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TITLE: A phase 2 trial of acalabrutinib for the treatment of relapsed/refractory autoimmune hemolytic anemia

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Clinical Trial Protocol

Protocol Title: A phase 2 trial of acalabrutinib for the treatment of relapsed/refractory autoimmune hemolytic anemia

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Sponsor/IND Holder:	City of Hope
Industry Partner:	AstraZeneca
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Participating Sites:	City of Hope (Duarte), Ohio State University
Short Title	…Acalabrutinib in AIHA…

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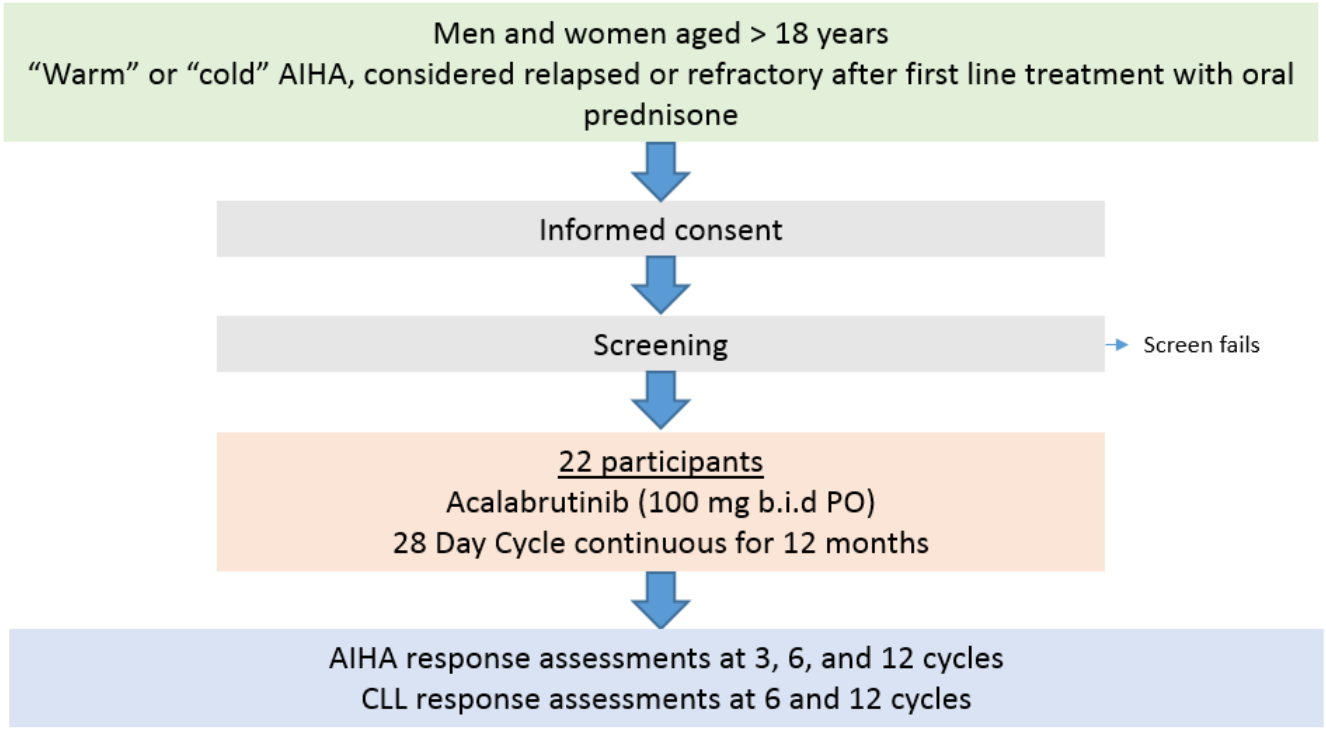
STUDY SCHEMA



PROTOCOL SYNOPSIS

Protocol Title

A phase 2 trial of acalabrutinib for the treatment of relapsed or refractory autoimmune hemolytic anemia

Study Detail

Population/Indication(s):	AIHA in patients with CLL
Phase:	Phase 2
Sample Size:	22
Estimated Accrual Duration:	36 months
Estimated Study Duration	60 months
Participant Duration:	24 months (12 months treatment, 12 months follow-up)
Participating Sites:	• City of Hope Duarte, CA • Ohio State University, OH
Study Agents:	Acalabrutinib
Sponsor:	City of Hope
Industry Partner:	AstraZeneca

Rationale for this Study

Autoimmune hemolytic anemia (AIHA) is a life-threatening disease with an incidence of 1-3 per 100,000 persons per year. In addition to idiopathic AIHA, a number of underlying conditions have been associated with this disorder, including viral infections, autoimmune and connective tissues diseases, and lymphoproliferative disorders. AIHA is particularly common among patients with chronic lymphocytic leukemia (CLL) with an incidence of ~2.3% as reported in a recent retrospective analysis of 1750 patients. First-line therapy of AIHA typically consists of corticosteroids, which induce initial responses in 70%-85% of patients with warm AIHA; however, only one-third of patients remain in long-term remission after stopping corticosteroids, and a further 50% require maintenance doses. Subsequent lines of immunosuppressive therapy carry initial response rates from 40-60%, though relapses are similarly common. Therefore, in the relapsed/refractory setting, safe and effective treatments for AIHA are needed. Ibrutinib, a small molecule inhibitor of Bruton tyrosine kinase (BTK), inhibits B-cell activity and has been shown to inhibit production of auto-antibodies in murine models of autoimmunity, suggesting their potential efficacy in multiple autoimmune conditions. Preliminary evidence suggests that ibrutinib may be efficacious in treatment of CLL-associated AIHA, as 50% of patients who presented with hemolysis and received therapy with the BTK inhibitor were able to discontinue immunosuppressive therapy. A second-generation selective BTK inhibitor, acalabrutinib, may be associated with fewer off-target effects including diminished frequency of side effects including bleeding and atrial fibrillation, and showed increased efficacy against AIHA in a murine model. This study will assess if acalabrutinib can increase hemoglobin and reduce transfusion requirements in patients with relapsed or refractory AIHA.

Treatment Description

Eligible participants enrolled in this study will receive acalabrutinib (100 mg, PO BID) for 12 cycles. Participants that experience disease progression or unacceptable toxicities will discontinue study drug and be removed from study. Treatment with acalabrutinib may be continued beyond 12 cycles, for a maximum of 36 cycles, if the study participant might benefit from ongoing therapy in the opinion of treating physician (e.g., ongoing therapy for CLL is required).

Objectives

Primary Objective(s)

- Assess the efficacy of acalabrutinib in patients with relapsed or refractory AIHA

Secondary Objective(s)

- Evaluate acalabrutinib's ability to induce short term and sustained hemoglobin response

- Assess the toxicity of acalabrutinib
- Evaluate efficacy of acalabrutinib in CLL

Exploratory Objective(s)

- Assess the effect of acalabrutinib on T-cell functionality in an autoimmune disorder.

Study Design

This is a phase 2, single-arm, open-label study to assess the efficacy and safety of acalabrutinib in the treatment of CLL patients with relapsed/refractory AIHA.

Evaluation Criteria and Endpoints

Primary Endpoint(s):

- AIHA Overall Response Rate (ORR) after 6 cycles, including complete and partial response

Secondary Endpoint(s):

- AIHA ORR after 3 and 12 cycles of therapy; frequency of PRBC (packed red blood cell) transfusion; Incidence of toxicity [per CTCAE v5.0] and IWCLL 2018[1] (hematologic) criteria; CLL ORR after 6 and 12 cycles of therapy; duration of AIHA respose and duration of CLL response

Exploratory Endpoint

- Percentage of T-cell subsets among study participants

Statistical Considerations

A sample size of 20 achieves an approximate 87% power using a one-sided binomial exact test with a significance level (alpha) of 0.05 for detecting improvement of 0.3 (0.6 from 0.3) in response rate, based upon the assumption that a response of 30% or less indicates no benefit. The actual type I error is 0.048 and the exact binomial test will require 10 or more responders in 20 patients evaluable for the primary endpoint to reject the null hypothesis of 0.3. Anticipating up to 10% patients not evaluable for the primary endpoint, a total of 22 participants will be enrolled.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Men and women, aged >18 years
- “Warm" or "cold" AIHA in patients with CLL, relapsed/refractory (RR) after first line treatment with oral prednisone (with or without rituximab), defined by:

  - anemia (Hgb≤10 g/dL; or Hgb>10 g/dL dependent on transfusions to maintain this level of hemoglobin), and

  - laboratory evidence of hemolysis: 3 of 4 markers present (increased reticulocyte count, increased indirect bilirubin, increased lactate dehydrogenase, haptoglobin < institutional lower limit of normal)
- Positive DAT (score ≥ 1+) – either IgG DAT, C3 DAT, or both. Eligibility of patients with Coombs-negative AIHA should be confirmed by the trial investigator at each respective study site.
- ECOG performance status grade ≤2
- Histologically or flow cytometry confirmed diagnosis of CLL/SLL
- Prior to starting study agent, participant must have organ function as defined below:
  - Direct bilirubin ≤3 X institutional upper limit of normal (ULN) or 1 mg/dL, whichever is higher, if deemed related to hemolysis by the investigator
  - AST or ALT ≤3 X institutional ULN
  - Estimated CrCL using the Cockroft-Gault equation (or an alternative equation, per institutional standard) ≥30 mL/min.
  - Absolute neutrophil count (ANC) ≥500/mm^3, platelet count ≥30,000/mm^3.
  - PT/INR or aPTT <2 x ULN. Exception: subjects receiving warfarin are excluded; however, those receiving other anticoagulant therapy who have a higher INR/aPTT are permitted to enroll

Main Exclusion Criteria

- Prior therapeutic intervention with any of the following:
  - Therapeutic anticancer antibodies within 2 weeks;
  - Radio- or toxin-immunoconjugates within 10 weeks;
  - BH3-mimetic venetoclax, PI3K inhibitors and other "targeted" therapy– within 6 half-lives;
  - Treatment with ibrutinib, acalabrutinib or another BTK inhibitor within 12 months
- All other chemotherapy, radiation therapy within 3 weeks prior to initiation of therapy.
- Inadequate recovery from adverse events related to prior therapy to grade 1 or baseline (excluding Grade 2 alopecia and neuropathy).
- Chronic use of corticosteroids in excess of prednisone 60 mg/day or its equivalent.
- Allogeneic stem cell transplant within the past 12 months or ongoing immunosuppressive therapy.
- History of prior malignancy except:
  - malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of therapy on current study;
  - adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease;
  - adequately treated in situ carcinomas (e.g., breast, cervical, esophageal, etc.) without evidence of disease;
  - asymptomatic prostate cancer managed with "watch and wait" strategy;
- History of Human Immunodeficiency Virus (HIV) infection or active hepatitis B or C.
- Major surgery (requiring general anesthesia) within 28 days prior to initiation of therapy.
- Patients with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting or any other condition that will interfere significantly with drug absorption.
- Requires treatment with strong CYP3A inhibitors or inducers. If the patient requires a strong CYP3A inhibitor/inducer, they should not be enrolled even if it could be held for 14 days before the first dose of study drug.
- Requirement for concurrent therapy with vitamin K antagonists (e.g., warfarin)
- Active uncontrolled infection
- Positive pregnancy test or breastfeeding

Investigational Product Dosage and Administration

- Acalabrutinib, 100 mg by mouth every 12 hours daily on a 28-day cycle for 12 cycles; however, particpants deriving clinical benefit may, at the discretion of the Pincipal Investigator, receive additional cycles of this treatment.

