Medications

All concomitant medications (including over-the-counter medications and herbal preparations) must be recorded in the subject's chart. There are no required concomitant medications on this study.

Avoid co-administration of strong CYP3A inhibitors with acalabrutinib. Alternatively, if the inhibitor will be used short term, interrupt acalabrutinib. When acalabrutinib is administered

with moderate CYP3A inhibitors, reduce acalabrutinib dose to CCI [redacted] Avoid co-administration of strong CYP3A inducers with acalabrutinib. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to CCI [redacted] A list of inhibitors/inducers of CYP3A can be found in Appendix 1.

Separate dosing of acalabrutinib with antacids by at least 2 hours. Acalabrutinib should be taken 2 hours before an H2-receptor antagonist. Avoid co-administration with proton pump inhibitors.

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and area under the plasma concentration-time curve [AUC]) and may increase the risk for TLS at initiation and during ramp-up phase [see VENCLEXTA prescribing information, Contraindications (4)]. For subjects who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when strong CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of venetoclax with moderate CYP3A inhibitors or P-gp inhibitors. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. Monitor these subjects more closely for signs of toxicities [see prescribing information, Dosage and Administration (2.4)]. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor [see VENCLEXTA prescribing information, Dosage and Administration (2.4) and Drug Interactions (7.1)].

At the systemic exposure levels expected in this study, venetoclax inhibition of CYP metabolism is not anticipated.

The following is a list of permitted and prohibited medications:

Permitted

- Allopurinol at a dose of up to 300 mg daily is recommended for subjects at high risk TLS and should begin at least 3 days prior to the start of protocol therapy.
- Rasburicase is permitted at the discretion of the investigator if clinical suspicion for TLS is very high, or if TLS occurs.
- IVIG at standard doses for prophylaxis of recurrent infections
- Anti-emetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms.
- Prophylactic antivirals are permitted at the discretion of the treating physician.
- Prophylactic filgrastim or pegfilgrastim is not permitted before the first dose of medications but may be administered in subjects who experience Grade 3 or 4 neutropenia per American Society of Clinical Oncology (ASCO) guidelines.

- Transfusions of packed red blood cells or platelets are permitted at the discretion of the investigator. All transfusions should be leukopore filtered and irradiated.

Prohibited

- Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited if being used to treat the disease initially under study.
- Short course use of steroids (≤2 weeks) >20 mg/day is permitted for premedication use, or to manage infusion related reactions or to manage other inflammatory reactions, such as asthma exacerbations. High-dose corticosteroids used to treat the underlying CLL are not allowed on study. Localized, short courses of radiotherapy are allowed for the treatment of lesions unrelated to the disease under study, if approved by the medical monitor. Should a subject develop a second primary malignancy while on trial, continuation on trial medication after curative treatment of the second primary malignancy may be considered after discussion with the medical monitor.
- Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited.
- For subjects in Cohorts 3 and 4, use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of venetoclax is prohibited. Concomitant use of strong inhibitors of CYP3A during venetoclax ramp-up phase is contraindicated.

6.4 Risks Associated with Study Treatment

6.4.1 Risks Associated with Acalabrutinib Treatment

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

6.4.1.1 Hemorrhage

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

The mechanism for hemorrhage is not well understood. Patients 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 necessary.

6.4.1.2 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).

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Section 6.4.5 and Section 7.2.2.2 for additional information and monitoring guidance for viral hepatitis and Section 6.4.6 and Section 7.2.2.2 for additional information and management guidance for signs and symptoms of PML.

6.4.1.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the Schedule of Assessments and as medically appropriate. Please refer to Section 7 for study drug modification guidance.

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

6.4.1.4 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. Please refer to Section 10.5.1 for second primary malignancy reporting guidance.

6.4.1.5 Atrial Fibrillation

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

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

6.4.2 Contraindications, Warnings, and Precautions

For study drugs other than acalabrutinib, please refer to the respective US prescribing information.

6.4.2.1 Obinutuzumab

Contraindications

Obinutuzumab is contraindicated in subjects with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use.

Warnings and Precautions

- Infusion-related Reactions: IRR were the most frequently observed adverse drug reactions in subjects receiving obinutuzumab and occurred predominantly during infusion of the first CCI IRR may be related to cytokine release syndrome, which has also been reported in obinutuzumab-treated subjects. In the majority of subjects, IRRs were mild to moderate and could be managed by slowing or temporary halting of the first infusion, but severe and life-threatening IRRs have also been reported. Mitigation measures to reduce IRRs should be followed (see local prescribing information and Section 7.2.2).

Patients must not receive further obinutuzumab infusions if they experience:

- Acute life-threatening respiratory symptoms,
- Grade 4 (i.e., life-threatening) IRR or,
- Second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Subjects who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and post-infusion period. Since hypotension may occur, withholding of antihypertensive treatments should be considered for 12 hours before and throughout each obinutuzumab infusion and for the first hour after administration.

- Hypersensitivity Reactions: Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g., serum sickness) have been reported in subjects treated with obinutuzumab and may be difficult to clinically distinguish from IRRs. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped, and treatment permanently discontinued. Subjects with known hypersensitivity to obinutuzumab are not eligible for enrollment in this study.
- Tumor Lysis Syndrome: TLS has been reported with obinutuzumab. Subjects who are considered to be at risk of TLS (e.g., subjects with a high tumor burden and/or a high circulating lymphocyte count [>25 x 109/L] and/or renal impairment [CrCl <70 mL/min]) should receive prophylaxis as described in the obinutuzumab prescribing information. Mitigation measures to reduce risk of TLS should be followed (see local prescribing information and Section 7.1.1).
- Neutropenia: Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Refer to Section 7.1.1 and local

prescribing information for dose modification and discontinuation guidance. Supportive measures for any signs of infection should be considered. Subjects with renal impairment (CrCl <50 mL/min) are more at risk of neutropenia.

- Thrombocytopenia: Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in Cycle 1 in subjects treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established.
- Worsening of Pre-existing Cardiac Conditions: Worsening of pre-existing cardiac conditions has been reported with obinutuzumab. In subjects with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction, and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore, subjects with a history of cardiac disease should be monitored closely.
- Infections, Including HBV and PML: Obinutuzumab should not be administered in the presence of an active infection, and caution should be exercised when considering the use of obinutuzumab in subjects with a history of recurring or chronic infections. Fatal infections have been reported.

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in subjects treated with anti-CD20 antibodies including obinutuzumab. Refer to Section 6.4.5 for additional information and monitoring guidance for viral hepatitis.

PML has been reported in subjects treated with obinutuzumab. Refer to Section 6.4.6 for additional information and management guidance for signs and symptoms of PML.

Obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML.

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

6.4.2.2 Venetoclax

Contraindications

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated.

Warnings and Precautions

- TLS: TLS, including fatal events and renal-failure requiring dialysis, has occurred in previously treated patients with CLL and high tumor burden when treated with venetoclax. Mitigation measures to reduce risk of TLS should be followed (see venetoclax prescribing information and Section 5.3.2).

- Drug interactions, including CYP3A: Although the risk of TLS is a continuum based on multiple factors, concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and at the dose titration phase. Inhibitors of P-gp or breast cancer resistance protein (BCRP) may also increase venetoclax exposure. Additional information on venetoclax drug interactions is provided in Section 6.3, and dose modification information is provided in Section 7.1.2.
- Neutropenia: Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax. Refer to Section 7.1.2 for local prescribing information for dose modification and discontinuation guidance. Supportive measures for any signs of infection should be considered.
- Immunization: Do not administer live attenuated vaccines prior to, during, or after venetoclax treatment until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied.
- Embryofetal toxicity: Based on its mechanism of action and findings in animals, venetoclax may cause embryofetal harm when administered to a pregnant woman. Refer to Section 6.4.3 for additional reproductive toxicity information and contraception guidance.

6.4.2.3 Rituximab

- TLS: Administer aggressive IV hydration, antihyperuricemic agents, and monitor renal function.
- Infections: Withhold rituximab and institute appropriate anti-infective therapy.
- Cardiac arrhythmias and angina: Discontinue infusions in case of serious or life-threatening events.
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms.
- Live virus vaccines: Do not administer live virus vaccines prior to or during rituximab.
- Cytopenias: Monitor blood counts at regular intervals.
- Infusion reactions: Rituximab administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue rituximab infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion reactions.
- Severe mucocutaneous reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab.
- HBV reactivation: HBV reactivation can occur in patients treated with rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients

for HBV infection before treatment initiation and monitor patients during and after treatment with rituximab. Discontinue rituximab and concomitant medications in the event of HBV reactivation. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug, have antiviral therapy instituted, and have a consultation with a physician with expertise in managing hepatitis B. Patients who are anti-HBc positive may receive prophylactic antiviral agents while undergoing CLL therapy, per institutional guidelines.

- PML, including fatal PML, can occur in patients receiving rituximab.

6.4.2.4 Immunizations

Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax, obinutuzumab, or rituximab until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Advise subjects that vaccinations may be less effective.

Based on nonclinical data, no changes are recommended to standard of care practices with regard to vaccinations in subjects treated with acalabrutinib. As appropriate, vaccines consistent with standard practices for specific subject populations (e.g., patients with CLL) should be used.

6.4.2.5 Dietary Restrictions

As acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St. John's wort, which is a potent CYP3A inducer). These restrictions also apply to venetoclax.

6.4.3 Reproductive Toxicity

Definition of women of nonreproductive potential:

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

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

OR

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

OR

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

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

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

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

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatment as the subject's preferred and usual lifestyle.

Period abstinence (e.g., calendar, ovulation, symptom-thermal, and post-ovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together as an effective method of contraception.

Please refer to the acalabrutinib Investigator Brochure for information on reproductive toxicity studies.

Obinutuzumab is likely to cause fetal B cell depletion, although there are no data from the use of obinutuzumab in pregnant women to inform a drug-associated risk.

There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving rituximab and for 12 months following treatment. Rituximab is a pregnancy class C drug.

There are no available human data on the use of venetoclax in pregnant women. Based on toxicity observed in mice, venetoclax may cause fetal harm when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure

based on AUC at the recommended human dose of [redacted] If venetoclax is used during pregnancy or if the patient becomes pregnant while taking venetoclax, the subject should be apprised of the potential risk to a fetus.

Women who are sexually active and can bear children (see definition above) must agree to use highly effective forms of contraception during the study and 30 days after the last dose of venetoclax, 2 days after the last dose of acalabrutinib, 12 months after the last dose of rituximab, or 18 months after the last dose of obinutuzumab, whichever is the longest period following the subject's study drug discontinuation. Men who are sexually active and are able to have children must agree to use highly effective forms of contraception and use a barrier method (condom, even if the subject had a vasectomy) during the study and for 18 months after the last dose of obinutuzumab, or 12 months after the last dose of rituximab, or 30 days after the last dose of venetoclax, whichever is longer. Men must also refrain from donating sperm during the study and for 18 months after the last dose of obinutuzumab, or 12 months after the last dose of rituximab, or 30 days after the last dose of venetoclax, whichever is longer.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab, whichever is longer. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. 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 in the same manner as any serious adverse event (SAE). All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab (whichever is longer) will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

6.4.4 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 electronic case report form (eCRF).

