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TITLE: A Phase 2 Study of Acalabrutinib, Umbralisib and Ublituximab in Relapsed and Previously Untreated CLL Patients

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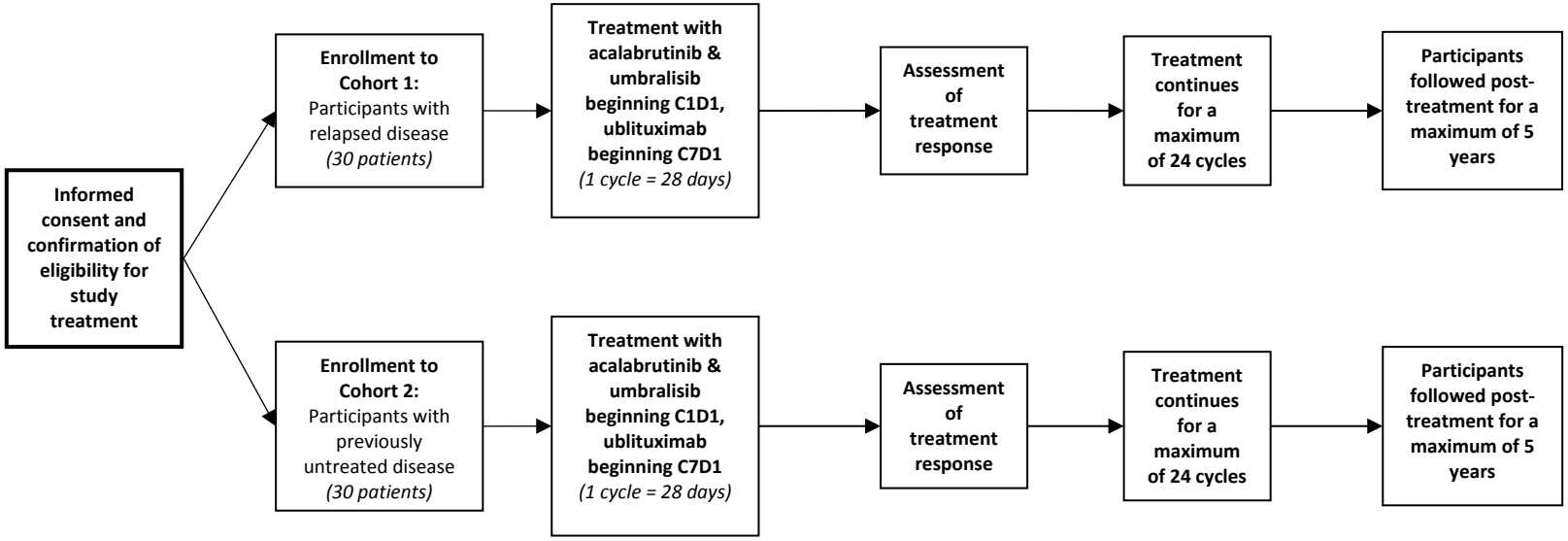
SCHEMA


Informed consent and confirmation of eligibility for study treatment
Enrollment to Cohort 1: Participants with relapsed disease (30 patients)
Enrollment to Cohort 2: Participants with previously untreated disease (30 patients)
Treatment with acalabrutinib & umbralisib beginning C1D1, ublituximab beginning C7D1 (1 cycle = 28 days)
Treatment with acalabrutinib & umbralisib beginning C1D1, ublituximab beginning C7D1 (1 cycle = 28 days)
Assessment of treatment response
Assessment of treatment response
Treatment continues for a maximum of 24 cycles
Treatment continues for a maximum of 24 cycles
Participants followed post-treatment for a maximum of 5 years
Participants followed post-treatment for a maximum of 5 years

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1. OBJECTIVES

1.1 Study Design

An open label, non-randomized phase 2 trial assessing the combination of acalabrutinib, umbralisib, and ublituximab in adult participants with chronic lymphocytic leukemia (CLL). Participants will be enrolled to one of two treatment cohorts:

- **Cohort 1:** Participants with relapsed disease
- **Cohort 2:** Participants who are treatment naïve

1.2 Primary Objective

- Assess the rate of complete remission (CR) after 24 cycles of treatment with acalabrutinib, umbralisib, and ublituximab in previously untreated and relapsed CLL patients per 2018 IW-CLL criteria.[1]

1.3 Secondary Objectives

- Determine the rates of partial remission (PR) and complete remission with incomplete count recovery (CRi) after 24 cycles of therapy.
- Evaluate the median progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS), as well as the rates at 2 years, 3 years, and 5 years.
- Assess the rates of CR with bone marrow minimal residual disease (MRD)-negativity, peripheral blood MRD-negativity, and correlation between blood and bone marrow MRD-negativity after 6, 12, and 24 cycles of treatment.
- Determine the rate of early therapy discontinuation and time to clinical progression.
- Evaluate the association between established CLL prognostic factors (including *FISH* cytogenetics, somatic mutations and *IGHV* mutation status) and treatment response.
- Confirm the safety and tolerability of the combination.

1.4 Exploratory Objectives

- Explore the association between novel CLL prognostic factors (including somatic mutations such as *SF3B1, TP53, NOTCH1,* and other mutations in the BCR/NFκB pathway) and rates of MRD-negativity, CR, PR, PFS, and OS.
- Perform BH3 profiling and explore rates of MRD-negativity, CR, PR, PFS, and OS.
- Assess the development and kinetics of *BTK*, *PLCG2* and *CARD11 s*omatic resistance mutations.
- Evaluate MRD measurements by flow cytometry as compared to those of the Adaptive ClonoSEQ sequencing technology after 12 cycles and at the primary response (24 cycle) endpoint.
- Assessment of baseline and on study levels of newly identified biomarker indicators of response and resistance.

- Characterization of T-cell phenotype of patients treated with the combination and comparison to previous patients treated with single agent umbralisib.

2. BACKGROUND

2.1 Study Disease and Rationale

CLL is the most common leukemia in Western countries, with about 19,000 new cases per year in the US. Most patients are over 70 years old at diagnosis, and over 75 when first treated. At this age multiple comorbidities and prescription medications are common, thereby limiting treatment choices in this population and making time-limited oral therapy for CLL appealing.[2]

CLL patients are divided according to their prognostic factors, and specifically, by the mutation status of the immunoglobulin heavy-chain rearrangement (*IGHV*), chromosomal abnormalities, and specific somatic mutations. Patients with deletion of the short arm of chromosome 17 (del17p) and/or a mutated *TP53* are at the highest risk. They tend to have more steadily progressing disease, a shorter interval before first therapy and a reduced response rate to standard chemoimmunotherapy (CIT).[3] Patients with unmutated IGHV also have a more rapid progression to therapy than those with mutated IGHV, typically with good response but with continuous relapse and reduced durability after chemoimmunotherapy.

Treatment, especially for older patients or those with any of the higher risk markers, is increasingly based on novel targeted therapies, mainly Bruton tyrosine kinase (BTK) and PI3K inhibitors, that usually at least partially overcome these poor prognostic factors. Although most CLL patients respond to these targeted agents, in both the first line and relapsed setting the CR rate is modest (about 10%) and the drugs are given indefinitely.[4,5] MRD-negativity, which is an independent predictor for survival in CLL after CIT or venetoclax, is seldom achieved with BCR inhibitor monotherapy.[6] Moreover, each drug has its own unique toxicity profile, in part due to off-target effects.[7] Ibrutinib, the first FDA approved BTK inhibitor and most widely used targeted small-molecule-agent in CLL, increases bleeding risk (up to 5% high-grade bleeding) and the incidence of atrial fibrillation (up to 16% at 18 months) and hypertension (25% and rising at 36 months).[8]Idelalisib, a first-generation PI3Kδ inhibitor, has a characteristic autoimmune toxicity profile, mainly colitis, hepatitis and pneumonitis.[5,9]