Clinical Observations and Tests to be Performed

- Safety assessments (CBCs with differential, comprehensive chemistry panel, and coagulation)
- Response assessments
- CT/PET scans
- Correlative tumor blood samples.

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ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
AIC	Autoimmune cytopenia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CR	Complete response
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational new drug application
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable

NCI	National Cancer Institute
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
ORR	Overall response rate
PET	Positron emission tomography
PI	Principal Investigator
PO	*Per os* (by mouth, orally)
PR	Partial response
RNI	Reportable new information
RR	Relapsed/refractory
SAE	Serious adverse event
SLL	Small lymphocytic lymphoma
ULN	Upper limit of normal
UP	Unanticipated problem

1.0 OBJECTIVES

1.1 Primary Objective(s)

- Assess the efficacy of acalabrutinib in CLL patients with relapsed or refractory AIHA

1.2 Secondary Objective(s)

- Evaluate acalabrutinib's ability to induce short term and sustained hemoglobin response
- Assess the toxicity of acalabrutinib
- Evaluate efficacy of acalabrutinib in CLL

1.3 Exploratory Objective(s)

- Assess the effect of acalabrutinib on T-cell functionality in an autoimmune disorder.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Overview of Autoimmune hemolytic Anemia (AIHA)

Autoimmune hemolytic anemia (AIHA) is a life-threatening autoimmune disease characterized by autoantibodies targeting antigens on erythrocytes. This process subsequently results in the destruction of erythrocyte by either extravascular phagocytosis in the spleen, liver, and bone marrow, or via intravascular complement-mediated lysis.[2] The incidence of AIHA is approximately 1-3 per 100,000 persons per year, and though often cases are often idiopathic (~50% of cases), they can also occur secondary to another disease such as viral infections, autoimmune diseases (~20% of cases), and lymphoproliferative disorders (~20% of cases).[2-4]

Warm AIHA (wAIHA) is the most common subtype, accounting for 65% to 70% of AIHA.[2] The warm subtype of AIHA is characterized by immunoglobulin G (IgG) autoantibodies binding to erythrocytes at 37°C, resulting in their destruction via tissue macrophages (i.e., extravascular phagocytosis). Depending on the IgG subtype, warm antibody hemolytic anemia may also promote intravascular hemolysis by binding complement to erythrocytes. Accounting for approximately 20% to 25% of AIHAs, cold agglutinin disease (CAD) is characterized by production of IgM autoantibodies that optimally fix to complement at 4°C, and prevalently causes intravascular hemolysis.[2,5,6] Another 8% of patients with AIHA have both warm IgG and cold IgM antibodies and are termed mixed autoantibody hemolytic anemias.[7]

2.1.2 Management of AIHA in Chronic Lymphocytic Leukemia

Autoimmune cytopenias (AIC) are frequently observed in patients with chronic lymphocytic leukemia (CLL), and include AIHA, immune thrombocytopenia (ITP), pure red cell aplasia (PRCA) and autoimmune granulocytopenia (AIG).[8] AIHA is common among patients with chronic lymphocytic leukemia (CLL), with warm AIHA being the most common subtype in these patients. The incidence of CLL-associated AIHA is ~2.3% conservatively and as high as 15% in some cohorts.[9,10] Patients with CLL developing AIHA may carry prognostic significance as this subset of patients is linked to poor survival[11], with the late onset of AIHA in the course of CLL associated with inferior outcomes compared to early onset of AIHA.[8] Reasons for such inferior survival may, in part, be explained by AIHA patients having higher risk infections, and bleeding and cardiovascular complications.[8]

The treatment of AIHA has typically included use of corticosteroids, splenectomy and conventional immunosuppressive drug.[2] Importantly, the therapeutic strategy is largely dependent on the AIHA subtype. Use of corticosteroids in the frontline is widely adopted for treating warm antibody AIHA, but are relatively ineffective for cases of cold AIHA. For warm AIHA, initial treatment with prednisone is associated with responses in 70%-85% of patients; however, even this is short-lived as only 15% to 20% of patients achieve long-term remission upon

withdrawal of corticosteroid.[4] Subsequent lines of immunosuppressive therapy (e.g., cyclophosphamide, rituximab) carry initial response rates from 40-60%, but durable responses occur in only 20% to 30% treated patients.[2,12,13] For example, in a cohort of 14 steroid-refractory patients with AIHA secondary to CLL, rituximab monotherapy was associated with a complete response (CR) and partial response (PR) of 3 (22%) and 7 (50%) patients, respectively.[14] Of the 8 patients still alive at the mean follow-up of 17 months, only 6 (40%) were transfusion-free.

Many treatment approaches have also examined the use of corticosteroids in combination with cyclophosphamide and rituximab.[9] Using a combination regimen of dexamethasone (12 mg), rituximab (375 mg/m^2) and cyclophosphamide (750 mg/m^2) (RCD) in a cohort of 48 CLL patients including 26 with AIHA, 9 with immune thrombocytopenia (ITP), and 8 with Evans syndrome. Overall, the RCD regimen achieved a response rate of 89.5% for AIHA, but relapse occurred in nearly 40% of patients with a median response duration of 24 months.[15]

2.1.3 Bruton Tyrosine Kinase Inhibitors for Treating AIHA

Bruton's tyrosine kinase (BTK) mediates B-cell signaling and is also present in innate immune cells, but not T cells.[16] Specifically, activation of the B-cell receptor (BCR) in response to antigen-binding, and/or other stimulation (e.g., CD40, toll-like receptors [TLRs], Fc receptors [FCRs] and chemokine receptors) elicits activation of Src family kinases, SYK (spleen tyrosine kinase) and LYN, which in turn activates BTK.[16] As such, BTK plays a central role in modulation of BCR signaling, and while overexpression of BTK can result in autoimmunity, decreased BTK expression improves the outcomes of autoimmune diseases.[16-18] Moreover, unlike normal B cells, autoreactive B cells appear to be more dependent upon BTK for survival.[19]

Ibrutinib, a small molecule inhibitor of BTK, inhibits B-cell activity and has been shown to inhibit production of auto-antibodies in murine models of autoimmunity suggesting their potential efficacy in multiple autoimmune conditions.[16,20,21] Additionally, ibrutinib also inhibits IL-2 inducible T-cell kinase (ITK), and thereby can modulate activation of certain T-cell subsets that contribute to the development of humoral autoimmunity.[22] As Th1 cytokines (IFN-gamma, IL-12 and TNF-alpha) are reduced in AIHA, the ability of BTK inhibitors to potentiate Th1-mediated immune responses may play an important role in their activity in this condition.[22,23]

While AIHA is a common complication of CLL, many clinical trials with BTK inhibitors have typically excluded patients with uncontrolled hemolysis; recent clinical findings, however, point to the utility of BTK inhibition in the treatment of AIHA.[10,24-26] Rogers et al[10] conducted a retrospective cohort review of 301 patients that participated in several clinical trials investigating ibrutinib (with or without anti-CD20 monoclonal antibody therapy) for treatment of CLL. Of these 301 patients, 78 patients had a history of autoimmune cytopenias (AIC), of which 44 (56%) were AIHA. Of those with AIC, 22 were receiving AIC therapy prior to start of ibrutinib. Notably, of these 22 patients, 19 (86%) were able to discontinue the AIC therapy after a median of 4.7 months from start of ibrutinib. Though not statistically significant, the treatment emergent cases of AIC was decreased from 13 AIC episodes per 1000 patient-years of ibrutinib exposure for those receiving ibrutinib alone to 7 episodes per 1000 patient-years of ibrutinib treatment for those receiving concomitant anti-CD20 monoclonal antibody treatment.

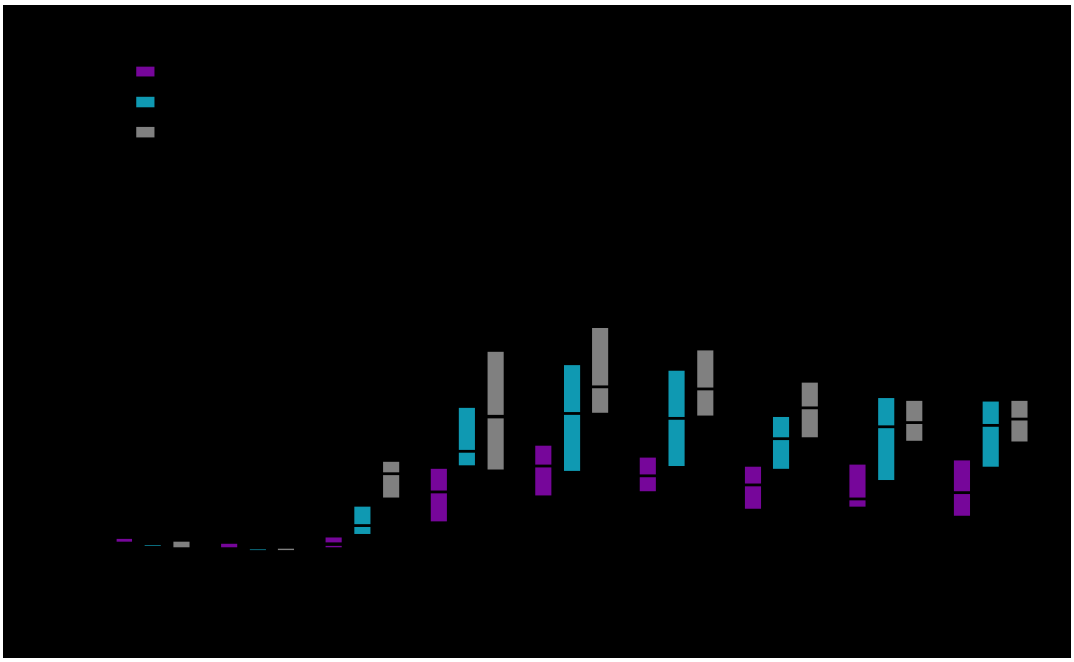
Montillo et al[25] retrospectively assessed data from the phase 3 RESONATE trial, in which patients with previously treated CLL were randomized to receive treatment with ibrutinib (n=195) or ofatumumab (n=191). Median treatment duration was 18.3 months for patients on ibrutinib versus 5.3 months for ofatumumab. A total of 38 and 42 patients with a history of AIHA or ITP were identified in the ibrutinib and ofatumumab treatment arms, respectively. While no new AIC were observed among those treated with ibrutinib, 4 patients randomized to the ofatumumab arm developed AIC (n = 2 AIHA and n = 2 ITP).