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

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

Subjects who experience an overdose of venetoclax should be closely monitored and provided appropriate supportive treatment. During the ramp-up phase, interrupt venetoclax and monitor carefully for signs and symptoms of TLS along with other toxicities. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

6.4.5 Hepatitis B Virus Reactivation

Cases of HBV reactivation have been reported in patients treated with acalabrutinib with one case resulting in liver failure and death. Any subject with a rising viral load (above lower limit of detection: approximately 10 IU/mL) should discontinue study treatment, have antiviral therapy instituted, and have a consultation with a physician with expertise in managing hepatitis B. Patients who are anti-HBc positive may receive prophylactic antiviral agents while undergoing CLL therapy, per institutional guidelines.

Refer to the Schedule of Activities for frequency and duration of HBV monitoring.

6.4.6 Progressive Multifocal Leukoencephalopathy

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

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

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

If PML is confirmed, permanently discontinue acalabrutinib.

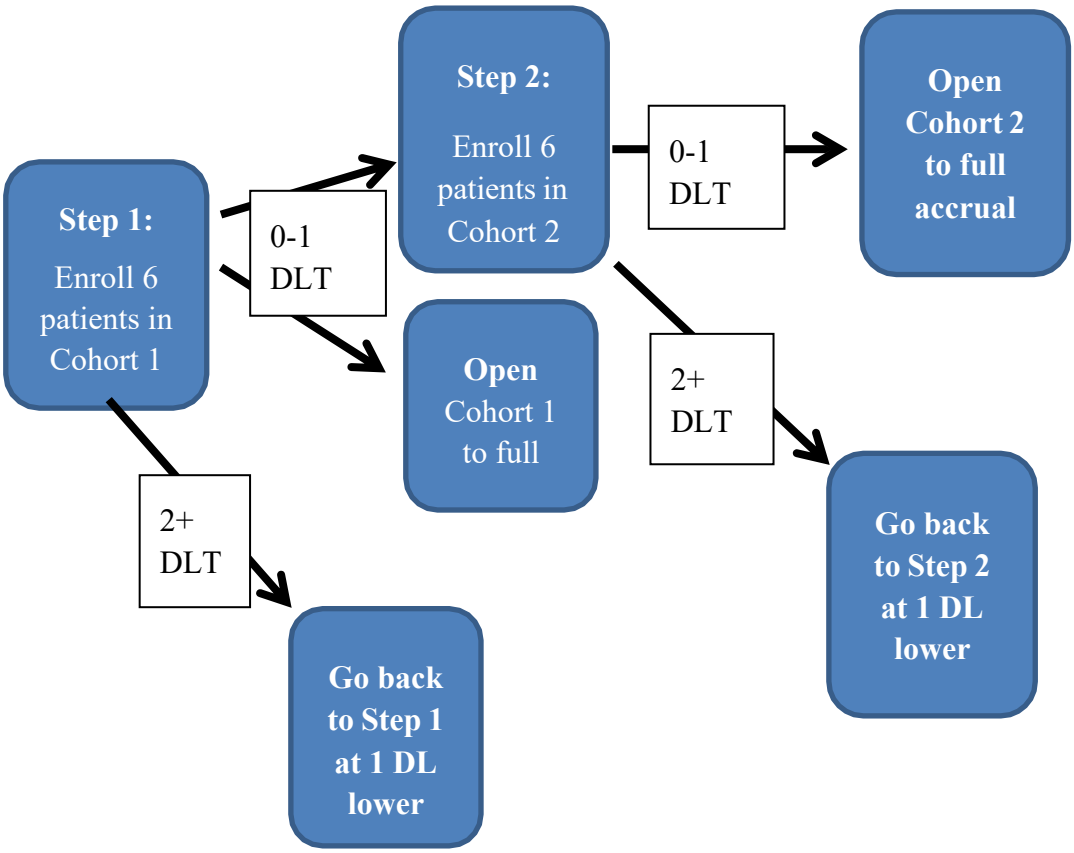
6.4.7 Elevated Liver Function Tests

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. The process to be followed in identifying and reporting cases of PHL and HL is summarized in Appendix 3.

6.5 Phase 1b Dose Escalation Portion

Figure 1 depicts the dose escalation schema Cohorts 1 and 2 of this study.

Figure 1: Phase 1b Dose Escalation Schema for Cohorts 1 and 2



As this combination has not previously been evaluated in a clinical trial, a toxicity assessment will occur after the first 6 subjects with relapsed/refractory CLL have been accrued to dose level 1. At this time, accrual will be held until all subjects are followed for 8 weeks (2 cycles). Toxicities will then be reviewed by the principal investigator. If, during this time, there is ≤1 DLT (outlined below), Phase 1b expansion will begin for Cohort 1. If more toxicity than expected is observed and there are 2 or more DLTs in this group, the next 3 to 6 subjects will be

accrued at CCI [redacted] and this group will be monitored until all have completed CCI [redacted] of therapy. If there are 2 or more DLTs in this group, 3 to 6 subjects will be accrued at CCI [redacted] The highest dose level at which less than 2/6 subjects experience DLT will be the recommended Phase 1b expansion dose. Once the Phase 1b dose-escalation portion is complete for Cohort 1 and dose level is established, this cohort will open to full accrual and Cohort 2 will open enrollment for 6 subjects at the recommended Phase 1b expansion dose for Cohort 1. A safety analysis for Cohort 2 will be performed after the first 6 subjects are followed for at least 8 weeks (2 cycles). The Acerta Review Committee will discuss the data in conjunction with the principal investigator and, once safety is established in this cohort, Cohort 2 will open for full Phase 1b expansion.

Dose-limiting toxicity will be defined as the following toxicities related to protocol therapy during the first CCI [redacted] of therapy:

- ≥ Grade 3 nonhematologic toxicity lasting for ≥7 days
- ≥ Grade 3 prolongation of the QTc interval
- Grade 4 neutropenia (ANC <500/μL) lasting ≥7 days after discontinuation of therapy without growth factors or lasting ≥5 days after discontinuation of therapy while on growth factors in subjects with pre-treatment ANC ≥1 x 10^9/L
- ≥ Grade 3 febrile neutropenia
- Grade 4 thrombocytopenia (platelet count <20,000/μL) lasting ≥7 days after discontinuation of therapy or requiring transfusion in subjects with pretreatment platelet count >50,000/μL.
- Dose delay due to toxicity for >14 consecutive days

Prior to amending dosing from CCI [redacted] the 6 subjects in the relapsed/refractory disease cohort had been enrolled. Since the new dose is the same daily dose of acalabrutinib, the previously accrued safety cohort can still be used to evaluate toxicity of the combination.

Table 4: Dose Levels for Phase 1b Dose Escalation Portion for Cohorts 1 and 2

Dose level	Acalabrutinib	Obinutuzumab
CCI		

6.6 Phase 1b Expansion Portion for Cohorts 1 and 2

For both Cohort 1 and Cohort 2, after 6 subjects have been treated in the Phase 1b dose-escalation portion and followed for 8 weeks (2 cycles) with ≤1 DLT in Cohort 1 and satisfactory safety observed in Cohort 2, this dose level will be considered the recommended Phase 1b expansion dose and that cohort of the study will open to full accrual.

6.7 Duration of Therapy

For Cohorts 1 and 2, acalabrutinib treatment can continue until the end of study for subjects without disease progression and who are tolerating therapy. The end of study is defined as 36 cycles after the last subject is enrolled to allow for long term follow-up beyond 36 cycles.

For Cohorts 3 and 4, protocol therapy with obinutuzumab or rituximab will continue for up to CCI (until the end of CCI in responding subjects. Subjects will discontinue venetoclax at the end of CCI Treatment with acalabrutinib is continued until evidence of disease progression, toxicity, or end of study, whichever occurs first. Acalabrutinib; however, can be discontinued by investigator decision after CCI in subjects with CR/CRi and/or negative MRD.

CCI In Cohorts 1 and 2, subjects who achieve a bone marrow MRD-negative CR have the option to discontinue acalabrutinib.

Subjects who are still on treatment at the end of study and deriving clinical benefit from acalabrutinib monotherapy may continue treatment. At the time of the final data cutoff (DCO)

and database closure, subjects who remain in the study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study will be considered closed. There will be no further data collection other than reporting of SAEs per Section 10.5. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

See Section 7 for dose modifications and Section 11 for criteria for removal from the study.

7 Dose Adjustments and Modifications

7.1 Subject Monitoring and Dose Modifications

7.1.1 Obinutuzumab

Please refer to the GAZYVARO prescribing information for subject monitoring during infusion and management of infusion reactions.

7.1.1.1 Obinutuzumab Dose Modification and Discontinuation

Refer to Section 7.2 for dose adjustments for toxicities relating to obinutuzumab.

7.1.2 Venetoclax

Venetoclax Dose Modifications Based on Toxicities

Please refer to the VENCLEXTA® prescribing information for recommendations regarding dose modifications for toxicity and Section 7.1.2 and Section 7.2.

7.1.3 Rituximab

7.1.3.1 Subject Monitoring During Infusion

Refer to RITUXAN® prescribing information.

7.1.3.2 Management of Infusion Reactions with Rituximab

Management of infusion reactions are per RITUXAN® prescribing information and Section 7.2.2.1.

7.1.3.3 Rituximab Dose Modification and Discontinuation

Dose modification of rituximab is not recommended; please refer to the RITUXAN® prescribing information and Section 7.1.2 and Section 7.2 for details. If rituximab is discontinued, subjects can continue acalabrutinib and venetoclax as outlined in the protocol. If acalabrutinib or venetoclax is discontinued, a subject may continue to receive rituximab up to the maximum number of infusions as outlined in the protocol.

The US Prescribing Information for rituximab will serve as Reference Safety Information (RSI) for this study to facilitate determination of expectedness or unexpectedness of AEs possibly associated with rituximab.

7.2 Dose Adjustment and Management of Toxicity for Phase 1b After CCI and Phase 1b Expansion Phase, and Phase 1b Venetoclax Cohorts

This section describes management of hematologic and nonhematologic toxicities for subjects in the Phase 1b dose-escalation portion after CCI subjects in Cohorts 1 and 2 in the Phase 1b expansion portion. This section also describes management of hematologic and nonhematologic toxicities in the Phase 1b portion wherein venetoclax is added during CCI (Cohorts 3 and 4).

7.2.1 Dose Adjustments for Hematologic Toxicity

7.2.1.1 Cohorts 1 and 2

Hematologic toxicity will be graded according to the IWCLL 2008 guidelines (Hallek et al. 2008).