Targeting the B-cell receptor pathway with either inhibitors of BTK or PI3Kδ is highly effective for the treatment of CLL. However, deep remissions are uncommon, and drug resistance with single-agent therapy can occur. *In vitro* studies support the effectiveness of combining PI3Kδ and BTK inhibitors in CLL.[10] Combination treatment for dual blockade of pathways downstream of BCR could increase the effectiveness of each single agent, enable lower dose administration thus minimizing side effects, and potentially prevent drug-resistance. The combination of ibrutinib and idelalisib has been shown to synergistically inhibit *in-vitro* BCR-controlled adhesion in both mantle cell lymphoma (MCL) cell lines and primary MCL and CLL cells. This is a crucial mechanism of cell survival and likely explains the surge in lymphocytosis after BTK/PI3K-inhibitor administration.[10] This combination may increase initial lymphocytosis even further,

although this would not be clinically meaningful. The combination of acalabrutinib, a highly specific BTK inhibitor, with a different PI3K inhibitor (ACP-319) in a CLL mouse model resulted in significantly larger reductions in tumor burden and survival compared to single-agent therapy. It also reduced phosphorylation of pathways downstream of NF-kB signaling.[11]. Our group has recently combined ibrutinib with umbralisib and found that the combination was tolerable, with encouraging PFS and an early suggestion of higher CR rate.[12]

Ublituximab is a type I, chimeric, glycoengineered anti-CD20 monoclonal antibody that causes increased ADCC activity against B cells and shows activity as a single-agent in relapsed NHL and CLL patients, with an overall response rate of 50%.[13] A phase 2 study of its combination with ibrutinib in 45 patients with relapsed CLL showed a 90% PR rate at 6 months, due to clearance of lymphocytosis that is usually seen with ibrutinib alone. The combination was well tolerated. The most common AEs were infusion-related reactions (IRRs), diarrhea, fatigue, nausea, and rash. Grade 3/4 AEs were mainly hematological (7-11% cytopenias) and IRRs, and 9% of subjects discontinued study due to AEs.[14]

Previous phase 1 studies of umbralisib, a PI3K inhibitor highly selective for the δ isoform, and ublituximab in relapsed refractory NHL and CLL have demonstrated that the combination is well tolerated.[15] A recent phase 1/2 trial combining ibrutinib, umbralisib and ublituximab has established that the triplet is also well tolerated and can be given at the full phase 2/3 doses of each drug (see **Section 2.5**).[16]

There had been some concern that ibrutinib would interfere with anti-CD20 antibodies' activity. *In-vitro* data suggested that the off-target inhibition of ITK by ibrutinib would lead to decreased NK-mediated ADCC with rituximab[17] which was largely overcome with the Fc engineered obinutuzumab. However, this has not been shown *in-vivo*, and ublituximab is more similar to obinutuzumab. Moreover, ibrutinib was shown to downregulate CD20 expression in samples from patients' blood. *Ex-vivo*, tumor cells from patients on ibrutinib were less susceptible to anti-CD20 mAb-mediated complement-dependent-cytotoxicity (CDC), although opsonization by the complement protein C3d, which targets cells for phagocytosis, was relatively maintained. Interestingly, ibrutinib significantly inhibited trogocytosis, which is a major contributor to antigen loss and tumor escape during mAb therapy.[18,19] While the significance of these data are conflicting and unclear, clinical trials combining ibrutinib with anti-CD20 antibodies have shown no evidence of antagonism, although it is unclear that the antibody significantly increases CR rates when given early in therapy, nor does rituximab increase PFS.[20,21]

Acalabrutinib is a second-generation FDA approved BTK inhibitor that is highly specific for BTK. While a head-to-head comparison study has not been done, clinical data reported from separate clinical trials have indicated acalabrutinib is likely typically better tolerated by patients and has fewer off-target side effects than ibrutinib, including less cardiac toxicity.[22] Incorporating the more specific next-generation kinase inhibitors in therapy shows marked activity with less off-target activity.