A retrospective cohort study[27] done at Mayo Clinic included 193 patients who received ibrutinib for CLL outside of a clinical trial had 11 cases of treatment-emergent AIC which is 6% of the cohort and consistent with the findings in the cohort reported by Rogers et al.[10] In this cohort 29/193 (15%) had a prior history of AIC and 12 were on a chronic therapy for AIC. Of these 12, 8 (67%) were able to discontinue their chronic AIC therapy while taking ibrutinib with no relapses or worsening of AIC.[28]

Manda et al[24] published a case report of a 70 year-old man with asymptomatic CLL (with del(17p)) that presented 12 months later with fatigue, generalized weakness, dyspnea and chest pain on mild exertion. Warm AIHA was confirmed using a direct antiglobin test (DAT), and the patient was initially treated with prednisone (1 mg/kg), but remained symptomatic at 2 week follow-up. A subsequent 2-week treatment with cyclophosphamide (500 mg/m2) and vincristine (2 mg) in addition to steroid therapy also failed to improve symptoms. The patient was then started on ibrutinib (420 mg daily), which after 3 weeks, was associated with a complete resolution of AIHA and CLL-related symptoms.

The above findings provide clinical data that targeting of the BTK pathway may have a role in controlling AIHA in CLL. Among the new agents, acalabrutinib has gained increasing favor as a second-generation selective BTK inhibitor. It is hoped that fewer off target effects will result in a better safety profile compared to ibrutinib.

Supporting this, laboratory studies in the rat-RBC inducible murine model of AIHA demonstrate that pharmacologic BTK inhibition reduces anti-RBC autoantibody production (Rogers et al[20], unpublished). In this study C3H/B6 F1 WT mice were treated with either vehicle (10% β-cyclodextrin), acalabrutinib (0.16 mg/mL) or ibrutinib (0.16 mg/mL) via drinking water for 2 weeks then injected intraperitoneally with washed rat RBCs weekly for 4 weeks while the drug water was continued. The rat RBC injections induce a measurable autoimmune response starting around 14 days after the first injection and peaking around days 28-35. Autoantibody production was measured by a flow cytometry assay which detects IgG on the surface of RBCs taken from the circulation of the treated mice. Treatment with acalabrutinib reduced anti-RBC autoantibody compared to both vehicle and ibrutinib (see figure). There was a trend towards decreased autoantibody production compared to vehicle in the mice treated with ibrutinib that did not reach statistical significance. This supports that acalabrutinib may be more beneficial for the treatment of AIHA compared to ibrutinib.



2.2 Overview of Acalabrutinib (ACP-196)

2.2.1 Acalabrutinib in Treating CLL

Acalabrutinib (CALQUENCE®, ACP-196) is a second-generation BTK inhibitor that shows higher selectivity for BTK, while simultaneously lacking irreversible inhibition of activities of other kinases such as epidermal growth factor

receptor (EGFR), interleukin-2-inducible T-cell kinase (ITK), and T cell X chromosome kinase (Txk), among others.[29,30] This higher target selectivity is expected to contribute to the improved safety profile over that of ibrutinib.[31] In the phase II ACE-LY-004 trial consisting of 124 patients with mantle cell lymphoma (MCL), administration of acalabrutinib (100 mg PO twice daily [bid]) was associated with an objective response rate (ORR) of 80.6%, including a complete response (CR) rate of 42.7% and a partial response (PR) rate of 37.9%. The estimated duration of response (DOR) rates at 12 and 24 months were 73.2% and 52.4%, respectively; and the median DOR was 25.7 months.[32] The most common adverse events (AE) were primarily grade 1 or 2, with headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%). The most common grade 3 or worse AEs were neutropenia (10%), anemia (9%), and pneumonia (5%).[31] Based on these findings, acalabrutinib received FDA approval in August 2017 for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.[33,34]

Acalabrutinib has received FDA approval in therapy of CLL based on two large randomized trials, ASCEND and ELEVATE TN, in patients with R/R and TN CLL, respectively, which were conducted after encouraging results of the phase I/II ACE-CL-001 trial (NCT02029443) evaluating the safety and efficacy of acalabrutinib for patients with relapsed CLL.[35] A total of 61 patients that had received a median of 3 previous therapies were enrolled and assigned to receive oral acalabrutinib dose of 100, 175, 250 or 400 mg once daily in the phase I dose-escalation portion, or 100 mg (bid) in the phase II portion of the study. The authors reported an ORR of 95% (57 of 60 evaluable patients). Notably, ORR was 100% (n = 18) in patients with chromosome 17p13.1 deletion. Additional sub-analyses of patient subgroups from the ACE-CL-001 trial have reported that among study participants that were intolerant to treatment with ibrutinib (i.e., experienced ibrutinib-related AEs), the ORR was 76% (22 of 29 evaluable patients), including 1 complete, 14 partial and 7 partial responses with lymphocytosis. A median time of 3.7 months to at least partial response was observed.[36] Additionally, in a sub-group of patients with Richter Transformation (n = 29), the ORR was 38%, with the median duration of response reported as 5.7 months.[37]

The efficacy of acalabrutinib in patients with relapsed or refractory CLL was based upon a multicenter, randomized, open-label trial (ASCEND; NCT02970318). The trial enrolled 310 patients with relapsed or refractory CLL after at least 1 prior systemic therapy but excluded patients who had previous treatment with either venetoclax, a BTK inhibitor, or a phosphoinositide-3 kinase inhibitor. Patients were randomized in a 1:1 ratio to receive either: acalabrutinib 100 mg or Investigator's choice of idelalisib plus a rituximab product (IR) or bendamustine plus a rituximab product (BR). Acalabrutinib monotherapy was found to significantly improve PFS with a more tolerable safety profile versus IdR/BR in R/R CLL patients.[38] At a median follow-up of 16.1 months, PFS in the acalabrutinib arm vs the IdR/BR arm was significantly prolonged (median NR versus 16.5 months; HR 0.31, 95% CI 0.20 - 0.49, P<0.0001). Twelve-month PFS rates were 88% vs 68% with acalabrutinib vs IdR/BR. ORR and 12-month OS rates were both similar with acalabrutinib and IdR/BR arms (ORR: 81% and 75%, 12-month OS: 94% and 91%). The most common AEs with acalabrutinib were headache (22%), neutropenia (19%); diarrhea (18%), anemia and cough (15% each). Grade ≥3 AEs (≥5%) with acalabrutinib were neutropenia (16%), anemia (12%) and pneumonia (5%). AEs of interest were atrial fibrillation (5.2% on acalabrutinib vs 3.3% on IdR/BR), bleeding AEs (26% vs 7.2%), Grade ≥3 infections (15% vs 24%) and second primary malignancies (excluding NMSC; 6.5% vs 2.6%).

In the ELEVATE TN trial in treatment-naïve CLL patients with a median follow-up of 28 months acalabrutinib + obinutuzumab (O) significantly prolonged PFS vs O + chlorambucil (Clb) (median not reached [NR] vs 22.6 mo; HR 0.10, 95% CI 0.06-0.18, P<0.0001), reducing the risk of progression or death by 90%. Acalabrutinib also prolonged PFS vs O + Clb (HR 0.20, 95% CI 0.13-0.31, P<0.0001). Estimated 30-mo PFS rates with acalabrutinib + O, acalabrutinib, and O + Clb were 90%, 82%, and 34%, respectively.[39]

2.2.2 Rationale for Acalabrutinib in AIHA

Second-line therapy of AIHA with cytotoxic and immunosuppressive drugs such as azathioprine, cyclophosphamide, and cyclosporine is reported to provide a 40%-60% response rate, but their use is often associated with serious side effects.[2,12,13] Anti-CD20 targeting with rituximab for the treatment of

relapsed/refractory AIHA achieves a 60-70% response rate, with a median duration of response of 19 months.[40] However, most of these patients inevitably relapse. Although splenectomy remains an option in this setting, surgical morbidity and risk for serious infectious complications are inherent challenges to this treatment approach.[2,4] Likewise, other treatment options such as plasmapheresis, and danazol have not proved effective.[4] Altogether, these findings highlight the need for novel treatment approaches, especially in CLL-associated AIHA where there is little prospective or retrospective data on these approaches and immunosuppression will have higher risks due to the already increased risk for infection in patients with CLL.

Preclinical and preliminary clinical evidence strongly suggests that BTK inhibition modulates the immune system and may be efficacious in the treatment CLL-associated AIHA.[10,16-18,24-26] A second generation BTK inhibitor, acalabrutinib, provides a novel approach to evaluate the impact of BTK inhibition on treating AIHA, as well as control the underlying autoimmune or lymphoproliferative disorder that may be driving AIHA. Moreover, acalabrutinib has gained increasing favor as a second-generation BTK inhibitor with potentially fewer off-target effects leading to side effects such as bleeding and atrial fibrillation.[29] This makes acalabrutinib an attractive option for treatment of AIHA. The aim of this study is to investigate whether acalabrutinib will be effective in the treatment of relapse or refractory AIHA, and assess its effect on T-cell function in patients with CLL.

2.3 Background for Correlative Studies

Recent data suggests that ibrutinib increased CD4 and CD8 T-cell numbers, resulting in an increased Tcon/Treg ratio in CLL patients, but this effect was not observed with acalabrutinib.[41] However, both ibrutinib and acalabrutinib reduced expression of PD-1 and CTLA-4, suggesting that an immunolodulatory effect may still be observed with acalabrutinib. Thus, this study will evaluate the effects of acalabrutinib on T-cell populations. Particularly, these in vitro studies will measure T-cell activation across participant samples pre-acalabrutinib, then 3 and 6 months after initiating therapy with acalabrutinib.

2.4 Overview and Rationale of Study Design

Refer to Section 12.0 Statistical Considerations for additional information regarding statistical methods used in this study.

This is a single-arm, open label, phase II study to assess the efficacy of acalabrutinib in controlling relapsed or refractory AIHA in a setting of CLL. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

In this study, eligible participants will have a diagnosis of wAIHA or CAD (cold agglutinin disease) who had a recurrence, did not respond to, or did not tolerate at least one prior AIHA treatment with corticosteroid. Eligible participants will be administered acalabrutinib (100 mg PO BID) daily for 12 cycles (each cycle is 28 days). Treatment with acalabrutinib may be continued beyond 12 cycles if the study participant might benefit from ongoing therapy in the opinion of treating physician (e.g., ongoing therapy for CLL is required); the maximum number of cycles allowed on this study in such situations is 36 cycles. At the end of this treatment period (i.e. after acalabrutinib is discontinued), participants will be considered off-treatment and undergo follow-up evaluations in accordance with institutional standards (refer to Section10.0 Study Calendar).