Table 5: IWCLL 2008 Grading for Hematologic Toxicity

Grade	Decrease in Platelets[a] or HGB[b] from Pretreatment Value	Absolute Neutrophil Count (µL)[c]
1	11% to 24%	≥1500 and <2000
2	25% to 49%	≥1000 and <1500
3	50% to 75%	≥500 and <1000
4	≥75%	<500

[a] Platelet counts must be below normal levels for any grade toxicity to be recorded. If platelet count is <20 x 10^{12}/L, this will be considered Grade 4 toxicity.
[b] Hgb levels must be below normal levels for any grade toxicity to be recorded.
[c] If ANC is <1000 prior to study, the patient is not evaluable for toxicity assessment based on ANC.

During Cycle 1, laboratory parameters will be monitored according to the Schedule of Assessments and will be used in the evaluation of hematologic toxicities. Beginning Cycle 8, laboratory parameters will be monitored monthly and used in the evaluation of hematologic toxicities. If subjects experience Grade ≥3 hematologic toxicity, febrile neutropenia, or significant bleeding attributable to study drug, acalabrutinib should be held until toxicity resolves to ≤ Grade 1 or to baseline. For the first occurrence, acalabrutinib may be restarted at the same dose level CCI however, for the second occurrence acalabrutinib should be restarted at CCI

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) may not be used prophylactically but may be used at the treating physician's

discretion in subjects with neutropenia related to obinutuzumab or acalabrutinib who are otherwise tolerating therapy and responding well.

Table 6: Dose Adjustments During CCI CCI Phase 1b Expansion Subjects Only During CCI All Subjects During CCI

Dose Level	Acalabrutinib Dose	Obinutuzumab Dose
CCI		

For any Grade ≥3 hematologic toxicity, febrile neutropenia, or clinically significant bleeding attributable to study drug, obinutuzumab and acalabrutinib should be held and complete blood count (CBC) monitored weekly. When toxicity resolves to ≤ Grade 1 or to baseline, study drugs should be resumed with 1 dose level reduction (obinutuzumab to restart at the next cycle). If subjects are stable at a reduced dose level for CCI dose escalation can occur by 1 dose level.

7.2.1.2 Cohorts 3 and 4

During Cycle 1, laboratory parameters will be monitored weekly and will be used in the evaluation of hematologic toxicities. Beginning Cycle 4, laboratory parameters will be monitored on Day 1 of each cycle, while on Cycle 7 results will be monitored Day 1 every 3 cycles. Results will be used in the evaluation of hematologic toxicities.

If subjects experience Grade ≥3 hematologic toxicity, febrile neutropenia, or significant bleeding attributable to study treatment within Cycles 1 and 2, acalabrutinib should be held until toxicity resolves to ≤ Grade 1 or to baseline. For the first occurrence, acalabrutinib may be restarted at the same dose level CCI however, for the second occurrence acalabrutinib should be restarted at CCI

After start of venetoclax in CCI for any Grade ≥3 hematologic toxicity, febrile neutropenia, or clinically significant bleeding attributable to study treatment, recommendations regarding dose interruptions or modifications should be applied to venetoclax first. Recommendations are provided in the current prescribing information for venetoclax (please refer to Table 9 for venetoclax dose reduction guidelines). Consider discontinuing venetoclax for subjects who require dose reductions to less than CCI for more than CCI

If subjects continue to experience Grade ≥3 hematologic toxicity, febrile neutropenia, or significant bleeding, please follow the recommendations for acalabrutinib as noted for CCI [redacted]

G-CSF and GM-CSF may not be used prophylactically but may be used at the treating physician's discretion in subjects with neutropenia related to obinutuzumab, rituximab, venetoclax, or acalabrutinib who are otherwise tolerating therapy and responding well.

Missed doses of either drug should not be made up.

7.2.2 Dose Adjustments for Specific Nonhematologic Toxicities

7.2.2.1 Infusion Reactions with Obinutuzumab or Rituximab

Manage as in Section 7.1.1. Subjects with Grade 3 infusion reaction upon re-challenge or Grade 4 infusion reactions should not receive further doses of obinutuzumab but can continue acalabrutinib. For rituximab, please refer to the product information for guidance.

7.2.2.2 Progressive Multifocal Leukoencephalopathy or Hepatitis B Reactivation

Permanently discontinue all study drugs.

7.2.3 Dose Adjustments for All Other Nonhematologic Toxicities

Table 7 and Table 8, respectively, display the acalabrutinib and obinutuzumab dose adjustments for all other nonhematologic toxicities (dose reductions are not recommended for rituximab). Table 9 displays dose modification for toxicity during venetoclax treatment, and Table 10 displays dose adjustments for all other nonhematologic toxicities for which individual study drug attribution is not possible.

Table 7: Acalabrutinib Dose Adjustments for All Other Nonhematologic Toxicities (All Cohorts)

Dose Level	Acalabrutinib Dose
CCI	

Table 8: Obinutuzumab Dose Adjustments for All Other Nonhematologic Toxicities (All Cohorts)

Dose Level	Obinutuzumab Dose
CCI	

7.2.3.1 Cohorts 1 and 2

For ≥ Grade 3 nonhematologic toxicity attributable to acalabrutinib, acalabrutinib should be held until toxicity resolves to ≤ Grade 1, and then restarted at the same dose CCI with the first occurrence; however, for the second occurrence, acalabrutinib should be restarted at CCI Missed doses should not be made up. Subjects who are stable at a lower dose level for CCI may be dose-escalated by 1 dose level.

For ≥ Grade 3 nonhematologic toxicity attributable to obinutuzumab, obinutuzumab should be held until toxicity resolves to ≤ Grade 1, and then restarted at 1 dose level lower CCI for each occurrence. Missed doses should not be made up. Subjects who are stable at a lower dose level for CCI may be dose-escalated by 1 dose level.

For ≥ Grade 3 nonhematologic toxicity for which individual study drug attribution is not possible, subjects should have all drugs held until toxicity resolves to ≤ Grade 1, and then subjects should be restarted at 1 dose level lower using Table 10. Subjects who are stable at a lower dose level for CCI may be dose-escalated by 1 dose level.

7.2.3.2 Cohorts 3 and 4

After start of CCI for ≥ Grade 3 nonhematologic toxicity attributable to study drugs, apply dose medication guidelines to venetoclax first. Per current prescribing information, venetoclax should be held until toxicity resolves to ≤ Grade 1, and then restarted at the same dose with the first occurrence; however, for the second occurrence, venetoclax should be restarted following

the reduction guidelines in Table 9. Missed doses should not be made up. Subjects who are stable at a lower dose for CCI may be dose-escalated by 1 dose level.

For Grade ≥3 nonhematologic toxicity in Cycles 1 and 2 or despite following recommendations for venetoclax, please follow the guidelines noted in Section 7.2.2 for acalabrutinib and/or obinutuzumab.

For ≥ Grade 3 nonhematologic toxicity for which individual study drug attribution is not possible, subjects should have all drugs held until toxicity resolves to ≤ Grade 1, and then subjects should be restarted at 1 dose level lower again using Table 10. Subjects who are stable at a lower dose level for CCI may be dose-escalated by 1 dose level.

Table 9: Dose Modification for Toxicity During Venetoclax Treatment (Cohorts 3 and 4)

Dose at Interruption, mg	Restart Dose, mg[a]
CCI	

[a] During the CCI continue the reduced dose for CCI before increasing the dose.

Table 10: Dose Adjustments for All Other Nonhematologic Toxicities for Which Individual Study Drug Attribution is Not Possible (All Cohorts)

Dose Level	Acalabrutinib Dose	Rituximab Dose	Obinutuzumab Dose	Venetoclax[a]
CCI				

[a] During the CCI continue the reduced dose for CCI before increasing the dose.

8 Schedule of Activities

Table 11. Schedule of Activities: Cohorts 1 and 2

Tests & Observations (all labs listed here are standard of care except those labeled correlative studies and PK)	**Screening**	**Day 1, 8, 15 of Cycle 1**	**Day 2 of Cycle 1**	**Day 1 of Cycles 2-12**	**Day 1 of Cycles 15, 18, 21, 24[H]**	**Relapse/ Disease progression**	**Safety Follow-up[I]**	**Discontinuation Follow-up[J]**	**Long-term Follow-up[K]**
ACP-196 CCI PO administration		CCI							
Obinutuzumab administration									
History & physical examination with tumor measurements[1]	X	X		X	X	X	X		
Height	X								
Weight	X	X		X	X	X	X		
ECOG PS	X	X		X	X	X	X		
2 buccal swabs	X								
ECG[2]	X								
Concomitant medications	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	
FISH/stimulated karyotype[3]	X					X			
Zap-70 methylation[4]	X								
IGHV mutational status[4]	X								
Complete blood count (CBC)	X	X		X	X	X	X		
Chem 10	X	X		X	X		X		
Liver function panel	X	X		X	X		X		
LDH, uric acid	X	X		X	X		X		
Beta-2-microglobulin	X								
Direct antiglobulin test (Coomb's test)	X								

Table 11. Schedule of Activities: Cohorts 1 and 2

Tests & Observations (all labs listed here are standard of care except those labeled correlative studies and PK)	**Screening**	**Day 1, 8, 15 of Cycle 1**	**Day 2 of Cycle 1**	**Day 1 of Cycles 2-12**	**Day 1 of Cycles 15, 18, 21, 24[H]**	**Relapse/ Disease progression**	**Safety Follow-up[I]**	**Discontinuation Follow-up[J]**	**Long-term Follow-up[K]**
Serum or urine HCG[5]	X								
HBsAg, HBsAb, HCV, anti-HBc	X								
HBV PCR[6,7]	X			QM	See footnote 6				
Peripheral blood flow cytometry	X			A	X	X	X		
Serum immunoglobulins	X			A	X		X		
CT scan (chest, neck, abdomen, and pelvis)	X			B	B	X		X	
Bone marrow aspirate and biopsy	X			C	C	X			
Peripheral blood for correlative studies	D	D	D	D	D	D	D		
Peripheral blood for PK[8]		E							
Bone marrow for correlative studies	X			C	C	X			
Lymph node sample for correlative studies						F			
Quality of life assessment	G	G		G	G	G	G		
Survival status									X

Footnotes are on the next page.

Abbreviations: anti-HBc = hepatitis B core antibody; CCI CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human HCV = hepatitis C virus; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; PK = pharmacokinetics; PO = orally; Q = every; wks = weeks.

Footnotes for Table 11:

1. During the physical examination, palpable lymph nodes will be measured, and data will be collected on a separate case report form.