Furthermore, recent *in-vitro* data suggests that acalabrutinib, as opposed to ibrutinib, has favorable activity against CLL cells together with CD20 antibodies, and does not mitigate ADCC, likely because it is a much more specific inhibitor of BTK.[23] A later antibody administration, when disease is already reduced, is also employed here, as it should lead to more favorable antibody pharmacokinetics and perhaps better clearance of residual disease. This hypothesis has some support from an ASH abstract presented in 2018, which suggested that delayed administration of obinutuzumab with ibrutinib resulted in a significantly higher CR rate than early obinutuzumab administration.[24]

We therefore plan to build on the prior phase 1 experience with ibrutinib-umbralisib and ibrutinib, umbralisib, ublituximab, by substituting acalabrutinib in a phase 2 study of the three-drug combination. From data available from separate clinical studies, acalabrutinib appears to be better tolerated than ibrutinib so this should not cause any unexpected toxicity. This study targeting less heavily pretreated patients will better establish the efficacy of the combination as measured by CR rate and PFS in untreated CLL patients and early relapsed patients.

The trial will have another two novel therapeutic approaches. First, ublituximab administration will be delayed in an attempt to improve its ability to clear residual bone marrow disease at a point when significant cytoreduction has already occurred and the half-life of the antibody should be prolonged. Second, treatment will be given for only 12 – 24 cycles, thus mitigating long-term adverse events and potentially reducing selection pressure for resistant clones. Patients who are not heavily pre-treated, especially those who are treatment-naïve, may benefit from a long drug-free period before they progress, at which time they could theoretically receive the same regimen again.

2.2 **Umbralisib (TGR-1202)**

Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies.

2.2.1 Preclinical Evaluations of Umbralisib

The potency of umbralisib against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at its Km value (100 μM) (Umbralisib Investigator Brochure). Selectivity over the other three isoforms, namely, α, β, and γ was also determined. [25-27]

Data demonstrated the specificity of umbralisib towards PI3Kδ with >1000, 50 and 48-fold selectivity over α, β, and γ, respectively in an enzyme-based assay, indicating that the primary mode of action of this compound is via inhibition of the δ isoform.

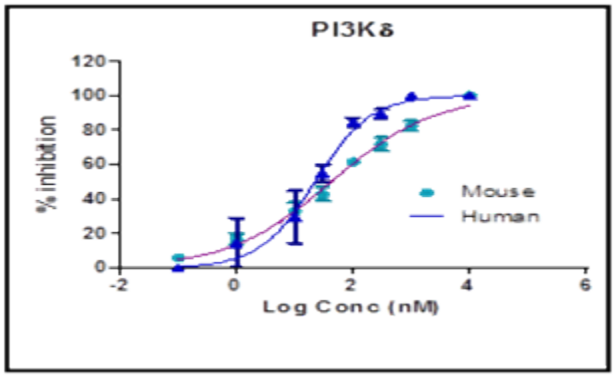


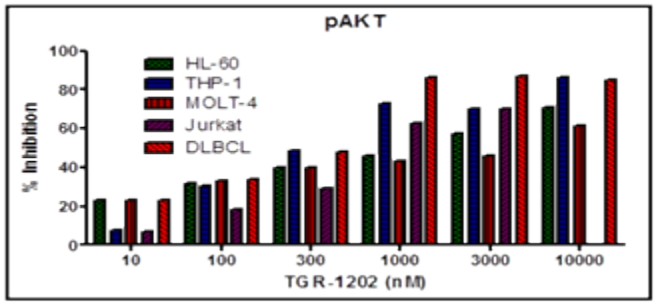
Figure 1: Umbralisib Potency Against Human and Mouse PI3K Isoforms

PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

Proliferation of immortalized leukemic cells representative of various indications was determined by a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (Umbralisib Investigator Brochure). Cells were incubated with umbralisib for different time-periods (72 -96 h) based on their doubling time. Data demonstrated the ability of umbralisib to inhibit leukemic cell proliferation albeit with different potencies based on the cell type. Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of umbralisib.