A total of 22 participants are planned for enrollment to this study over a period of 36 months. After 6 patients are enrolled on study, investigators will discuss whether it is reasonable to continue accrual based on overall drug safety profile seen in the first 6 patients. Further enrollment will be held if two or more patients (of the first 6 patients) develop any grade 4 toxicity (assessed as possibly, probably, or definitely related to study drug) during cycle 1 of treatment, or if ≥3/6 patients need to discontinue therapy with acalabrutinib during cycle 1 of treatment due to perceived lack of efficacy. Accrual will also be paused any time if any death possibly, probably, or definitely attributed to study treatment occurred.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

Age Criteria, Performance status

__2. Age: ≥ 18 years

__3. ECOG ≤ 2

Nature of Illness and Illness Related Criteria

__4. "Warm" or "cold" AIHA in patients with CLL, relapsed/refractory (RR) after first line treatment with oral prednisone (with or without rituximab), defined as:

- anemia (Hgb≤10 g/dL; or Hgb>10 g/dL dependent on transfusions or maintenance therapy (rituximab, cyclosporin, etc) to maintain this level of hemoglobin, and
- laboratory evidence of hemolysis – presence of 3 of 4 markers (increased reticulocyte count, increased indirect bilirubin, increased lactate dehydrogenase, absent haptoglobin)

__5. Positive DAT (score ≥ 1+) – either IgG DAT, C3 DAT, or both. Eligibility of patients with Coombs-negative AIHA should be confirmed by the trial investigator at each respective study site.

__6. Histologically or flow cytometry confirmed diagnosis of CLL/SLL

__7. Participant must be able to swallow tablets or capsules.

Clinical Laboratory and Organ Function Criteria (To be performed within 30 days prior to Day 1 of protocol therapy unless otherwise stated)

__8. ANC ≥ 500/mm^3 unless due to disease involvement in the bone marrow or autoimmune neutropenia.	ANC:	Date:
__9. Platelets ≥ 30,000/mm^3 unless due to disease involvement in the bone marrow or autoimmune thrombocytopenia (Evans syndrome).	Plts:	Date:
__10. Direct bilirubin ≤ 3.0 X ULN, or 1 mg/dL, whichever is higher, if deemed related to hemolysis by the investigator.	ULN: Bil:	Date:
__11. AST ≤ 3.0 x ULN	ULN: AST:	Date:
__12. ALT ≤ 3.0 x ULN	ULN: ALT:	Date:

__13. Creatinine clearance of ≥ 30 mL/min per 24 hour urine test or the Cockcroft-Gault formula or $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:		Date:
__14. **If not receiving anticoagulants**: International Normalized Ratio (INR) OR Prothrombin (PT) < 2 x ULN **If on anticoagulant therapy**: PT must be within therapeutic range of intended use of anticoagulants	ULN: INR: PT:		Date:
__15. **If not receiving anticoagulants**: Activated Partial Thromboplastin Time (aPTT) < 2 x ULN **If on anticoagulant therapy**: aPTT must be within therapeutic range of intended use of anticoagulants	ULN: aPTT:		Date:
__16. Seronegative for HIV Ag/Ab combo, HCV*, active HBV (Surface Antigen Negative), and syphilis (RPR) *If positive, Hepatitis C RNA quantitation must be performed.	HIV: HCV: HBV: Syphilis:		Date:
__17. **Women of childbearing potential (WOCBP)**: negative urine or serum pregnancy test within the screening window prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine:	Serum:	Date:

Contraception

__18. Agreement by females of childbearing potential to use highly effective methods of birth control or abstain from heterosexual activity starting with the first dose of study therapy through 2 days after the last dose of protocol therapy.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion Criteria

Prior and concomitant therapies

__1. therapeutic anticancer antibodies within 2 weeks;

__2. radio- or toxin-immunoconjugates within 10 weeks;

__3. BH3-mimetic venetoclax, PI3K inhibitors and other “targeted” therapy– within 6 half-lives;

__4. Ibrutinib, acalabrutinib or another BTK inhibitor within 12 months

__5. Patients on stable chronic AIHA treatments are allowed provided the dose has not changed in the 4 weeks prior to enrollment

__6. Allogeneic stem cell transplant within 1 year prior to Day 1 of protocol therapy, or ongoing immunosuppressive therapy for cGVHD

__7. Chemotherapy, radiation therapy, biological therapy, immunotherapy within 21 days prior to Day 1 of protocol therapy

__8. Strong CYP3A4 inducers/ inhibitors. If the patient requires a strong CYP3A inhibitor/inducer, they should not be enrolled even if it could be held for 14 days before the first dose of study drug.

__9. Proton pump inhibitors (but patients who switch to H2-receptor antagonists or antacids are eligible for enrollment).

__10. Chronic use of corticosteroids (>2 weeks) in excess of prednisone 60 mg/day or its equivalent within 4 weeks prior to start of study therapy. Rescue steroids are allowed during trial.

__11. Vitamin K antagonists

Other illnesses or conditions

__12. Known intolerance to acalabrutinib

__13. History of bleeding disorders or with active bleeding.

__14. Patients with suspected or confirmed progressive multifocal leukoencephalopathy (PML)

__15. Patients with history of stroke or intracranial hemorrhage within 6 months.

__16. Inadequate recovery from adverse events related to prior therapy to grade 1 or baseline (excluding Grade 2 alopecia and neuropathy).

__17. Active uncontrolled infection

__18. Known history of immunodeficiency virus (HIV) infection

- Subjects who have an undetectable or unquantifiable HIV viral load with CD4 > 300 and are on HAART medication are allowed. Testing to be done only in patients suspected of having infections or exposures.

__19. Active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).

- Participants who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Note that IVIG administration may lead to positive anti-HBc test result.
- Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.

__20. Major surgery (requiring general anesthesia) within 28 days prior to initiation of therapy.

__21. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease that would limit absorption of oral medication.

__22. History of prior malignancy except:

- Malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of therapy on current study;
- Adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease;
- Adequately treated in situ carcinomas (e.g., breast, cervical, esophageal, etc.) without evidence of disease;
- Asymptomatic prostate cancer managed with “watch and wait” strategy;

__23. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or left ventricular ejection fraction (LVEF) ≤ 40%.

__24. Psychiatric illness/social situations that would limit compliance with study requirements.

__25. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial.

__26. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__27. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration Process

Allow up to 24 hours for the DCC to review eligibility. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix E)
    - Completed eligibility checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Signed Informed Consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's bill of Rights (California only)
3. When all source documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay review and registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
4. The DCC will send a Confirmation of Registration Form, including the Subject Study Number to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).

- The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).

5. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (Appendix E) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multicenter, open-label, single-arm Phase 2 trial with acalabrutinib for patients with CLL with relapsed or refractory AIHA. Treatment will be administered on an out-patient basis (in-patient administration is allowed if deemed necessary by the Investigator). Participants will be followed at least every 4 months after removal from study drug until 12 months after end of treatment, introduction of next treatment (including standard-of-care BTK inhibitors) for AIHA or CLL, or death, whichever occurs first.

5.2 Cycle Definition

The treatment cycle will be 28 days. Cycle 1 Day 1 is defined as the first day of acalabrutinib administration, and should occur within 30 days of consent. The cycle day count will continue despite a hold in acalabrutinib administration due to toxicities (See Section 7.2). However, the next cycle will be delayed as long as acalabrutinib is held and will start once acalabrutinib is restarted.

5.3 Treatment Plan

Eligible participants enrolled in this study will receive acalabrutinib (100 mg PO BID) on an *out-patient* basis (however, treatment may also be given inpatient). On-study treatment with acalabrutinib will continue for up to 12 28-day cycles. Participants will be considered off-treatment once study drug is permanently stopped. Treatment with acalabrutinib may be continued beyond 12 cycles, for a maximum of 36 cycles, if the study participant might benefit from ongoing therapy in the opinion of treating physician (e.g., ongoing therapy for CLL with R/R AIHA is required). Participants will be followed for an additional 12 months from time of last administration of study drug.

Regimen Description				
Agent	Dose	Route*	Schedule	Cycle Length
Acalabrutinib	100 mg	PO, every 12 hours	Continuous	28 days

5.4 Agent Administration

Acalabrutinib capsules should be taken orally twice daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed whole and participants should not attempt to open capsules or dissolve them in water. If a dose is missed by more than 3 hours, participants should wait and take next dose at regularly scheduled time. Do not make up for missed dose.

Participants will self-administer oral study agent, acalabrutinib, and are required to maintain a medication diary to assess compliance (refer to Appendix D). Participants will receive instruction on how to administer study drug

from a physician, clinical research nurse, or other designated, qualified healthcare provider. Participants will be provided with a medical diary and are required to record the date, dose, and the time of the ingestion.

5.5 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.0.

Note: Initiate a new cycle after all procedures/safety assessments have been completed.

5.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

- Completed protocol therapy (see Section 5.3)
- AIHA relapse or progressive disease for CLL
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (See Section 17.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments, and then to follow-up (Refer to the Follow-Up section below).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.7 Follow-Up

All participants will enter follow-up after completing End of Treatment assessments (per Study Calendar in Section 10.0 footnote d), until one of criteria in Section 5.8 below is met.

Assessment time points and windows are detailed in Section 10.0.

5.8 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and 12 months of follow-up after protocol treatment)
- Withdrawal of consent (See Section 17.5)
- Start of new therapy for either AIHA or CLL (including standard-of-care BTK inhibitors)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.9 Prohibited and Concomitant Therapies/Medications

5.9.1 Allowed concomitant medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to

notify the investigational site about any new medications begun after the start of the study treatment. Each participant's medication and supplement profile should be reviewed by investigator and/or an oncology trained pharmacist to ensure compliance with this aspect of care. If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record/medical record.

5.9.2 Prohibited medications, treatments and procedures

Patients will not receive any other therapy for CLL besides the study therapy.

Participants are prohibited from receiving the following therapies during screening and for the duration of their participation in this study:

- Any anti-cancer systemic chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), or targeted agents (venetoclax, duvelisib, etc.)
- Any immunotherapy (e.g., rituximab, GA101, alemtuzumab, or ofatumumab)
- Bone marrow transplant or CAR T-cells
- Any other experimental therapy, or radiation therapy while receiving acalabrutinib
- Vitamin K antagonists (e.g., warfarin)

5.9.3 Cautionary medications, treatments and procedures

Co-administration of acalabrutinib with a proton pump inhibitor should be avoided. Co-administration of acalabrutinib with a strong or moderate CYP3A inhibitors may increase acalabrutinib plasma concentrations resulting in increased toxicity. Use of strong or moderate CYP3A inhibitors should be avoided. Conversely, co-administration of acalabrutinib with a strong CYP3A inducer should be avoided as this may decrease acalabrutinib concentrations. Refer to **Table 5.9.1** for examples of proton pump inhibitors, and CYP3A inhibitor and inducers.