2. ECGs may be obtained at unscheduled time points as clinically indicated.
3. Does not need to be repeated at screening if performed within 60 days of registration
4. Does not need to be repeated if previously performed
5. For women of child-bearing potential only
6. Hepatitis B DNA must be performed in any patient positive for HBsAg or HB core
7. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening. Subjects who receive combination therapy with an anti-CD20 monoclonal antibody (i.e., obinutuzumab) should have a quantitative PCR test monthly during treatment and until 12 months after the last dose of anti-CD20 therapy. After that, HBV PCR monitoring should continue quarterly (e.g., every 3 months) until at least 12 months after the last dose of acalabrutinib.
8. As outlined in Section 13.3

A. Cycles 4 and 7 only
B. Response evaluations will be done every 12 weeks from randomization for the first 24 months (with the 4th evaluation shifted to Cycle 12 Day 1 rather than Cycle 13 Day 1, to align with study visits), and then every 24 weeks thereafter. Hematology results must be done within 7 days of CT scans. Bone marrow biopsies/aspirates to confirm a CR must be done within 4 weeks of the CT scan, which showed CR.
C. PB samples will be used to evaluate for MRD every 3 cycles (at the discretion of the investigator, in line with scheduled response assessments, per protocol.
D. Specific times and tube types for correlative samples are outlined in Section 13.2.
E. PK analysis will be performed on the first 8 expansion group patients of Cohort 1. Schedule can be found in Section 13.3.
F. If performed as part of relapse analysis
G. As outlined in Section 13.4
H. Visits to continue every 6 cycles thereafter (± 7 days).
I. A safety follow-up (SFU) visit is required for all subjects 30 days (+7) from the last dose of study drug.
J. After discontinuation of study treatment for any reason, each subject should be followed until disease progression or the start of alternative anticancer therapy. If disease progression has not occurred at the time of the 30-day SFU visit, discontinuation follow-up (DFU) visits should occur approximately every 12 weeks until disease progression. During this period, subjects will be followed via CT scans every 24 weeks; after 2 years in DFU, CT scans will be yearly. AE and concomitant medication reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s).
K. After disease progression or the start of alternative anticancer therapy, all subjects (unless they have withdrawn consent) will be contacted approximately every 12 weeks by telephone, to assess survival until death or lost to follow up.

Table 12: Schedule of Assessments – Cohort 3

		Treatment Phase & Response Evaluation																	
		Cycle 1		Cycle 2				Cycle 3				Cycles 4 -7	Cycles 10, 13, 16, 19, 22	Cycle 24	Cycle 24 q6 cycles	SFU	Discontinuation follow-up[1]	Relapse/ Disease Progression	Long-term follow-up
Day	**Screening**	**1**	**15**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**				
Study Windows (days)	-28	±3		±3				±3				±3	±3	±3	±7	+7	±7		±7
Study Drug Administration[1]																			
Acalabrutinib		CCI																	
Rituximab																			
Venetoclax																			
Procedures																			
History & physical examination with tumor measurements[2]	X	X		X				X				X	X	X	X	X	X		
Height	X																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X	X		X				X				X	X	X	X	X			
Disease-related symptoms	X	X		X				X				X	X	X	X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[3]	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[4]	X																	X	
Buccal swabs (2)	X																		
Hepatitis serologies[5]	X																		
HBV PCR[5,6]	X			QM				QM				QM[6]	See Footnote 6		Q3M				
Direct antiglobulin test (Coomb's test)	X																		
CBC with differential[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chem 10[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver Function Panel[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
LDH, uric acid[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Calculated CrCl	X																		

Table 12: Schedule of Assessments – Cohort 3

		Treatment Phase & Response Evaluation																
		Cycle 1		Cycle 2				Cycle 3				Cycles 4 -7	Cycles 10, 13, 16, 19, 22	Cycle 24	Cycle 24 q6 cycles	SFU	Discontinuation follow-up[I]	Relapse/ Disease Progression	Long-term follow-up
Day	**Screening**	**1**	**15**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**				
Study Windows (days)	-28	±3		±3				±3				±3	±3	±3	±7	+7	±7		±7
Beta-2-microglobulin	X																		
Serum immunoglobulins	X											C4, C7	X	X		X			
FISH/stimulated karyotype[8]	X																	X	
Zap-70 methylation, IGHV mutational status[9]	X																		
Peripheral blood flow cytometry for B/T/NK cells	X											C4, C7	C16, C19, C22	X	X	X		X	
Peripheral blood for correlative studies	X	C		C				C								C		C	
PK sample collection		D						D				D							
CT scan (chest, neck, abdomen, & pelvis)[10]	X						E					C4, C7	X	X	X; q12 cycles after C36		X[J]	X	
Overall response assessment[11]												C4, C7	X	X	X	X	X	X	
Bone marrow biopsy/aspirate[F]	X																	X	
MRD assessment[G]	X												C10, C16	X			q6 months	X	
Lymph node sample for correlative studies[12]	X																	X	
CCI																			
Cell death proteins[C]	X	X		X				X								X		X	
Immunophenotyping[C]	X	X		X				X								X		X	
CCI																			
QoL assessments[13]	X			X				X				X	C13, C19	X	X				

Table 12: Schedule of Assessments – Cohort 3

		Treatment Phase & Response Evaluation																
	Screening	Cycle 1		Cycle 2				Cycle 3				Cycles 4 -7	Cycles 10, 13, 16, 19, 22	Cycle 24	Cycle 24 q6 cycles	SFU	Discontinuation follow-up[1]	Relapse/ Disease Progression	Long-term follow-up
Day		1	15	1	8	15	22	1	8	15	22	1	1	1	1				
Study Windows (days)	-28	±3		±3				±3				±3	±3	±3	±7	+7	±7		±7
Survival status																			H

Note: All labs listed here are standard-of-care except those labeled correlative studies and PK.
Abbreviations: CCI C = cycle; CBC = complete blood count; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; IGHV = immunoglobulin heavy-chain variable; LDH = lactate dehydrogenase; MRD = minimal residual disease; PCR = polymerase chain reaction; PK = pharmacokinetics; PO = orally; Q = every; QoL = quality of life; SFU = safety follow-up; wks = weeks.
Additional footnotes are on the next page.

Footnotes to Table 12:

1. Subjects will receive CCI of acalabrutinib CCI before beginning rituximab, starting CCI Venetoclax will commence CCI with standard CCI dosing for CCI prior to full-dose therapy starting CCI Starting CCI venetoclax should be given first, followed at least 30 minutes later by acalabrutinib. Rituximab should be administered last on days of concomitant dosing.
2. During the physical examination, palpable lymph nodes will be measured, and data will be collected on a separate case report form.
3. Screening laboratory tests and ECG must be done within 14 days prior to initiating treatment. ECGs may be obtained at unscheduled time points as clinically indicated.
4. Serum or urine HCG for women of child-bearing potential only.
5. Hepatitis serologies must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing (see exclusion criterion #16).
6. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening. Subjects who receive combination therapy with an anti-CD20 monoclonal antibody (i.e., rituximab) should have a quantitative PCR test monthly during treatment and until 12 months after the last dose of anti-CD20 therapy. After that, HBV PCR monitoring should continue quarterly (e.g., every 3 months) until at least 12 months after the last dose of acalabrutinib.
7. Laboratory evaluations must be performed on the date specified, ± 3 days.
8. Does not need to be repeated at Screening if performed within 60 days of registration.
9. Does not need to be repeated if previously performed.
10. CT scans and bone marrow biopsies may be performed within 7 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within 42 days prior to initiating treatment provided no prior therapy has been given. Screening bone marrow biopsies may, likewise, be used if obtained as standard of care within 90 days prior to initiating treatment provided no prior therapy has been given.

11. Overall response evaluations will be done every 12 weeks from randomization for the first 24 months, and then every 24 weeks. After Cycle 36, CT scan is yearly. Hematology results must be done within 7 days of CT scans. Bone marrow aspirates/biopsies to confirm complete response (CR) must be done within 4 weeks of the CT scan, which showed CR.
12. LN sample should also be sent for correlative studies at time of progressive disease/relapse, if performed as part of disease analysis.
13. EORTC QLQ-C30 will be assessed. See Appendix 2.

A. At investigator decision subjects who are in CR or CR with incomplete bone marrow recovery (CRi) and/or MRD negativity may discontinue acalabrutinib after Cycle 24.
B. CCI [redacted]
C. Specific times and tube types of correlative samples are outlined in Section 13.2.
D. As outlined in Section 13.3. Drug and metabolite concentrations in plasma will be done by a bioanalytical contract research organization (CRO). CCI [redacted] Refer to the laboratory manual for instructions on collection and shipment of PK samples.
E. On Day 21, if indicated based on TLS risk.
F. To confirm CR, bone marrow aspirate/biopsy may be performed at any time. At time of bone marrow (BM) biopsy for CR confirmation, bone marrow should also be sent for correlative studies.
G. To confirm CR, draw PB for flow cytometry MRD at any time point if (i) PE/Lab/CT suggestive of CR OR (ii) there is lone residual splenomegaly and/or probable lone reactive lymphadenopathy in absence of other peripheral signs of residual CLL disease. If PB MRD is negative, in 2 to 3 months check BM biopsy/aspirate with BM MRD. If PB MRD is positive, PB MRD may be repeated q3 months until negative and then proceed to BM 3 months after negative PB MRD. Post-CR/CRi, PB MRD is completed every 6 cycles until PD (per Hallek et al 2008). Site may synchronize this activity with any protocol scheduled PB MRD if the blood draws are ±2 months apart.
H. After disease progression, subjects will be contacted to assess survival status approximately every 12 weeks until death, withdrawal of consent by subject, lost to follow-up, or study terminated by sponsor, whichever comes first.
I. If disease progression has not occurred at the time of the 30-day SFU, discontinuation follow-up visits should occur approximately every 12 weeks until disease progression. AE and concomitant medication reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s).
J. CT scans should be performed every 24 weeks. After 2 years in discontinuation follow-up, CT scans will be performed annually.
K. CCI [redacted]

Table 13: Schedule of Assessments – Cohort 4

		Treatment Phase & Response Evaluation																	
		Cycle 1		Cycle 2				Cycle 3				Cycles 4 -7	Cycles 10, 13, 16, 19, 22	Cycle 24	> Cycle 24 q6 cycles	SFU	Discontinuation follow-up[1]	Relapse/ Disease Progression	Long-term follow-up
Day	**Screening**	**1**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**				
Study Windows (days)	-28	±3		±3				±3				±3	±3	±3	±7	+7	±7		±7
Study Drug Administration[1]																			
Acalabrutinib		CCI																	
Obinutuzumab																			
Venetoclax																			
Procedures																			
History & physical examination with tumor measurements[2]	X	X		X				X				X	X	X	X	X	X		
Height	X																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X	X		X				X				X	X	X	X	X			
Disease-related symptoms	X	X		X				X				X	X	X	X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[3]	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[4]	X																	X	
Buccal swabs (2)	X																		
Hepatitis serologies[5]	X																		
HBV PCR[5,6]	X			QM				QM				QM	See footnote 6	X	Q3M				
Direct antiglobulin test (Coomb's test)	X																		
CBC with differential[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chem 10[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver function panel[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
LDH, uric acid[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Calculated CrCl	X																		