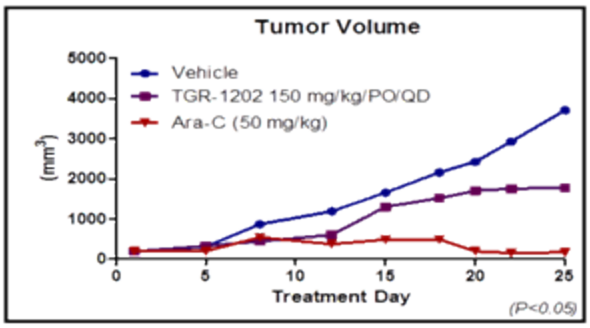
Subsequent to cell viability, the effect of umbralisib on AKT phosphorylation (Umbralisib Investigator Brochure) was determined. AKT, a serine threonine kinase, mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated AKT by umbralisib in representative cell lines was determined by Western blotting using a phospho-AKT (Ser473) antibody.

FIGURE 2: REDUCTION OF PAKT BY UMBRALISIB IN CELL LINES BY WESTERN BLOTTING



In vivo efficacy of umbralisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model. Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth.

FIGURE 3: UMBRALISIB *IN VIVO* EFFICACY



2.2.2 Toxicology

To assess the safety and toxicity of umbralisib a 28-day repeat dose study with a 14-day recovery period was conducted in CD-1 mice and beagle dogs, to evaluate the potential reversibility of findings and to support the use in humans. Umbralisib was administered orally in order to mimic the planned mode of clinical administration.

Once daily oral administration of umbralisib was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at 750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.
Once daily oral administration by capsule of umbralisib was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species.
Refer to the Umbralisib Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

2.2.3 Clinical Development of Umbralisib

2.2.3.1 Single-Agent in Subjects with Relapsed or Refractory Hematologic Malignancies

Umbralisib was evaluated in a single-agent Phase I dose-escalation study (Study TGR-1202-101; NCT01767766) in subjects with relapsed and refractory hematologic malignancies. There were 90 subjects enrolled and eligible for safety evaluation, and 73 subjects evaluable for efficacy in the modified intention to treat population. The median age was 64 years (range 51-72), 63% male, median number of prior therapies was 3, and 49% of subjects were refractory to their most recent prior therapy. Histological diagnoses included; CLL (n=24), FL (n=22), DLBCL (n=16), HL (n=11), MCL (n=6), MZL (n=5), WM (n=2), HCL and TCL (n=1 each). The majority of subjects (58%) had received 3 or more prior therapies.

Patients were enrolled in a 3+3 dose-escalation design starting at 50 mg QD with subsequent cohorts evaluating doses as high as 1800 mg QD. In an effort to further improve the oral bioavailability of umbralisib, the particle size of the drug product was reduced through a micronization process, resulting in greater absorption when tested in a bioequivalence crossover study in healthy subjects. This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1800 mg QD. The maximum tolerated dose (MTD) was 1200 mg QD of the micronized formulation, with 800 mg of this formulation selected as the recommended phase 2 dose based on changes in tumor burden correlated with dose-proportional plasma exposure. Intra-subject dose escalation rules allowed subjects enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts cleared safety evaluation. The most common treatment-emergent adverse events irrespective of causality were diarrhea (in 39 [43%] of 90 subjects), nausea (38 [42%]), and fatigue (28 [31%]). The most common grade 3 or 4 adverse events were neutropenia (in 12 [13%] subjects), anemia (eight [9%]) and thrombocytopenia (six [7%]). Serious adverse events considered at least possibly related to umbralisib occurred in seven subjects: pneumonia in three (3%) subjects, lung infection in one (1%), febrile neutropenia in one (1%), and colitis in two (2%), one of whom also had febrile neutropenia. Both cases of colitis occurred above the recommended phase 2 dose. No time-related trends in toxicity were noted. See the umbralisib investigator's brochure for a complete overview of the umbralisib side effect profile.

Dosing of umbralisib initially occurred in the fasting state, but was transitioned mid-study to fed state dosing, with subjects instructed to take umbralisib with food. All dosing of umbralisib is now conducted using the micronized formulation and in the fed state.