Table 5.9.1. Examples of proton pump inhibitors, and CYP3A inhibitors and inducers

Proton-pump inhibitors[1]
Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole, Dexlansoprazole
Strong CYP3A Inhibitors[1,2]
Ketoconazole, Clarithromycin, Itraconazole, Nefazodone, Saquinavir, Ritonavir, Indinavir, Nelfinavir, Voriconazole, Lopinavir, Telithromycin, Conivaptan, Posaconazole, Boceprevir, Telaprevir, Cobicistat, Idelalisib, Grapefruit, Starfruit, Seville Oranges
Moderate CYP3A Inhibitors[1,2]
Erythromycin, Verapamil, Diltiazem, Cyclosporine, Ciprofloxacin, Fluvoxamine, Fluconazole, Aprepitant, Imatinib, Nilotinib, Dronedarone, Crizotinib, Atazanavir, Letermovir, Duvelisib
Strong CYP3A Inducers[1,2]
Phenytoin, Carbamazepine, Rifampin, Mitotane, Fosphenytoin, St John's Wort, Enzalutamide Lumacaftor
[1]This is not an exhaustive list. Investigators should consult additional resources (e.g., website, drug label) for a full list or for more info on individual drugs. [2]Refer to Flockhart Table™ for a more detailed list of CYP3A inducers and inhibitors (https://drug-interactions.medicine.iu.edu/Main-Table.aspx).

5.10 Supportive care

With the exception of prohibited therapies (refer to Prohibited therapies sub-section above), participants should receive prophylactic or supportive as clinically indicated per institutional policies.

5.10.1 Corticosteroids

Participants are not permitted to be receiving chronic corticosteroids (>2 weeks within the 4 week period prior to first dose of study medication; at dosages equivalent to prednisone >60 mg/day) at time of screening and enrollment on to this study – see Section 3.2. Concomitant use of corticosteroids for management of AIHA in conjunction with study drug is permitted at this dose, but it is anticipated that a taper will occur while patient is receiving acalabrutinib, and should be completed by the end of 8 weeks on study to a dose of ≤20 mg/day of prednisone or equivalent. The use of corticosteroids for treating AIHA should be in accordance with institutional standards.

5.10.2 Infection prophylaxis and treatment

Participants receiving acalabrutinib are at risk for infection, and appropriate prophylaxis in accordance with institutional standards is recommended. In general, participants with documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the Investigator for a given infectious condition, according to standard institutional practice.

5.10.3 Nausea/vomiting

No routine prophylactic anti-emetic treatment is required at the start of treatment; however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter per institutional guidelines.

5.10.4 Diet

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

5.10.5 Gastric acid reducing agents

Co-administration of acalabrutinib and a proton pump inhibitor should be avoided. If treatment with a gastric acid reducing agent is required, investigators should consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate).

In the case of antacids, acalabrutinib dosing should be separated by at least 2 hours. For use of H2-receptor antagonists, acalabrutinib dosing should be taken 2 hours before administration of H2-receptor antagonist.

5.10.6 Transfusions of platelets and red blood cells

Platelet transfusions are permitted as medically necessary per institutional guidelines (e.g., for platelets <10,000/µL in the absence of clinical bleeding). Each transfusion event (and number of units given) will recorded in the CRF.

Red blood cell transfusion should be considered for all participants with anemia, especially those with hemoglobin values ≤6 g/dL. Each transfusion event (and number of units given) will be recorded in the CRF.

5.10.7 Anti-platelet agents and anticoagulants

Use of vitamin K antagonists (e.g., warfarin) is prohibited while on study.

Other anticoagulants (direct anticoagulants, heparin products) and antiplatelet agents may be used in participants who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Participants who develop a requirement for therapeutic anticoagulation while on study (e.g., new atrial fibrillation, or venous thrombosis) may stay on study, and will be carefully monitored for bleeding risks.

5.10.8 Tumor Lysis Syndrome

Tumor lysis syndrome associated with CLL should be monitored (e.g., uric acid) and appropriate hydration measure and therapy with anti-hyperuricemic (e.g., allopurinol) should be performed as clinically indicated per institutional guidelines.

5.10.9 Study Drug Overdose

In the event of participant ingestion of more than the prescribed dosage of acalabrutinib (100 mg BID), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated per institutional guidelines. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Overdoses should be reported by the Investigator to the Sponsor and AstraZeneca as described in Section 14.4.1.

6.0 ANTICIPATED ADVERSE EVENTS

6.1 Acalabrutinib

Per the Investigator Brochure edition 9.0 dated Feb 2020 [32]the expected toxicities for acalabrutinib are:

System Organ Class	Adverse Reactions
Infections and infestations[a]	
Very common	Infection[b], upper respiratory tract infection, lower respiratory tract infection[c], urinary tract infection
Common	Herpesvirus infection
Blood and lymphatic system disorders[d]	
Very common	Neutropenia[e], anemia[f], thrombocytopenia[g], lymphocytosis[h]
Nervous system disorders	
Very common	Headache, dizziness
Rare	Progressive multifocal leukoencephalopathy
Gastrointestinal system disorders	
Very common	Diarrhea, nausea
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[i], arthralgia
Metabolism and nutrition disorders	
Rare	Tumor lysis syndrome
General disorders and administration site conditions	
Very common	Fatigue[j]
Skin and subcutaneous tissue disorders	
Very common	Bruising[k], rash[l]
Vascular disorders	
Very common	Hemorrhage[m]
Cardiac disorders	
Common	Atrial fibrillation or flutter, hypertension
Laboratory abnormality	
Very common	Uric acid increase, ALT increase, AST increase, bilirubin increase
Neoplasms, benign, malignant, and unspecified	

System Organ Class	Adverse Reactions
Common	Second primary malignancy, non-melanoma skin cancer

a. Includes any adverse reactions involving infection or febrile neutropenia
b. Upper respiratory tract infection, nasopharyngitis and sinusitis
c. Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
d. Derived from adverse reaction and laboratory data
e. Includes neutropenia, neutrophil count decreased, and related laboratory data
f. Includes anemia, red blood cell count decreased, and related laboratory data
g. Includes thrombocytopenia, platelet count decreased, and related laboratory data
h. Includes lymphocytosis, lymphocyte count increased, and related laboratory data
i. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain
j. Includes asthenia, fatigue, and lethargy
k. Includes bruise, contusion, and ecchymosis
l. Includes rash, dermatitis, and other related terms
m. Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).

The important risks of acalabrutinib are the following:

Hemorrhage

Serious hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with acalabrutinib; some of these bleeding events resulted in fatal outcomes. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding.

Infections

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have been reported in clinical studies with acalabrutinib. The most frequently reported Grade 3 or 4 infection was pneumonia. Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation (resulting in liver failure and death in 1 case) and cases of progressive multifocal leukoencephalopathy have occurred in subjects with hematologic malignancies. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects should be closely monitored as appropriate.

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 primary investigator.

Atrial fibrillation

Events of atrial fibrillation/flutter have been reported in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. The mechanism for atrial fibrillation is not well understood.

7.0 DOSE DELAY / MODIFICATION GUIDELINES

7.1 Dose Delays

Any toxicity observed during the course of the study could be managed by an interruption of the study drug treatment. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. Please refer to Tables 7.2.1 and 7.2.2 for dosing delays and modifications.

In general, dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e., elective surgery, unrelated medical events) not related to study therapy. Participants should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the investigator. The reason for interruption should be documented in the participant's study record.

7.2 Dose Modifications

Please refer to Acalabrutinib Investigator Brochure edition 9.0[32] for dosing delays and modifications.

Unavoidable use of strong CYP3A inhibitor or inducer may also require a reduction or increase of acalabrutinib dose (refer to Table 7.2.2).

Table 7.2.1 Recommended Dose Modifications for Adverse Reactions

Event	AE Occurrence	Dose Modification
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	1st or 2nd occurrence:	Interrupt acalabrutinib until resolved to Grade 1 or baseline and resume at 100 mg PO BID.
	3rd occurrence:	Interrupt acalabrutinib until resolved to Grade 1 or baseline and resume at 100 mg PO once daily (QD)
	4th occurrence:	Discontinue study drug. Remove participant from study

Table 7.2.2 Dose Modifications for Acalabrutinib with concomitant CYP3A inhibitors or inducers

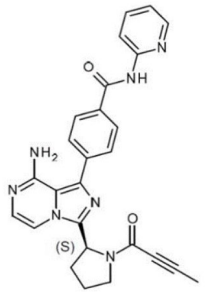
CYP3A*	Co-administered Drug	Acalabrutinib Dose Modification
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to 7 days), interrupt acalabrutinib.
	Moderate CYP3A inhibitor	100 mg QD
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase acalabrutinib dose to 200 mg BID.
*Refer to Section 5.9 for examples of CYP3A inhibitor and inducers		

8.0 AGENT INFORMATION

8.1 Acalabrutinib (Calquence®, ACP-196)

Acalabrutinib has been FDA approved for adult patients with CLL or SLL or mantle cell lymphoma (MCL) with have received at least one prior therapy.

8.1.1 Description

Structural Formula	
Molecular Formula	$C_{26}H_{23}N_7O_2$
Molecular Weight	465.51 kDa

Acalabrutinib is a white to yellow powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH > 6. Acalabrutinib supplied as yellow and blue hard capsules for oral administration, where each capsule contains 100 mg acalabrutinib and the following inactive ingredients: silicified microcrystalline cellulose, partially pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink stating “ACA 100 mg”.

8.1.2 Mechanism of action

Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumor growth in mouse xenograft models.

8.1.3 Pharmacokinetics and Metabolism

Half-life:	1 hr acalabrutinib, 3.5 h ACP-5862
Distribution:	Highly bound to plasma protein
Metabolism:	Predominantly metabolized by CYP3A enzymes; ACP-5862 is a major metabolite
Excretion:	84% feces, 12% urine

8.1.4 Toxicology

See Section 6.1 for detailed list of anticipated AEs.

8.1.5 Storage

Store at 20°C-25°C (68°F-77°F). Excursions are permitted to 15°C-30°C (59°F-86°F).

8.1.6 Handling

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package. Use caution when handling acalabrutinib, avoid eye or skin contact with the drug product. If there is exposure to the drug product, the individual should be treated for physical exposure (skin washing) or inhalation (move to fresh air, as necessary), and, if needed, seek medical advice.