Table 13: Schedule of Assessments – Cohort 4

		Treatment Phase & Response Evaluation																
		Cycle 1		Cycle 2				Cycle 3				Cycles 4 -7	Cycles 10, 13, 16, 19, 22	Cycle 24	> Cycle 24 q6 cycles	SFU	Discontinuation follow-up[I]	Relapse/ Disease Progression	Long-term follow-up
Day	**Screening**	**1**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**				
Study Windows (days)	-28	±3		±3				±3				±3	±3	±3	±7	+7	±7		±7
Beta-2-microglobulin	X																		
Serum immunoglobulins	X											C4, C7	X	X		X			
FISH/stimulated karyotype[8]	X																	X	
Zap-70 methylation, IGHV mutational status[9]	X																		
Peripheral blood flow cytometry for B/T/NK cells	X											C4, C7	C16, C19, C22	X	X	X		X	
Peripheral blood for correlative studies	X	C		C				C								C		C	
PK sample collection		D						D				D							
CT scan (chest, neck, abdomen, & pelvis)[10]	X						E					C4, C7	X	X	X; q12 cycles after C36		X[J]	X	
Overall response assessment[11]												C4, C7	X	X	X	X	X	X	
Bone marrow biopsy/aspirate[F]	X																	X	
MRD assessment[G]	X												C10, C16	X			q6 months	X	
Lymph node sample for correlative studies[12]	X																	X	
CCI [redacted]																			
Cell death proteins[C]	X	X		X				X								X		X	
Immunophenotyping[C]	X	X		X				X								X		X	
CCI [redacted]																			
QoL assessments[13]	X			X				X				X	C13, C19	X	X				
Survival status																			H

Note: All labs listed here are standard-of-care except those labeled correlative studies and PK.
Abbreviations: BID = twice daily; C = cycle; CBC = complete blood count; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; IGHV = immunoglobulin heavy-chain variable; LDH = lactate dehydrogenase; MRD = minimal residual disease; PCR = polymerase chain reaction; PK = pharmacokinetics; PO = orally; Q = every; QoL = quality of life; SFU = safety follow-up; wks = weeks.
Additional footnotes are on the next page.

Footnotes to Table 13:

1. Subjects will receive CCI of acalabrutinib CCI before beginning obinutuzumab, starting CCI Venetoclax will commence CCI with standard CCI dosing for CCI prior to full-dose therapy starting CCI Starting CCI venetoclax should be given first, followed at least 30 minutes later by acalabrutinib. Obinutuzumab should be administered last on days of concomitant dosing.
2. During the physical examination, palpable lymph nodes will be measured, and data will be collected on a separate case report form.
3. Screening laboratory tests and ECG must be done within 14 days prior to initiating treatment. ECGs may be obtained at unscheduled time points as clinically indicated.
4. Serum or urine HCG for women of child-bearing potential only.
5. Hepatitis serologies must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing (see exclusion criterion #16).
6. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening. Subjects who receive combination therapy with an anti-CD20 monoclonal antibody (i.e., obinutuzumab) should have a quantitative PCR test monthly during treatment and until 12 months after the last dose of anti-CD20 therapy. After that, HBV PCR monitoring should continue quarterly (e.g., every 3 months) until at least 12 months after the last dose of acalabrutinib.
7. Laboratory evaluations must be performed on the date specified, ± 3 days.
8. Does not need to be repeated at Screening if performed within 60 days of registration.
9. Does not need to be repeated if previously performed.
10. CT scans and bone marrow biopsies may be performed within 7 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within 42 days prior to initiating treatment provided no prior therapy has been given. Screening bone marrow biopsies may, likewise, be used if obtained as standard of care within 90 days prior to initiating treatment provided no prior therapy has been given.
11. Overall response evaluations will be done every 12 weeks from randomization for the first 24 months, and then every 24 weeks. After Cycle 36, CT scan is yearly. Hematology results must be done within 7 days of CT scans. Bone marrow aspirates/biopsies to confirm CR must be done within 4 weeks of the CT scan, which showed CR.
12. LN sample should also be sent for correlative studies at time of progressive disease/relapse, if performed as part of disease analysis.
13. EORTC QLQ-C30 will be assessed. See Appendix 2.

A. At investigator discretion, subjects who are in CR or CRi and/or MRD negativity may discontinue acalabrutinib after Cycle 24.
B. CCI
C. Specific times and tube types of correlative samples are outlined in Section 13.2.
D. As outlined in Section 13.3. Drug and metabolite concentrations in plasma will be done by a bioanalytical contract research organization (CRO). CCI Refer to the laboratory manual for instructions on collection and shipment of PK samples.

E. On Day 21, if indicated based on TLS risk.
F. To confirm CR, bone marrow aspirate/biopsy may be performed at any time. At time of bone marrow (BM) biopsy for CR confirmation, bone marrow should also be sent for correlative studies.
G. To confirm CR, draw PB for flow cytometry MRD at any time point if (i) PE/Lab/CT suggestive of CR OR (ii) there is lone residual splenomegaly and/or probable lone reactive lymphadenopathy in absence of other peripheral signs of residual CLL disease. If PB MRD is negative, in 2 to 3 months check BM biopsy/aspirate with BM MRD. If PB MRD is positive, PB MRD may be repeated q3 months until negative and then proceed to BM 3 months after negative PB MRD. Post-CR/CRi, PB MRD is completed every 6 cycles until PD (per Hallek et al 2008). Site may synchronize this activity with any protocol scheduled PB MRD if the blood draws are ±2 months apart.
H. After disease progression, subjects will be contacted to assess survival status approximately every 12 weeks until death, withdrawal of consent by subject, lost to follow-up, or study terminated by sponsor, whichever comes first.
I. If disease progression has not occurred at the time of the 30-day SFU, discontinuation follow-up visits should occur approximately every 12 weeks until disease progression. AE and concomitant medication reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s).
J. CT scans should be performed every 24 weeks. After 2 years in discontinuation follow-up, CT scans will be performed annually.
K. CCI [redacted]

8.1 Pre-Treatment (Screening) Evaluation

Subjects will be evaluated prior to registration after signing informed consent. Laboratory evaluations and ECG must be done within 14 days, CT scans within 42 days, and bone marrow within 90 days provided no prior therapy has been given. Therapy must begin within 28 days following registration. Required pre-treatment evaluation includes:

- History and physical examination, including medication reconciliation, weight, ECOG performance status, and clinical tumor measurement
- ECG
- Complete blood count (CBC) with differential
- Chem 10 panel
- Lactate dehydrogenase (LDH)
- Uric acid
- Calculated CrCl
- ALT/AST, total and direct bilirubin, albumin, total protein, alkaline phosphatase
- Direct antiglobulin (Coomb's test)
- Quantitative immunoglobulins
- Peripheral blood flow cytometry
- Beta 2 microglobulin
- Zap-70 methylation
- Stimulated karyotype and FISH analysis (CLL panel) on either blood or bone marrow (required within 60 days of registration)
- CLL mutational screen
- CT scans of chest/abdomen/pelvis including index lesion measurement
- Bone marrow biopsy with pathology evaluation and flow cytometry
- Psychological/behavioral measures Section 13.4)

8.2 Study Evaluations

The schedule of required procedures for each cycle is detailed in the tables in Section 8. Laboratory evaluations must be performed on the date specified and within the window specified in Section 8. CT scans and bone marrow biopsies may be performed within 7 days of the specified dates. Clinical evaluations and laboratory studies may be repeated more frequently if

clinically indicated. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

Radiological imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck. Subjects who are intolerant to IV CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations).

8.3 Safety Follow-up

Each subject should be followed until the safety follow-up (SFU) visit at 30 (+7) days after his or her last dose of all study drug(s) to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the Safety Follow-up assessments before withdrawing consent, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedule of Activities (Section 8) describes the procedures required for the Safety Follow-up visits.

8.4 Discontinuation Follow-up

After discontinuation of study treatment for any reason (except for death, lost to follow up, or withdrawal of consent), each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, discontinuation follow-up visits should occur approximately every 12 weeks until disease progression. During this period, subjects will be followed via CT scans (every 24 weeks), CBC with differential, physical examinations (including vital signs and weight), serum chemistry, peripheral blood MRD (every 6 months for subjects in Cohorts 3 and 4 who will be monitored while off study drugs), and bone marrow biopsy and aspirate (as clinically indicated); after 2 years in discontinuation follow-up, CT scans will be yearly. Refer to the Schedule of Assessments (Section 8) for a full list of assessments required during this period.

8.5 Long-Term Follow-up

After disease progression, subjects will be contacted to assess survival status approximately every 12 weeks until death, withdrawal of consent by subject, lost to follow-up, or study terminated by sponsor, whichever comes first.

9 Criteria for Response, Progression, and Relapse

Any subject who has confirmed objective evidence of cancer progression while receiving regimens of acalabrutinib and obinutuzumab; acalabrutinib, venetoclax, and obinutuzumab; or

acalabrutinib, venetoclax, and rituximab should be withdrawn from the study treatment. If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiologic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred.

Criteria for response for CLL and prolymphocytic leukemia (PLL) will utilize the IWCLL 2008 (Hallek et al. 2008, Table 14) for response, which includes clinical, hematologic, and bone marrow features. Responses will be classified as follows:

Complete response: Requires all of the following for a period of at least 2 months:

- Absence of lymphadenopathy >1.5 cm on physical examination and CT scan
- No hepatomegaly or splenomegaly on physical examination (a CT scan also may be used to assess)
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥1,500/µL, platelets >100,000/µL, hemoglobin >11.0 g/dL (untransfused); absolute lymphocyte count <4,000/µL
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, subjects should be considered to be a PR. Additionally, if bone marrow is positive by immunohistochemistry (IHC) for CLL cells, it should be considered a PR. If the marrow is hypocellular a bone marrow should be performed in 2 to 3 months. If blood counts (polymorphonuclear leukocytes <1,500/µL, platelets <100,000/µL) fail to recover at the time of the response evaluation but there is otherwise no evidence of CLL, a repeat determination should be performed at the time of count recovery (polymorphonuclear leukocytes ≥ 1,500/µL, platelets >100,000/µL) but should not exceed 6 months.
- Subjects who fulfill the criteria for CR with the exception of a persistent cytopenia (i.e., anemia, thrombocytopenia, or neutropenia) that is believed to be unrelated to CLL but related to drug toxicity will be considered a CR with incomplete marrow recovery (CRi). As stated above, subjects falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at full count recovery reveals no CLL, these subjects will be considered to be in complete remission at that time.
- Subjects who fulfill the criteria of CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR), and assessed prospectively for similarity to outcome with CR.

Partial Response: Requires a ≥50% decrease in peripheral lymphocyte count from pre-treatment value or absolute lymphocyte count <5,000/µL, ≥50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥50% reduction in splenomegaly/hepatomegaly for a period of at least 2 months. Additionally, these subjects must have 1 of the following:

- Polymorphonuclear leukocytes ≥1,500/µL or 50% improvement from pre-treatment value
- Platelets >100,000/µL or 50% improvement from pre-treatment value
- Hemoglobin >11.0 g/dL (untransfused) or 50% improvement from pre-treatment value
- Subjects who meet the criteria for PR with the exception of having less than a 50% reduction in peripheral lymphocyte count AND absolute lymphocyte count >5,000/µL will be considered a PRL. These subjects should continue to be followed on therapy and response status updated if the lymphocyte count does decrease by ≥50% or absolute lymphocyte count <5,000/µL is achieved.