Among 73 subjects in the modified intention-to-treat population, which included subjects who received at least 800 mg per day of the original formulation or any dose of the micronized formulation and had at least one response assessment, 53 (73%) had reductions in disease burden, including 33 (45%) subjects with reductions of 50% or more, of which three (4%) were a complete response and 30 (41%) were a partial response. In subjects with relapsed or refractory CLL, 17 (85%) of 20 achieved an objective response, with ten (50%) achieving an objective response per 2008 IWCLL criteria, seven (35%) achieving a partial response with lymphocytosis, and the remaining three (15%) achieving stable disease. Of eight assessable subjects with CLL who had high-risk cytogenetic features, six (75%) had a response, of whom two (25%) had a partial response with lymphocytosis, and the remainder had stable disease. In subjects with follicular lymphoma, nine (53%) of 17 subjects achieved an objective response, including two (12%) who achieved a complete response; the remainder had a partial response. In subjects with diffuse large B-cell lymphoma, four (31%) of 13 achieved an objective response and two (15%) further subjects achieved stable disease. Responses for the other subject subgroups were Hodgkin lymphoma: one complete response, four stable disease, four progressive disease; marginal zone lymphoma: one partial response, four stable disease; Waldenström's macroglobulinemia: two stable disease; and mantle cell lymphoma: one partial response, four stable disease, and one progressive disease. In a post-hoc exploratory analysis, tumor reductions in most subjects with indolent lymphoma and CLL treated with umbralisib

tended to improve over time. The mean duration of response was 13.4 months (95% CI 7.7–19.1) in 16 subjects in the CLL cohort, 6.4 months (4.5–17.3) in four subjects in the DLBCL cohort, and 9.3 months (3.6–15.1) in nine subjects in the follicular lymphoma cohort. In a post-hoc exploratory analysis of progression-free survival, median progression-free survival was 24.0 months (95% CI 7.4 months–not reached) in 20 subjects with CLL, and 16 months (9.2 months–not reached) in 24 subjects with indolent non-Hodgkin lymphoma (follicular lymphoma, Waldenström's macroglobulinemia, and marginal zone lymphoma). Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts. Umbralisib monotherapy is being studied in a registration directed trial in various NHL subtypes (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583).

2.2.3.2 Healthy Subject Pharmacokinetic Studies

In parallel with the Phase 1 single-arm, dose-escalation study in patients with relapsed or refractory hematologic malignancies; two healthy subject, crossover, bioequivalence pharmacokinetics studies have been completed. The first pharmacokinetic study was a Phase 1 drug-food interaction study with a single 200 mg oral dose of umbralisib in healthy volunteers followed by a second single dose Phase 1 pharmacokinetic study evaluating the absorption, distribution, metabolism and excretion characteristics of two different oral formulations of 200 mg umbralisib (original formulation vs. micronized formulation) in healthy volunteers.

2.2.3.3 Food Effect

Study TGR-1202-PK 101 was two-period, randomized, two-way crossover, drug-food, drug-gender interaction study in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a single oral dose of 200 mg of umbralisib under fasting and fed condition using the original formulation. In general, administration of umbralisib under fed conditions results in a higher rate of exposure relative to when the product was given under fasting conditions.

The statistical comparisons of umbralisib pharmacokinetic parameters under fasted and fed condition are shown below.

Table 1: Umbralisib Food Effect PK Parameters

Parameters	Geometric LS		% Geometric Mean Ratio	Confidence Interval
	Fasting	Fed		
AUC_{0-t} (ng·hr/mL)	6029.87	9692.02	160.73	140.25 – 184.21
AUC_{0-inf} (ng·hr/mL)	8391.35	14047.17	167.40	141.59 – 197.92
C_{max} (ng/mL)	176.78	483.15	273.31	234.04 – 319.17

Food increased both the extent and rate of exposure of umbralisib. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure increased by 61% and 67%, respectively, when umbralisib

was administered under fed conditions compared to fasting conditions. The peak plasma levels of umbralisib increased by over 173% when umbralisib was administered with food.