8.1.7 Administration

See Section 5.4

8.1.8 Supplier

Acalabrutinib will be supplied by the manufacturer, Astra Zeneca, and prepared by the local site pharmacy per manufacturer instructions. Following submission and approval of the required regulatory documents, a supply of acalabrutinib may be ordered from Astra Zeneca by completing a Drug Request Form.

8.1.9 Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to Astra Zeneca for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Astra Zeneca.

8.1.10 Destruction and Return

At the end of the study, or earlier upon approval from study management, unused supplies of study drug should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

9.0 CORRELATIVE/ SPECIAL STUDIES

The exploratory objectives of this study are to evaluate the T-cell repertoire in participants with AIHA-associated CLL that receive acalabrutinib. The effects of acalabrutinib treatment on T-cell repertoire will be evaluated by flow cytometry. Plasma cytokine level will be measured by relevant methods (for example, ELISA Research Sample Collection and Dispensation

9.1.1 Correlative blood

9.1.1.1 Overview and Time points

Peripheral blood will be collected prior to study treatment/procedures at the time points indicated in Table 9.1.2.1

Table 9.1.2.1 Overview of correlative blood studies

Time points of collection	Total volume collected	Tube type	Receiving laboratory	Type of analysis
C1D1, C4D1, C7D1, C13D1	15-20 ml	Green-top (sodium or lithium heparin)	Investigator Laboratory	FACS/Cytokine

9.1.1.2 Labeling of blood samples

Label tubes with COH protocol #, subject ID (issued by DCC), institution, date and actual time point of collection (e.g. C1D1 for Day 1 of Cycle 1), and if applicable patient initials.

9.1.1.3 Collection and post-collection guidelines

Refer to Table 9.1.2.3 for collection and post-collection instructions.

Table 9.1.2.3 Blood sample collection and post-collection instructions.

Tube Type	Collection details	Site of collection	Post-collection instructions
Green-top	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. 2- Invert tubes eight times after collection. 3- **Immediately** place the tubes on **ice**.	COH Only	**Promptly** deliver the blood samples for processing **within 4 hours to:** Alexey Danilov Laboratory Kaplan Clinical Research Bldg 1st Floor, 158-1022 City of Hope National Medical Center 1500 E Duarte Rd, Duarte, CA.
		OSU Site Only	**Promptly** deliver the blood samples for processing **within 4 hours to:** Kerry Rogers Laboratory Ohio State University 460 West 10th Ave Columbus, OH
		MDACC Site Only	**Ship whole blood samples** on day of collection overnight at room temp to: Alexey Danilov Laboratory Kaplan Clinical Research Bldg 1st Floor, 158-1022 City of Hope National Medical Center 1500 E Duarte Rd, Duarte, CA 91010. Please refer to **Appendix F** and **Appendix G**

Peripheral blood mononuclear cells (PBMCs) and plasma will be separated by density gradient centrifugation. Cells will be frozen and stored in liquid nitrogen. Plasma will be stored at -70°C.

9.2 Laboratory Studies Performed

Flow cytometry will be used to evaluate leukocyte subpopulations (e.g., CD3, CD4, CD45, TCRγδ, CD14, CD16, CD56). Additional surface markers will be used to discriminate different maturation stages of effector cells (CD28, CD27, CD45RA, CD3, CD8, CCR7, CD4, CD45): naive T cells, central memory, effector memory and CD45RA expressing effector memory cells; Tregs (CD4+CD25+FoxP3+CD127low); Th17 (IL-17positive). To assess activation levels of circulating T-cells, a panel of activation markers will be used (e.g., CD38, CD25, CD69, HLA-DR). The immunology panel may be expanded to include other markers. Plasma cytokine levels will be measured by ELISA.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Treatment or Assessment (± 7 days)[a]	Screening[b]	Cycle 1				C2-3	C4	C5-6	C7	C8-12	C13 & every 3 Cycles[c]	EoT[d]	Follow-up[e]
		D1	D8	D15	D22	D1	D1	D1	D1	D1	D1		
Informed consent	X												
Medical history[g]	X	X											
Inclusion/Exclusion Criteria[h]	X												
Registration[i]	X												
Other anti-cancer treatment[j]	X												
Concurrent med review	X	X	X	X	X	X	X	X	X	X	X		X
Physical exam[l]	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X		X
ECOG Performance Status (Appendix A)	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Event Eval[n]		X											
12-lead EKG[o]	X												
Pregnancy test[p]	X	X										X	
Hematology[q]	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Immunoglobulins[s]	X										X		
Hemolysis parameters[t]	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, aPTT, INR	X												
HBsAg, HBcAb, HCVAb, RPR	X												
HIV test	X												
CT Imaging and CLL assessment (Appendix C)[u]	X								X		X		
Bone Marrow Biopsy[v]											X		
AIHA disease assessment (Appendix B)	X						X		X		X		X

Molecular and Genetic Tests[w]	X												
Acalabrutinib[x]		*Orally, every 12 hours*											
Medication diary[y]		X	X	X	X	X	X	X	X	X	X		
Research blood collection[z]		X					X		X		X		

a. Ideally the clinic visit and all the study requirements should be performed on Day 1 of each cycle as indicated, but may be performed within 7 days before or after the scheduled day. Each treatment cycle is 28 days

b. Screening activities to occur within 30 days prior to the start of protocol therapy.

c. Protocol therapy may last up to 12 cycles, until unacceptable toxicity or disease progression (see Section 5.6 for more comprehensive list). At the end of 12 cycles, treatment with acalabrutinib may be continued if the study participant might benefit from the ongoing therapy in the opinion of the treating physician.

d. An End of Treatment (EOT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason, including disease progression. This visit should occur at 30 (±7) days from time of the last dose of study drug 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 CLL therapy or demonstrates disease progression within this timeframe Subjects who withdraw consent for study treatment should still be encouraged to complete the EOT assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn.

e. Follow-up assessment are to occur in accordance with standard of care, with participants visits occurring at least every 4 months, up to 12 months from time last dose of study drug.

f. Informed consent process to be fully documented (see Section 17.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.

g. A medical history will be obtained by the investigator or qualified designee. To include information on demographics, all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's cancer will be recorded separately and not listed as medical history.

h. Eligibility criteria are detailed in Section 3.0.

i. Registration into a COH clinical trial management system (CTMS)

j. Document the following disease-specific information: number of prior treatment regimens for CLL and AIHA; drugs previously used in the therapy of CLL and AIHA; including (if available): therapy dates, and response, concomitant autoimmune disorders, including hematologic (immune thrombocytopenia, immune-mediated neutropenia) and non-hematologic (e.g., rheumatoid arthritis and other rheumatologic conditions; inflammatory bowel disease [Crohn's disease, ulcerative colitis]), History of ibrutinib intolerance (present versus not), Rai stage at diagnosis (if known) and the time of study entry.

k. Current list of medications will be acquired concurrent with medical history. See Section 5.9 for concomitant medication restrictions and guidelines. Baseline transfusion requirements must be assessed prior to start of study drug. Transfusion requirements prior to study start up to 6 months will be collected/documented, if available. Transfusion requirement will be assessed on day 1 of each cycle and number of units of PRBCs and platelets transfused during the previous cycle will be documented. Enter new medications started during the trial through the end of treatment visit. Record all medications taken for grade 3 and 4 SAEs.

l. Physical examination must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. Baseline complete physical exam per institutional standards and may include evaluating: weight, general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, and nervous system. Height is only required as part of screening. Weight should be recorded at each visit. More extensive physical exams will be performed if guided by the development of new symptoms.

m. Vital signs: blood pressure, heart rate, temperature, and oxygen saturation by pulse oximetry.

n. Adverse events will be assessed using the CTCAE v5.0 (non-hematologic) and IWCLL 2018 (hematologic). SAEs related to study procedures will be recorded and reported from the time the participant signs the Consent Form. Please see Section 14 for routine AE assessing and reporting (Section 14.6) and SAE reporting (Section 14.7).

o. Electrocardiogram (ECG): resting 12-lead ECGs will be recorded at screening, and as clinically indicated throughout the study.

p. A serum or urine pregnancy test is required during screening for women of childbearing potential. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required. For Day 1 Cycle 1, a pregnancy test may be omitted if previously obtained within 72 hours prior to first dose of trial treatment. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines. A serum or urine pregnancy test will be done for women of childbearing potential any time for missed or late menses, and at the end of treatment. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

q. Hematology: Hemoglobin; hematocrit; mean corpuscular volume (MCV); reticulocyte count (absolute and relative); leukocyte count; differential count; platelets. Additional hematology may be performed thereafter as clinically indicated

r. Biochemistry: Comprehensive metabolic panel (CMP), including: Na, K, Cl, CO_2, BUN, Creatinine, Ca, glucose, Albumin, Alkaline Phosphatase, total bilirubin, AST, ALT, total protein.

s. Serum immunoglobulins, IgG, IgM, and IgA are required at screening and on cycle 13 D1.

t. Hemolysis parameters: Reticulocytes, lactate dehydrogenase (LDH), bilirubin (direct/indirect), haptoglobulin and DAT.

u. Computed tomography (CT) scan of neck, chest, abdomen and pelvis per institutional guidelines (with intravenous contrast, wherever possible) will be performed for response assessment at screening, C7D1, C13D1 and annually thereafter. CLL response will be evaluated every time imaging is performed. A bone marrow biopsy will be performed only if CR is suspected. Positron emission tomography with CT (PET-CT) and/or magnetic resonance imaging studies may be performed as clinically indicated, per institutional guidelines, and is acceptable in place of CT, if performed.

v. Bone Marrow Biopsy - A bone marrow biopsy will be performed to document CR within 90 days of the imaging test where CR was suspected. - A bone marrow biopsy may be performed at screening per investigator discretion, but is not required.

w. Molecular and Genetic Assays: testing results are not required to proceed with study enrollment. Cellular and molecular assays will be performed according to institutional standards, at screening on specimens obtained within 6 months if no intervening therapy. The following assays will be planned as per standard of care: CLL FISH Panel (as per institutional standards), immunoglobulin heavy chain (IGVH) mutational status (unless already known), prognostic gene panel (e.g., HopeSeq panel performed at COH).

x. Participants will self-administer oral study agent, acalabrutinib. Participants will receive instruction on how to administer study drug from a physician, clinical research nurse, or other designated, qualified healthcare provider

y. Assessment of study agent adherence. Participants will be provided with a medical diary (Appendix D) and are required to record the date, dose, and the time of the ingestion. This will be reviewed at each clinic visit to assess compliance.

z. Research blood may be collected as part of any planned blood draw that is performed per institutional standard.