Progressive Disease: Progressive disease will be characterized by any one of the following events:

- ≥50% increase in the products of at least 2 lymph nodes on 2 consecutive determinations 2 weeks apart (at least 1 lymph node must be ≥2 cm); appearance of new palpable lymph nodes
- ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present
- Transformation to a more aggressive histology (i.e., Richter's syndrome or PLL with ≥56% prolymphocytes)
- The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hgb levels >2 g/dL or to <10 g/dL, or by a decrease of platelet counts >50% or to <100,000/µL, which occurs at least 3 months after the initiation of treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.

Stable Disease: Subjects who do not fulfill the criteria for CR or PR as defined above but do not exhibit progressive disease will be considered as having stable disease (SD).

Table 14: IWCLL Response Assessment Criteria

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

Modified from Hallek et al. 2008.

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

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

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

b. Without need for exogenous growth factors

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

Response criteria for SLL subjects will use 2007 Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007). Responses will be classified as follows:

Complete response: Requires all of the following:

- Complete absence of all detectable clinical evidence of disease and disease-related symptoms present prior to therapy
- Regression of lymphadenopathy to normal size (≤1.5 cm) on physical examination and CT scan. Previously involved nodes that were 1.1 to 1.5 cm in long axis and more than 1 cm in short axis must have decreased to ≤1 cm in their short axis.
- No hepatomegaly or splenomegaly on physical examination or CT scan, and nodules related to lymphoma should disappear.
- Bone marrow aspirate and biopsy must be free of disease on an adequate biopsy sample. If indeterminate by morphology, IHC must be negative.

Partial Response: Requires all of the following:

- ≥50% decrease in sum of product of the diameters of up to 6 largest dominant masses. No increase in size of other nodes and no new lesions.
- ≥50% reduction in sum of product diameters of nodules in spleen/liver with no increase in size of liver or spleen.

Progressive Disease: Progressive disease will be characterized by any 1 of the following events:

- Appearance of a new lesion >1.5 cm in any axis
- ≥50% increase in the products of at least 2 lymph nodes
- ≥50% increase in the longest diameter of a previously identified node >1 cm in short axis
- ≥50% increase in the size of the liver and/or spleen or previously determined nodules in the liver or spleen
- New or recurrent bone marrow involvement

Stable Disease: Subjects who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having SD.

10 Patient Safety and Adverse Event Reporting

10.1 Reference Safety Information

For the purpose of reporting AEs and SAEs, the Investigator Brochure for acalabrutinib contains the RSI.

10.2 Monitoring of Adverse Events

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

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

The events must be detailed to include diagnostic term, severity, causality in relationship to the study drug, duration, action taken and outcome. The descriptions and grading scales found in the NCI-CTCAE version 4.03 or higher will be utilized for AE reporting.

10.3 Definitions of Adverse Events and Causality

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

This includes the following:

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

The following are NOT considered AEs:

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

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

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

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

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

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, or other means will be recorded in the subject's medical record and on the AE eCRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see

following guidance), and any actions taken. The causality of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements.

10.4 Definition of Serious Adverse Events

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (places the subject at immediate risk of death at the time of the occurrence)
- Required inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is an important medical event, that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above.

Any death (other than death due to disease progression; see Section 10.5) occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study, must be reported as a SAE. Any hospitalization <24 hours or hospitalizations for planned procedures will not be considered an SAE.

10.5 Reporting of Adverse Events

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

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

Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported.

Autopsy and postmortem reports must be forwarded to Acerta Pharma, BV, Drug Safety, or designee, as outlined for SAEs above.

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

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

Drug Safety Contact Information	
eFax:	PPD
Email:	PPD

10.5.1 Second Primary Malignancies

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

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of

normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B cell CLL into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

10.5.2 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) for subjects randomized to the acalabrutinib-containing combinations arm and must be reported to the sponsors expeditiously (see Section 10.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

For study treatment containing biologic products:

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

10.6 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness during the dose escalation phase of Cohorts 1 and 2. During this phase, Acerta and investigators will conduct continuous review of data and subject safety at regular intervals. This will include the review of frequency and severity of AEs and responses on the trial, where applicable, to determine if the risk/benefit ratio of the trial changes. SAEs and responses will also be reviewed by The Ohio State University CCC Data Safety Monitoring Committee (DSMC). The principal investigator will also submit a progress report quarterly that will be reviewed by the committee per the DSMC plan. All reportable SAE will be reported to the FDA and IRB of record as per the policies of the IRB. In addition, at the end of each DLT review period, mandatory safety meetings will be held with the sponsor.

For Cohorts 3 and 4, safety data will be reviewed for the first 3 subjects who complete Cycle 3 in each cohort. The review will be repeated for additional subjects if needed. Unless a safety concern is identified (e.g., dose delays >14 days in CCI enrollment in Cohorts 3 and 4 will continue during the safety review until the desired number of subjects is reached. There are no DLTs defined for this portion of the study. See Section 5 for study drugs and administration guidelines.

11 Withdrawal of Subject from Treatment or Assessment

11.1 Withdrawal of Subjects from Study Treatment

The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from the study at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Completed treatment
- Progressive disease
- Adverse event
- Pregnancy
- Physician decision (includes start of alternative anticancer therapy)
- Treatment withdrawal by subject
- Treatment terminated by sponsor
- Subject lost to follow-up
- Death
- Other

Subjects who discontinue study therapy will continue to be followed on study for follow up of safety (Section 8.3), disease progression, and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate eCRF.

11.2 Reasons for Study Exit

Reasons for study exit include:

- Death
- Subject lost to follow-up
- Study terminated by sponsor
- Study withdrawal by subject
- AE/SAE

- Other

12 Forms to Be Kept

On-study as well as follow-up data will be recorded on data sheets specific to this study. All study participants will sign a written informed consent, which will describe the objectives of the study and potential risks. All subject data will be identified by subject initials and study code number only. Subjects will not be identified by name.

13 Correlative Studies

13.1 Outline of Correlative Laboratory Studies

Correlative studies associated with this trial will focus on the CCI [redacted] as well as the consequences of BTK inhibition in CLL cells, T cells, and NK cells. MRD analysis will be performed to correlate long-term outcomes with MRD negativity. Additionally, from subjects who relapse after this combination, samples will be taken at relapse to determine mechanisms of resistance. Samples not used immediately will be stored for future research specifically investigating acalabrutinib or the combination of acalabrutinib and obinutuzumab in CLL. Residual material may be used to study other aspects of CLL related biology or other measures of treatment response. Stored samples will be housed in the CLL Experimental Therapeutics Laboratory at OSU. Subjects may withdraw consent to use their tissue at any time.

Pharmacokinetic analysis will be performed on samples from the first 8 subjects enrolled in the expansion of Cohort 1 as well as the first 8 subjects enrolled in each of Cohorts 3 and 4. Pharmacokinetics analysis is outlined in Section 13.3.

At baseline, peripheral blood and bone marrow will be collected as well as buccal cell sample for genomic DNA. Unselected or B cell selected peripheral blood cells at this time point will be compared with serial samples to determine changes in BTK occupancy and BCR signaling protein activation that occur with acalabrutinib alone or in combination with obinutuzumab. BTK occupancy analysis and select signaling studies will be performed by Acerta. In Cohorts 3 and 4, BCL-2 family members (Bcl-2, Mcl-1, and Bcl-xL) will be profiled in peripheral blood and/or bone marrow mononuclear cells. Samples for these studies will be batched and sent by the laboratory personnel to Acerta Pharma, BV, or designee.

CCI [redacted]

During serial follow up, we will assess for development of mutations to BTK and PLCG2, the most frequent mechanism of resistance to ibrutinib. This will be performed at 3-month intervals on blood or bone marrow. CCI [redacted]

CCI [redacted]

Peripheral blood flow cytometry will be performed serially to analyze how B, T, and NK cell total number and subset composition change during the course of this therapy. As well, T cells and NK cells will be selected from peripheral blood at baseline and serial time points to determine how cytokine expression, cytotoxicity directed by NK cells (direct or antibody mediated), NK cell direct cytotoxicity, activation markers of T-cells and NK cells, or T cell polarity is changed by acalabrutinib alone or in combination with obinutuzumab, rituximab, or venetoclax.

The expression of cell death pathway proteins such as MCL1, BCL-2 and others will be measured from peripheral blood using flow cytometry on serial sample to determine if the level of cell death proteins change with treatment and if a profile of cell death proteins is predictive of treatment outcomes.

CCI [redacted]

MRD status will be evaluated in all subjects at prespecified time points. In Cohorts 1 and 2, all subjects should have bone marrow biopsy with MRD analysis at Cycle 12 Day 1 (Table 11). CCI [redacted]

Figure 2: CCI

Figure 3: CCI

All samples, except PK samples outlined in Section 13.3, will be delivered to the CLL Experimental Therapeutics Laboratory for processing and shipment of selected samples.

13.2 Correlative Sample Requirements (Exclusive of Pharmacokinetic Samples)

13.2.1 Cohorts 1 and 2

Refer to the Schedule of Assessments (Table 11).

Screening

- 10 mL bone marrow in a heparin tube, which will be processed by Ficoll density gradient centrifugation and viably frozen
- 2 buccal swabs
- Peripheral blood 4 x 8.5 mL acid citrate dextrose (ACD) tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL ethylenediamine tetra-acetic acid (EDTA) tubes that will be centrifuged to obtain plasma

[redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen

[redacted]

- Peripheral blood 2 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen

[redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

[redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

[redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

[redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

CCI [redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen

CCI [redacted]

- 10 mL bone marrow in a heparin tube, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

CCI [redacted]

- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma

Relapse

- 10 mL bone marrow in a heparin tube, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 4 x 8.5 mL ACD tubes, which will be processed by Ficoll density gradient centrifugation and viably frozen
- Peripheral blood 2 x 6 mL EDTA tubes that will be centrifuged to obtain plasma
- If applicable, sample of lymph node biopsy to confirm transformation or relapse, which will be processed to a mononuclear cell suspension using manual disassociation and Ficoll density gradient centrifugation or red cell lysis.

13.2.2 Cohorts 3 and 4

Refer to the Schedules of Assessments (Table 12 and Table 13).

CCI [redacted]

Cell Death Protein Ratio Flow

Blood samples will be collected and analyzed within 48 hours of collection using flow cytometry for cell death proteins and pathway and/or disease-related proteins. Samples should consist of a 10-mL blood draw to be obtained at the following time points:

- Screening
- Cycle 1 Day 1, before acalabrutinib dose
- Cycle 2 Day 1, before anti-CD20 antibody
- Cycle 3 Day 1, before venetoclax
- Relapse/PD
- Safety Follow-up Visit

Immunophenotyping

Blood samples will be collected to evaluate tumor and immune microenvironment by flow cytometry. Samples should consist of a 10-mL blood draw to be obtained at the following time points:

- Screening
- Cycle 1 Day 1, before acalabrutinib dose
- Cycle 2 Day 1, before anti-CD20 antibody
- Cycle 3 Day 1, before venetoclax
- Relapse/PD
- Safety Follow-up Visit

On-treatment Bone Marrow

Remaining bone marrow will be analyzed to confirm findings from correlative analysis from peripheral blood samples. If bone marrow is being collected, surplus could be submitted for correlative analysis.

13.3 Pharmacokinetics

To supplement data from the Phase 1 study, the first 8 subjects accrued to the Phase 1b Expansion of Cohort 1 and the first 8 subjects enrolled in each of Cohorts 3 and 4 will have PK analysis performed. In Cohorts 3 and 4, subjects who have not previously participated in PK analysis will have PK analysis performed at predose and 2 hours postdose, relative to acalabrutinib administration. The plasma PK of acalabrutinib, a metabolite ACP-5862 and venetoclax will be characterized using noncompartmental analysis. Missing dates or times may be imputed for PK samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK analyses and an additional subject used.

The PK parameters will be tabulated and summarized using descriptive statistics. [redacted]

At each PK time point one 4 mL lithium heparin tube should be collected and sent to CTPL immediately. [redacted] Sample should be processed per laboratory manual. Samples will be batched for shipment.

Cohort 1 PK samples will be collected at the following time points on [redacted]

- Predose
- 30 minutes
- 1 hour
- 2 hours
- 3 hours
- 4 hours
- 6 hours
- 24 hours

For Cohorts 3 and 4, PK samples will be collected at the following time points on [redacted] relative to acalabrutinib administration:

- Predose
- 30 minutes (±5 minutes)
- 1 hour (±5 minutes)
- 2 hours (±15 minutes)
- 3 hours (±15 minutes)
- 4 hours (±15 minutes)
- 6 hours (±15 minutes)
- 24 hours (±15 minutes)

In Cohorts 3 and 4, subjects who have not previously participated in PK analysis will have PK analysis performed at predose and 2 hours postdose, relative to acalabrutinib administration.

- Predose
- 2 hours (±15 minutes)

13.4 Health Related Quality of Life and Emotional Distress Assessment

Cohorts 1 and 2:

As part of this study, data regarding health-related quality of life (HR-QOL) will be obtained to determine how acalabrutinib plus obinutuzumab affect HR-QOL. Baseline HR-QOL between subjects with untreated disease and those with relapsed and refractory CLL will also be compared.

During screening, sociodemographic information (e.g., age, race, marital status) and reports of recent stressful events will be obtained. In addition, the assessment will consist of measures of CLL specific stress, anxiety and depressive symptoms, social support, other symptoms (fatigue, pain, sleep problems), and quality of life. Across cycles, only a subset of measures is used as this reduces subject burden. See Appendix 2 for timeline for measure usage and descriptions of the psychometric properties of the measures.

Cohorts 3 and 4:

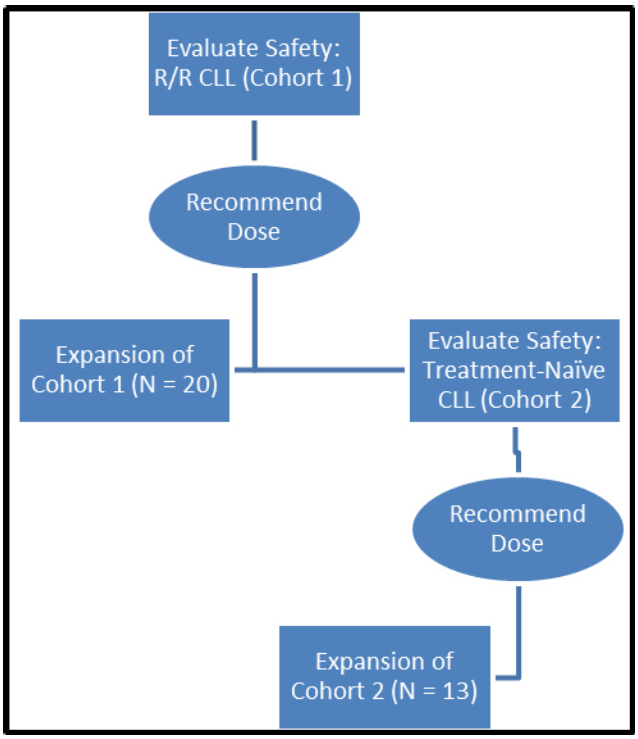
The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a cancer-specific instrument most frequently used to measure quality of life in cancer patients.

14 Statistical Considerations

14.1 Study Overview

This is a Phase 1b study with expansion to evaluate the safety and preliminary efficacy of acalabrutinib in combination with obinutuzumab, or with venetoclax and an anti-CD20 antibody (rituximab or obinutuzumab) in 4 separate cohorts of subjects: those with relapsed/refractory CLL (Cohorts 1 and 3) and those with treatment-naive CLL (Cohorts 2 and 4). Enrollment will begin in Cohort 1, where the recommended dose will be based on decision rules from a standard 3+3 Phase 1 trial design and will proceed as outlined in Figure 4. Both Cohorts 1 and 2 will be expanded to better evaluate the toxicity profile of these combination regimens, and also to detect moderate to large increases in ORR at 12 months relative to historical control. Cohorts 3 and 4 will be enrolled to establish the safety profile of the combination of acalabrutinib plus venetoclax plus an anti-CD20 antibody. The ORR will be defined as the proportion of treated subjects who achieve complete or partial remission at Cycle 16 for Cohorts 3 and 4. The cumulative ORR over time will be summarized for each of the 4 cohorts individually.

Figure 4: Trial Design



CLL = chronic lymphocytic leukemia; R/R = relapsed/refractory

14.2 Sample Size

The sample size for Cohorts 1 and 2 is based on: 1) dose de-escalation rules; and 2) the number of subjects required to detect moderate to large increases in ORR relative to historical control with sufficient power while constraining Type I error to 0.10. This study is expected to require 45 subjects, 6 subjects evaluated for safety in each cohort and an additional 20 and 13 subjects enrolled in Cohorts 1 and 2, respectively. More subjects may be enrolled if de-escalation of dose levels is indicated in the safety evaluation. The sample size of 12 subjects each for Cohorts 3 and 4 is chosen to provide evaluation for safety and tolerability.

14.3 Accrual Time and Study Duration

The anticipated accrual rate is 1 to 2 subjects per month for Cohort 1 and 1 subject per month for Cohort 2. It is anticipated that all subjects will be accrued to Cohort 1 within 2 years and accrual to Cohort 2 will occur over the course of approximately 3 years, resulting in a study duration of approximately 4 years to evaluate the primary endpoint. The anticipated accrual rate for Cohorts 3 and 4 is approximately 2 subjects per month.

14.4 Statistical Design

Cohorts 1 and 2 will use a Phase 1b study design with de-escalation to determine a safe and tolerable dose level to be recommended for the expansion portion. Section 6.5 provides the details of the study design for dose finding. Each of Cohorts 1 and 2 will be expanded at the recommended dose level to include, respectively, 26 and 19 total relapsed/refractory and treatment-naive CLL subjects. These sample sizes were chosen to obtain sufficient preliminary safety and efficacy information in these populations. With respect to toxicity and ability to detect common AEs, there is approximately a 60% chance of observing at least 1 subject with an AE occurring at a 5% rate with 19 treatment-naive subjects in Cohort 2, and approximately a 75% chance in the group of 26 relapsed/refractory CLL subjects in Cohort 1. If toxicity profiles are similar and it is appropriate to summarize AEs across all subjects, there is at least a 90% chance of detecting a common AE. With respect to clinical efficacy, a 50% ORR (PRL or better) (null) at the 12-month evaluation would be considered uninteresting as this can be achieved with either of acalabrutinib or obinutuzumab as single agents in both populations. However, an ORR of at least 75% in the relapsed/refractory setting for Cohort 2 and an ORR of at least 80% in the treatment-naive setting for Cohort 1 would be of considerable interest and would warrant further investigation of the combination regimen (alternative). If 16 or fewer responses are observed in 26 evaluable subjects with relapsed/refractory CLL in Cohort 1, the combination of acalabrutinib with obinutuzumab would not be considered promising; likewise, if 12 or fewer responses in 19 evaluable subjects who were previously untreated for CLL in Cohort 2 were observed, the combination would not be considered promising as upfront therapy. Each of these designs has at least 90% power with a 1-sided alpha level of 0.10.

The sample sizes for Cohorts 3 and 4 are chosen to obtain preliminary safety information in the relapsed/refractory and treatment-naive CLL populations. With respect to toxicity and ability to detect common AEs, there is a 46% chance of observing at least 1 subject with an AE occurring at a 5% rate with 12 subjects in each of Cohort 3 and 4. Below is a list of various AE rates with the chance of observing at least 1 subject with that AE.

Sample Size	Adverse Event Rate	Chance of Observing at Least 1 Adverse Event
12	1%	11%
12	2%	22%
12	5%	46%
12	10%	72%

14.5 Analysis Populations:

- All-treated Population: All enrolled subjects who receive ≥1 dose of study drug. The All-treated Population will be used for the efficacy and safety analyses.
- Efficacy-evaluable Population: All subjects in the All-treated Population who have ≥1 evaluable response assessment after the first dose of study drug. The Efficacy-evaluable Population will be used for sensitivity analysis.

For Cohorts 1 and 2, if in the DLT observation portion, a subject discontinues study prior to completing the second cycle of treatment at a dose level for reasons other than toxicity, an additional subject may be enrolled at that dose level for purposes of the DLT assessment and decision rules.

14.6 Analysis Plan

14.6.1 Primary Endpoints

For Cohorts 1 and 2, the ORR (PR or better) at the 12-month response assessment will be calculated and 95% exact binomial CIs will be provided. For Cohorts 1 to 4, toxicities will be tabulated by type and grade using NCI-CTCAE version 4.03 criteria or higher and displayed in summary form. In addition, the number of subjects requiring dose reductions, and the reason for going off each treatment may be summarized.

14.6.2 Secondary Endpoints

All secondary endpoints will be evaluated for each cohort separately. The ORR of the combination therapy of acalabrutinib plus venetoclax plus an anti-CD20 antibody at Cycle 16 (Cohorts 3 and 4) will be calculated and 95% exact binomial CIs will be provided. The CR rate and MRD-negative CR rate will be summarized. The degree of response will be summarized as well as the number of subjects who achieve CR but remain positive for MRD. Duration of response, time to CR, PFS, TTNT, time to response, and OS will be summarized with simple descriptive statistics obtained using the Kaplan-Meier method. DOR will be measured from the date of initial response to the date of disease progression or death. PFS will be measured from the date of first treatment to date of disease progression or death. For DOR and PFS, subjects who do not have disease progression or death will be censored at the date of last disease assessment. Subjects receiving stem cell transplant will be censored at the date of last disease assessment prior to the transplant. Time to next anti-CLL treatment will be measured from date of first treatment until date of next treatment or death, censoring those alive who have not started another treatment at last follow-up. OS will be measured from date of first treatment until date of death or last follow-up. These analyses will be useful in planning future studies.