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Primary Endpoint(s)

Objective	Endpoint	Start	End
Assess the efficacy of acalabrutinib in CLL patients with relapsed or refractory AIHA	AIHA ORR after 6 cycles [ORR defined as proportion of patients who achieve complete and partial response; refer to Appendix B]	First dose of study drug [i.e. C1 Day 1]	After 6 cycles of therapy

Primary endpoint of AIHA ORR after 6 cycles will be defined as the proportion of patients achieving AIHA complete or partial response after 6 cycles. Patients evaluable for this endpoint include: 1) those who receive at least 6 cycles of treatment and have AIHA response evaluation after 6 cycles (each cycle = 28 days); 2) patients who terminate acalabrutinib prior to completing 6 cycles due to AIHA or CLL progressive disease (they will be counted as non-responders).

11.1.1 Response Criteria for AIHA

See Appendix B: AIHA Response Criteria [42]for the definition of clinical response for AIHA.

11.2 Secondary Endpoint(s)

Objective	Endpoint	Start	End
Evaluate acalabrutinib's ability to induce short term and sustained hemoglobin response	AIHA ORR after 3 and 12 cycles	First dose of study drug [i.e., C1 Day 1]	After 12 cycles of treatment
	Frequency of PRBC transfusion while receiving acalabrutinib		Up to 30 days after last dose
	AIHA-specific Relapse-Free Survival (RFS)		Until time of AIHA relapse, death, or end of follow-up, whichever occurs first. [up to 12 months after the last dose of study drug]
	AIHA Sustained Response		
Assess the toxicity of acalabrutinib	Incidence and type of treatment-related toxicity [per CTCAE v5.0 and IWCLL 2018 criteria[1]]		Up to 30 days after last dose of study drug
Evaluate efficacy of acalabrutinib in CLL	CLL ORR after 6, 12 cycles, per standard IWCLL criteria	First dose of study drug [i.e., C1 Day 1]	After 6 or 12 cycles from treatment start
	CLL-specific event-free survival (EFS)		Until time of progression, death, start of new therapy, or end of follow-up, whichever occurs first. [up to 12 months after the last dose of study drug]
	Duration of CLL response	When CR/PR is first documented	

AIHA ORR after 3 and 12 cycles: it will be defined as the proportion of patients achieving AIHA CR/PR after 3 or 12 cycles respectively. Patients evaluable for this endpoint include: : 1) those who receive at least 3 or 12 cycles of acalabrutinib treatment and have AIHA response evaluation after 3 or 12 cycles; 2) patients

who terminate acalabrutinib prior to completing 3 or 12 cycles due to relapse of AIHA or CLL progressive disease (they will be counted as non-responders).

Frequency of PRBC transfusion: it will be defined as the number of PRBC transfusions from start of protocol treatment through EOT.

AIHA-specific Relapse-Free Survival (RFS): it will be defined as the time from start of acalabrutinib treatment until death, or relapse of AIHA.[42] Patients without death, or AIHA relapse will be censored at the last follow-up or when they begin new therapy for CLL or AIHA. **Relapse of AIHA will be determined by the investigator. A minimal requirement is Hgb<10 g/dL and evidence of hemolysis per laboratory parameters**. Investigators will document the criteria by which relapse was assessed.

Toxicity: incidence, type, severity, and attribution of toxicities on the study will be assessed by CTCAE v5.0 (non-hematologic) and IWCLL 2018 (hematologic). All patients who receive at least 1 dose of acalabrutinib will be included in the toxicity analysis.

CLL ORR after 6 or 12 cycles: it will be defined as the proportion of patients achieving CLL CR /PR after 6 or 12 cycles respectively. Patients evaluable for this endpoint include: 1) those who receive at least 6 or 12 cycles of acalabrutinib and have a CLL response evaluation at those timepoints; 2) patients who terminate acalabrutinib treatment prior to completing 6 or 12 cycles due to CLL progressive disease (they will be counted as non-responders).

CLL-specific Event-free Survival (EFS): it will be defined as the time from start of acalabrutinib treatment until death, time of CLL progression, or start of new therapy for CLL, whichever earlier. Patients without death, CLL recurrence/progression, or start of new therapy for CLL will be censored at the last follow-up.

Duration of CLL-response: it will be estimated among patients who achieve CLL CR/PR on protocol treatment. It will be defined as the time from the first documented CLL CR/PR until death, time of CLL recurrence/progression, or start of new therapy for CLL, whichever earlier. Patients without death, CLL recurrence/progression, or start of new therapy for CLL will be censored at the last follow-up.

AIHA sustained response: it will be estimated among patients who achieve AIHA CR/PR on protocol treatment. It will be defined as the time from the first documented AIHA CR/PR until death or relapse of AIHA, whichever is earlier. Patients without death or AIHA relapse will be censored at the last follow-up or when they begin new therapy for AIHA or CLL.

11.2.1 Response Criteria for AIHA and for CLL

See Appendix B: AIHA Response Criteria for the definition of clinical response for AIHA.

CLL response will be determined per the investigators' assessment, according to Hallek et al[1] (see Appendix C: CLL/SLL Response Criteria). Response assessments are to coincide with CT measurements.

11.2.2 CLL Evaluation

Physical examination – physical exams will focus on documenting a change in the number of sites and sizes of lymphadenopathies, hepatomegaly and splenomegaly at the scheduled time points defined above. More extensive physical exams will be performed if guided by the development of new symptoms.

CBC – white blood cell count, hemoglobin and hematocrit, platelet count, and differential count, including both percent and absolute number of lymphocytes. CBC with differential should be assessed at schedule time points defined above.

CT scan of neck, chest, abdomen and pelvis with contrast, will be performed at scheduled time points defined above.

11.3 Exploratory Endpoint(s)

Objective	Endpoint	Start	End
Assess the effect of acalabrutinib on T-cell functionality in an autoimmune disorder.	Percentage of T-cell subsets among study participants	Baseline values (prior start of study therapy)	After 3, 6 and 12 cycles

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a Phase 2, single-arm, open-label study to assess the efficacy and safety of acalabrutinib in the treatment of CLL patients with AIHA. Refer to Section 2.4 Overview and Rationale of Study Design for a detailed description of the study design and endpoints.

12.2 Sample Size and Power

For warm AIHA, initial treatment with prednisone is associated with responses in 70%-85% of patients; however, even this is short-lived as only 15% to 20% of patients achieve long-term remission upon withdrawal of corticosteroids.[4] Subsequent lines of immunosuppressive therapy (e.g., cyclophosphamide, rituximab) carry initial response rates from 40-60%, but durable responses occur in only 20% to 30% treated patients.[2,12,13]

A sample size of 20 achieves an approximate 87% power using a one-sided binomial exact test with a significance level (alpha) of 0.05 for detecting improvement of 0.3 (0.6 from 0.3) in response rate , based upon the assumption that a response of 30% or less indicates no benefit. The actual type I error is 0.048 and the exact binomial test will require 10 or more responders in 20 patients evaluable for the primary endpoint to reject the null hypothesis of 0.3. Anticipating up to 10% patients not evaluable for the primary endpoint, a total of 22 participants will be enrolled.

Study enrollment is anticipated to occur over 36 months at a rate of approximately 7 patients per year

12.2.1 Analysis Populations

The evaluable patients for the clinical endpoints will be eligible participants who received at least 1 dose of protocol treatment, unless otherwise specified in Section 11.1 under the specific/particular endpoint.

The evaluable patients for the exploratory endpoints will be eligible participants who received at least 1 dose of protocol treatment and has at least 1 correlative blood specimen collected on the study.

12.3 Study Stopping Rules

The overall study will be paused if any of the following occurs:

- ≥2 of the first six participants develop any grade 4 toxicity (assessed as possibly, probably, or definitely related to study drug) during cycle 1 of treatment, or
- ≥3 of the first 6 participants need to discontinue therapy with acalabrutinib during cycle 1 of treatment due to perceived lack of efficacy, or
- Death with possible or higher attribution to acalabrutinib.

12.4 Statistical Analysis Plan

For continuous variables, descriptive statistics will include the mean, standard deviation (or standard error), median, range, and interquartile range. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of participants with no missing data (i.e. will add up to 100%). Kaplan-Meier survival curves will be displayed for time-to-event variables. Survival at specific timepoint will be estimated by the Kaplan-Meier product limit estimator along with the Greenwood estimator of standard error; 95% confidence interval will be constructed based on log-log transformation. Median survival time will be estimated when available, along with 2-sided 95% confidence interval (CI) based on Brookmeyer and Crowley method.

12.4.1 Analysis of Primary Endpoint

The probability of having AIHA-ORR at 6 cycles will be measured and reported with 95% exact confidence interval (CI). An exact binomial test against a null hypothesis of 30% rate will be performed at the 1-sided alpha of 0.05 to determine whether the AIHA-ORR rate at 6 cycles is disappointing or promising.

12.4.2 Analysis of the Secondary Endpoints

The probability of having AIHA-ORR at 3 or 12 cycles will be measured and reported with 95% exact confidence interval. AIHA-specific RFS will be estimated using Kaplan-Meier methods along with 95% confidence interval.

The CLL-ORR after 6 and12 cycles will be assessed and reported with 95% CI. The Kaplan-Meier method will be used to estimate CLL-specific PFS and DOR, and the summary statistics (e.g., 12-month survival, median survival, 95% confidence intervals) will be provided. DOR will be estimated only among responders (i.e. participants achieving CLL CR/PR at least once).

The frequency of PRBC transfusion will be summarized by descriptive statistics. The difference between the average number of PRBC transfusion per month during protocol treatment vs. the average number of PRBC transfusion at baseline (in the past 6 months before protocol treatment, if available) will be assessed by paired t-test.

Toxicity events will be tabulated and summarized using descriptive statistics such as count and percentages, by severity, attribution, and system organ class according to the CTCAE v5.0 (non-hematologic) and by severity according to IWCLL 2018 (hematologic). [1]

12.4.3 Analysis of the Exploratory Endpoint(s)

Flow cytometry will be used to assess T-cell repertoire and evaluate changes associated with acalabrutinib. The distribution of T-cell subtypes distribution will be described by mean, standard deviation (SD), minimal, and maximal values. Comparison of group variables will be as assessed using a nonparametric test of independence (e.g., Chi-square test or Fisher's exact test).

12.5 Handling of Missing Data

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the

COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in the most recent version of the NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Definite** - The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Possible** - The event may be related to study treatment as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Unlikely** - The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications.
- **Unrelated** - The event is clearly NOT related to the study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered.

14.2 Adverse Events of Special Interest (AESI)

The following events are adverse events of special interest (AESIs) for participants exposed to acalabrutinib, and must be reported to the sponsor and manufacturer expeditiously, irrespective of regulatory seriousness criteria or causality:

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

14.2.1 Overdose

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of acalabrutinib assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

If the associated AE fulfills serious criteria, Investigators should report the event to the Sponsor within 24 hours using the SAE Reporting Form. The Sponsor should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta-Pharma/AstraZeneca per contractual guidelines.

All reports of Overdose should be forwarded to Acerta Pharma/AstraZeneca Data Entry Site (see email address below) within 30 days unless the report meets serious criteria. If report meets serious criteria, it is to be reported to Acerta Pharma/AstraZeneca within 15 calendar days.