Cytogenetic and molecular marker data, including FISH and stimulated karyotype results, Zap-70 methylation, and IGHV mutational status will be summarized for all subjects. Relationships between these baseline variables and response rate or PFS will be explored graphically (e.g., side-by-side boxplots or Kaplan-Meier plots), where estimates with CIs will be presented as the primary method of analysis due to the limited number of subjects. If given a sufficient number of events, baseline markers may be correlated with response or survival using logistic regression or proportional hazards models, respectively, and adjusting for subject cohort (i.e., treatment-naive versus relapsed/refractory).

Correlative studies will assess the effects of acalabrutinib alone or in combination with other study drugs on [redacted] as well as B, T, and NK cell numbers over the course of therapy. With these data collected serially over time, patterns will be explored graphically using box plots and/or individual time plots as well as analytically with repeated measures analysis of variance.

[redacted]

15 Ethical and Regulatory Considerations

15.1 Ethical Principles

This study will be conducted according to the principles outlined by the Declaration of Helsinki and all applicable amendments; the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice; the US FDA regulations regarding the conduct of clinical trials and the protection of human subjects; the IRB, any applicable local health authority, and the Ethics Committee requirements.

15.2 Institutional Review Board Approval

This study must obtain the approval of the protocol, the informed consent document and any other material used to inform the subject about the nature of the trial by a properly constituted IRB. The trial should not start until a copy of this written approval has been received by the investigator. The investigator will supply Acerta Pharma BV, with a copy of the IRB approval letter stating that the study protocol and any subsequent amendments and informed consent have been reviewed and approved.

The investigator or designee will be responsible for obtaining annual IRB re-approval throughout the duration of the study including at completion or termination.

15.3 Protocol Amendments

Any changes to this protocol made by the investigator must be in the form of a written amendment and the amendment will be appended to the protocol. Approval of amendments by the IRB is required prior to their implementation, unless there are overriding safety reasons.

15.4 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all subjects participating in the trial and all of their medical information is maintained. Identifying information must be kept in a secure location with access limited to the study staff directly

participating in the trial. The investigator/institution will permit direct access to source data and documents to the sponsor's study monitors, IRB, the FDA and/or other regulatory authorities.

15.5 Case Report Forms and Record Retention

Authorized study site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed promptly. 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.

The investigator must maintain all study records, subject files and other source data for the duration of the trial and per applicable regulations.

15.5.1 Record Retention

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, BV, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

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

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

15.6 Study Monitoring Requirements

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, 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.

15.7 Investigational Study Drug Accountability

Study drugs must be kept in a locked limited access cabinet or space. The study drugs must not be used outside the context of the protocol. Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma, BV, and are open to inspections by regulatory authorities at any time.

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

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Appendix 1. Known Strong In Vivo Inhibitors and Inducers of CYP3A

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.

Note: 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 2. Health-Related Quality of Life and Emotional Distress Survey

The schedule for quality of life assessments is included in Table 15.

Sociodemographic information

Single items are used to assess age, race/ethnicity, marital status, education, occupation, work-related functioning, and income.

Medical Comorbidities

The *Charlson Comorbidity Index* (Charlson et al., 1987) is a method of classifying comorbid health conditions. It was designed to capture risk of death from comorbid disease for use in longitudinal studies. Various medical conditions are listed, each with a point value (1, 2, 3, or 6) that contributes to a total score. More serious medical conditions are weighted more heavily and contribute more points to the total score. Higher scores indicate higher risk of death from a comorbid medical condition. To be completed by research staff.

Stressful Life Events

The *Life Events Scale* was adapted from the Women's Health Initiative study (Matthews et al., 1997). Participants indicate if they have experienced any of 5 stressful life events during the previous year (death, financial difficulty, divorce or break-up of family member or friend, major conflict with children or grandchildren, robberies or accidents). Two scores are calculated: presence versus absence of each event (*0 = not occurred, 1 = occurred)*, and the total number of events reported (range 0 to 5). Higher scores indicate more frequent life events and greater distress.

Health-Related Quality of Life

The Medical Outcomes Study-Short Form-36 (SF-36; Ware, Kosinski, & Keller, 1996; Ware, Kosinski, Turner-Bowker, & Gandek, 2002) is used to assess health-related quality of life during the past *month*. The SF-36 assesses 8 aspects of quality of life including physical functioning, role functioning physical, general health perceptions, vitality, social functioning, role functioning-emotion, and mental health. Higher scores reflect better quality of life.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; Aaronson et al., 1993) is a cancer-specific instrument most frequently used to measure quality of life in cancer patients.

The Generalized Anxiety Disorder 7-item (GAD-7; Spitzer et al., 2006) is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder (GAD). GAD-7 has 7 items, which measure severity of various signs of GAD according to reported response categories with assigned points.

The *Brief Pain Inventory* (BPI; Cleeland & Ryan, 1994) is a 7-item self-report measure of pain severity and daily functional interference. Higher scores indicate greater interference.

The *Fatigue Symptom Inventory* (FSI: Hann et al., 1998) disruption index is a 7-item assessment of the impact of fatigue on quality of life on an 11-point Likert-type scale ranging from 0 = *no interference* to 10 = *extreme interference*; higher scores indicating greater interference.

The *Medical Outcomes Study-Sleep Scale* (MOS-Sleep; Hays, Martin, Sesti, & Spritzer, 2005) is a 12-item measure that will be used to assess sleep disturbance. Participants report how long it usually takes them to fall asleep in the past 4 weeks and on average how many hours of sleep they got each night in the last 4 weeks. They also report how often they have experienced 10 specific difficulties with sleep (e.g., "Awaken during your sleep and have trouble falling asleep again") on a 6-point Likert scale (1 = All of the time to 6 = None of the time) to form a sleep problems index. Higher scores on the sleep problem index indicate higher levels of sleep problems.

Perceptions of Illness

The *Brief Illness Perception Questionnaire* (BIPQ; Broadbent et al., 2006) is a 9-item questionnaire to assess patients' perceptions of their illness. The BIPQ uses a single-item scale approach to assess perceptions on a continuous linear 0- to 10-point scale. For example, patients are asked, "How much control do you feel you have over your illness?" or "How much do you experience symptoms from your illness?" Although each item can stand alone as its own scale, a sum score can be computed by reverse scoring items 3, 4, and 7, and summing them with remaining items 1 through 8. The sum score ranges from 0 to 80, with higher scores representing a more negative perception of the illness.

Depressive Symptoms

The *Center for Epidemiological Studies-Depression Scale* (CES-D; Radloff, 1977) is a 20-item scale that assesses participants' depressive symptoms in the past week. Participants are asked to rate how often each statement applied to them in the previous week on a 4-point scale from 0 ("rarely or none of the time") to 3 ("most or all of the time"). Scores range from 0 to 60, with higher scores representing greater depressive symptoms.

The Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke, & Williams, 1999) is a self-report scale that assesses symptoms of major depressive disorder as defined by the DSM-IV. The domain is depressive symptoms and its accompanying functional impairment. The traditional cutoff score for the PHQ-9 is ≥10, with higher scores indicating higher levels of depressive symptoms.

Anxiety

The state subscale of the *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1970) will be used to assess symptoms of anxiety. It is a 20-item scale that asks respondents to indicate how they are feeling "right now, at this very moment." Sample items include "I feel at ease" and "I feel nervous." A sum score can be computed, with higher scores indicating higher levels of state anxiety.

Emotional Distress

The *Profile of Mood States* (McNair et al., 1971) is used to assess patient mood. The POMS is a 65-item self-report inventory asking the subject how they have felt during the past *week*, yielding six mood subscales: Anxiety, Depression, Anger, Vigor, Fatigue, and confusion. Individual scale scores can be computed, as well as an overall mood disturbance score. Higher scores indicate higher levels of that particular mood.

The *Impact of Events Scale* (Horowitz et al., 1979; Weiss & Marmar, 1996) is a 22-item standardized self-report questionnaire used to assess reactions to cancer diagnosis and treatment. Responses are rated on a 5-point scale; higher scores indicate greater distress.

Appendix 3. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law

Aspartate aminotransferase (AST) or ALT ≥3 x upper limit or normal (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 (ALP).

Hy's Law

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

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

As soon as possible after the biochemistry abnormality is initially detected, the study medical monitor and the investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP and to ensure that

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

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

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

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

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

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

- Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.
- Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAEreport following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The requirement to conduct

follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

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

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

- If the answer is **No:**

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

- If the answer is **Yes**:

  > Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.
  >
  > - If there is no significant change, no action is required.
  > - If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this appendix for reporting PHL as an SAE.

LABORATORY TESTS

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

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

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HbsAg HBV DNA IgM and IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA
Other viral infections	IgM 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 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Table 15: Chronic Lymphocytic Leukemia Health-Related Quality of Life and Emotional Distress Assessment

	Screening	Cycle 1, Day 1 (Only if not finished from screening).	Cycle 2, 3, 4, Day 1	Cycle 5, Day1	Cycle 6, 7, 8, Day 1	Cycle 9 Day 1	Cycle 10, 11 Day 1	Cycle 12, Day 1 (Cycle 13 Day 1 for Cohorts 3 and 4)	Cycle 18 Day 1 (Cycle 19 Day 1 for Cohorts 3 and 4)	Cycle 24 Day 1	End of Study (36 months complete or off prior to this)
Charlson Comorbidity Index (Completed by Study Personnel)	x	x									
Sociodemographics	x	x						x		x	x
Life Events	x	x						x		x	x
Social Support	x	x		x		x		x	x	x	x
Social Contacts	x	x						x	x	x	x
Patient Health Questionnaire (PHQ-9)	x	x						x	x	x	x
Impact of Events	x	x		x		x		x	x	x	x
Feelings in the Past Month (SF-36)	x	x		x		x		x	x	x	x
EORTC-QLQ-C30 Questionnaire	x	x		x		x		x	x	x	x
GAD-7 Questionnaire	x	x						x	x	x	x
Anxiety (STAI)	x	x		x		x		x	x	x	x
Depressive Symptoms (CES-D)	x	x		x		x		x	x	x	x
Perception of CLL	x	x		x		x		x	x	x	x
Fatigue	x	x	x	x	x	x	x	x	x	x	x
Moods (POMS)	x	x	x	x	x	x	x	x	x	x	x
Sleep	x	x	x	x	x	x	x	x	x	x	x
Pain	x	x	x	x	x	x	x	x	x	x	x