14.2.2 Secondary Malignancies

Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious 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 Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy. For studies in Early Stage and Late Stage Immuno-Oncology and Oncology Studies: 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 IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

14.3 Pregnancies

14.3.1 Female participants:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy up to 2 days post-last dose of acalabrutinib are considered immediately reportable events. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI and the DCC immediately within 24 hours of awareness (Section 14.5)**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines.

Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines. The Study PI or designee will subsequently inform Acerta Pharma/AstraZeneca (Section 14.7)

14.3.2 Male participants:

If a female partner of a male participant becomes pregnant, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the Study PI.

14.4 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

Adverse events will be assessed using the CTCAE v5.0 (non-hematologic) and IWCLL 2018 (hematologic). AEs recorded in the eCRF include:

- For Cycle 1, highest grade of each AE type, plus any grade 3 or higher adverse event (regardless of whether or not it is the highest grade);
- For Cycle 2+ through EOT, during each cycle/period, highest grade of each AE type
- All SAEs/AESIs

14.5 Expedited Reporting

Table 14.5 indicates what events must be reported expeditiously.

Table 14.5 Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	• All UPs
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy • All UPs and AEs that meet the definition of a UP • AESIs (Section 14.4), overdose
From Day 1 of protocol therapy up to 120 days post-last acalabrutinib dose	• Pregnancies and lactation
Post Safety Follow-Up to removal from study	• All SAEs that are considered possibly, probably or definitely related to acalabrutinib.
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator. **The DCC should be consulted prior to ending the follow-up of events that have stabilized.**	

14.5.1 Expedited reporting guidelines **(COH only)**

14.5.1.1 To the DCC/Study PI

All events that meet the criteria specified in Table 14.5 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

Email the following information to DCC@coh.org and the Study PI (adanilov@coh.org): Participant ID, date the event met criteria for reporting, whether the event meets the definition of serious, whether the event is an unanticipated problem, grade of event, attribution of event, whether the event is a known expected toxicity to study agent.

14.5.1.2 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites.

14.5.1.3 To Participating Investigators

Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

Forward to participating sites all IND safety reports received from Acerta Pharma/AstraZeneca, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

14.5.2 Expedited reporting guidelines **(non-COH sites only)**

14.5.2.1 To the DCC/Study PI

All events that meet the criteria specified in Table 14.5 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Non-COH participating sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
    *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet. A modifiable Microsoft Word document is also available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the study PI (adanilov@coh.org) and DCC@coh.org with the subject title as "Acalabrutinib in AIHA SAE COH IRB #20311".
    a. If available and applicable, sites may include the local IRB submission for this event in the submission.

4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

14.6 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, regardless of the site of occurrence, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days (via COH OIDRA) of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.7 Reporting to Acerta Pharma/AstraZeneca

The Study PI (or designee) will:

- Report the following to Acerta Pharma/AstraZeneca per the guidelines provided in Table 14.6.
  - email: AEMailboxClinicalTrialTCS@astrazeneca.com
- Assist Acerta Pharma/AstraZeneca in investigating any SAE and will provide any follow-up information reasonably requested by Acerta Pharma/AstraZeneca.

Table 14.6 Timeframes for Reporting to Acerta Pharma/AstraZeneca

Type of Report	Reporting Timeframes
Pregnancy	**Within 24 hours** of being aware of the event
All expedited SAE reports (includes AESIs)	**Within 24 hours** of being aware of the event via a MedWatch 3500A form.
Aggregate safety reports	Forward Acerta Pharma/AstraZeneca quarterly (e.g. at time of COH PMT report).

- Forward to Acerta Pharma/AstraZeneca copies of initial/annual/final FDA IND submissions. Email: AEMailboxClinicalTrialTCS@astrazeneca.com.

The Sponsor will submit appropriate reports to applicable local regulatory agencies and to ethics committees (ECs) as per local regulations. The Sponsor will notify Acerta Pharma/AstraZeneca in parallel with submission to the IRB and concerned Regulatory Authority for Suspected Unexpected Serious Adverse Reactions (SUSARs) and within fifteen (15) calendar days of awareness for other SAEs or Special Situation Reports using individual unblinded or blinded case reports (Institution's Standard SAE Report Form, MedWatch, or CIOMS). New information will be submitted to Acerta Pharma/AstraZeneca within the same time frame as initial reports.

Whenever possible, 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 (EDC) system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to AstraZeneca, as outlined above. If study drug is discontinued because of an SAE, this information must be included in the SAE report.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

15.1 Reporting by COH

All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

15.2 Reporting by non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet to the Study PI (adanilov@coh.org) and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of "[Acalabrutinib in AIHA] Deviation COH IRB #20311". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.
3. Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The PMT, minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/UP/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site monitoring/auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring/auditing for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within the City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These document specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring to the study team and the COH DSMC.

16.5 Risk Determination

This is a high risk study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because this study involves a COH IND.

16.6 City of Hope Data and Safety Monitoring Committee (DSMC)

Data and safety will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the

safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the effects of the study drug on embryogenesis and reproduction are unknown.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study because safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to the DCC for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The Investigator/Institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository (COH IRB #16020) with some clinical information and potentially PHI attached or (b) discarded.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Acalabrutinib will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible

for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and AstraZeneca, and participating non-COH institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

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APPENDIX A: PERFORMANCE STATUS SCALES

Karnofsky Scale %	Karnofsky Description	ECOG* Scale	ECOG Description
100	Normal, no complaints, no evidence of disease.	**0**	Fully active, able to carry on all pre-disease activities without restriction.
90	Able to carry on normal activity, minor symptoms or signs of disease.		
80	Normal activity with effort, some signs or symptoms of disease.	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work.
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of own needs.	**2**	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
30	Severely disabled, hospitalization is indicated although death is not imminent.		
20	Hospitalization necessary, very sick, active supportive treatment necessary.	**4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
10	Moribund, fatal processes		
Dead		**5**	**Dead**

*also known as Zubrod, SWOG or WHO scale

APPENDIX B: AIHA RESPONSE CRITERIA

Treatment response will be determined per the investigators' assessment, according to Barcellini et al.[42]

AIHA Complete Response (CR^{AIHA}):	Hemoglobin >12 g/dL, **AND** no transfusion requirements. No laboratory evidence of ongoing hemolysis (haptoglobin, indirect bilirubin WNL, reticulocyte count <1.5 ULN)
AIHA Partial Response (PR^{AIHA}):	Hemoglobin level ≥10 g/dL (without transfusions), **OR** hemoglobin increase of at least 2 g/dL above pretreatment level, Presence of laboratory evidence of ongoing hemolysis.

APPENDIX C: CLL/SLL RESPONSE CRITERIA

Treatment response will be determined per the investigators' assessment, according to Hallek et al[1].

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.
CR, complete remission (all of the criteria have to be met);
PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve);
PD, progressive disease (at least 1 of the criteria of group A or group B has to be met);
SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

APPENDIX D-1: ACALABRUTINIB MEDICATION DIARY INSTRUCTIONS

Remember to bring this diary, all pill bottles, and any unused pills to each clinic visit.
Call your study doctor or nurse immediately if you are having any new or worsening side effects.

Study drug Instructions – When and How:

- Take acalabrutinib **twice a day** by mouth
- Take the pills with a large glass of water (~250ml) at approximately the same times each day
- Swallow pills; do not chew them or crush them
- Do not skip any doses unless your doctor tells you to.

When to stop taking acalabrutinib

- Do not stop taking acalabrutinib unless your doctor tells you to.

What if I miss a scheduled dose?

- If **less than 3 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If more than 3 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit after taking acalabrutinib?

- If you vomit your pills, write this down in your pill diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- Bring this diary, all pill bottles, and any unused pills to each clinic visit.
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty pill bottles or unused pills.
- **Your dose may be adjusted based on your side effects**

Contact Information		
Study Doctor **Phone:** **Name:**	**Study Coordinator** **Phone:** **Name:**	**Backup Study Coordinator** **Phone:** **Name:**

APPENDIX D-2: MEDICATION DIARY

Study Name: A phase 2 trial of acalabrutinib for the treatment of relapsed/refractory autoimmune hemolytic anemia

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken	Time since last meal	If dose missed, please provide reason:
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

Participant/Caregiver signature (please sign when submitting your diary): _____ Date ___/____/____

Study Name: A phase 2 trial of acalabrutinib for the treatment of relapsed/refractory autoimmune hemolytic anemia

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken	Time since last meal	If dose missed, please provide reason:
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							

Participant/Caregiver signature (please sign when submitting your diary): _____ Date ___/____/____

Study personnel ONLY:	# of Pill Bottles Returned: _____ # of Pills Returned: _____	**Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of pills returned), please reconcile (initials & date):**_____

APPENDIX E: REGISTRATION COVERSHEET

COH IRB# 20311: A phase 2 trial of acalabrutinib for the treatment of relapsed/refractory autoimmune hemolytic anemia

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
	PI/ Sub-Investigator:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX F: CORRELATIVE BLOOD COLLECTION FORM FOR MDACC ONLY

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **non-COH sites** for the following blood samples being sent to **COH Danilov Laboratory**:

Sample #	Collection Timepoint *	Expected Volume	Tube Type Used	Collected Volume	Time of Collection	Date of Collection	Indicate which sample was collected
1.	C1D1	15-20 ml	Green-top	____ mL	___:___ AM/ PM	___/___/___	☐
2.	C4D1	15-20 ml	Green-top	____ mL	___:___ AM/ PM	___/___/___	☐
3.	C7D1	15-20 ml	Green-top	____ mL	___:___ AM/ PM	___/___/___	☐
4.	C13D1	15-20 ml	Green-top	____ mL	___:___ AM/ PM	___/___/___	☐

A copy of this form should accompany the sample shipments to COH Danilov Laboratory. **Refer to the blood shipping guidelines for shipping instructions (Appendix G).**

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX G: BLOOD SHIPPING GUIDELINES TO CITY OF HOPE

*These guidelines apply to **MDACC site** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website*.*

1. Aim to ship samples on a **Monday through Thursday**. If this is not feasible, advance arrangements should be made with Danilov lab (DL-danilovlab@coh.org) or designee.

1. Blood samples in green-top tubes will be sent overnight at around 25°C in an appropriate container via FedEx.
2. On the day of shipment, email Danilov lab (DL-danilovlab@coh.org) or designee the FedEx shipment tracking#.
3. Ship samples with a copy of the correlative blood collection form (Appendix F) and a copy of the latest CBC results (with differential) and the date of the test to:

The Danilov Laboratory
Kaplan Clinical Research Bldg [(KCRB) Building 158], Room #1022
City of Hope, 1500 East Duarte Rd, Duarte CA 91010
DL-danilovlab@coh.org
626-218-1959