Using these mean values, a 334 mg oral dose of umbralisib under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of umbralisib under fed conditions in terms of exposure based on $AUC_{0\text{-}inf}$.

2.2.3.4 Formulation Effect

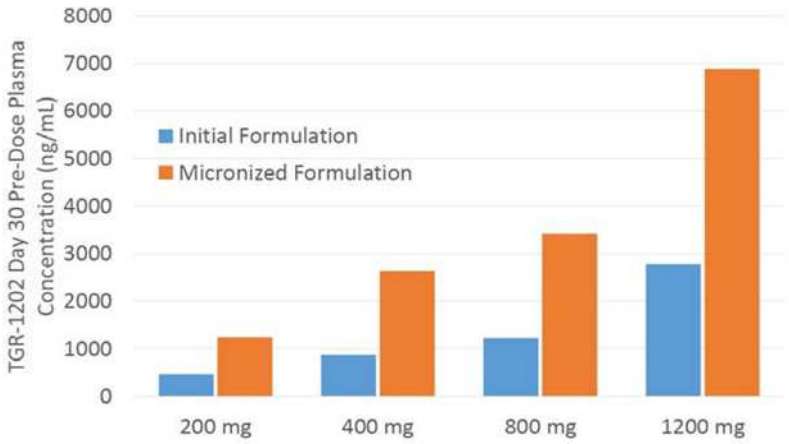
Study TGR-1202-PK 102 was a two-period, randomized, two-way cross over, relative bioavailability and pharmacokinetic bioequivalence study with two different drug product formulations of umbralisib. In this study, umbralisib was administered under fasted conditions in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a 200 mg single dose of the original drug product formulation and modified (micronized) drug product formulation of umbralisib. The mean rate and extent of exposure to umbralisib were higher following administration of the micronized drug product formulation compared to the original drug product formulation as mean concentrations were higher throughout most of the sampling interval.

Table 2: Umbralisib Formulation Effect

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
$AUC_{0\text{-}t}$ (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

The micronized drug product formulation increased both the extent and rate of exposure of umbralisib under fasted conditions. The extent ($AUC_{0\text{-}t}$) and total extent ($AUC_{0\text{-}inf}$) of exposure both increased by 60%, respectively, following administration of the modified drug product formulation relative to original drug product formulation. The Peak plasma (C_{max}) levels of umbralisib increased by over 124% following administration of the micronized drug product formulation relative to original drug product formulation under fasted conditions.

Using these mean values, a 320 mg oral dose of umbralisib in the original formulation under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation umbralisib under fasted conditions in term of exposure based on $AUC_{0\text{-}inf}$.
The improved exposure seen with the micronized formulation of umbralisib was confirmed in patients in the Phase 1 dose escalation as well. The chart below illustrates the pre-dose plasma concentrations of umbralisib on Day 1 of Cycle 2 in patients administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state.



2.3 **Ublituximab (TG-1101)**

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for potent activity, exhibiting a unique glycosylation profile with a low fucose content, designed to induce superior antibody-dependent cytotoxicity (ADCC). Ublituximab exhibits competitive complement-dependent cytotoxicity (CDC), on par with rituximab, and has also been demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies.[28]

2.3.1 Pre-Clinical Development Of Ublituximab

2.3.1.1 *In-Vitro* Activity

In an in-vitro assay using B-CLL cells from patient donors, ublituximab demonstrated an enhanced ability to kill CLL cells compared to rituximab. Ublituximab demonstrated improved Fcγ receptor IIIA (FcγRIIIA)/CD16 binding and FcγRIIIA dependent effector functions compared to rituximab. Additionally, ublituximab induced higher in vitro ADCC against CLL cells, and a higher FcγRIIIA mediated interleukin-2 (IL2) production by FcγRIIIA+ Jurkat cells.[29] Ublituximab demonstrated high ADCC against both patient-derived CLL cells and NHL cell lines. Ublituximab's engagement to FcγRIIIA triggers a stronger NK cell cytotoxicity against CLL as compared to rituxan (*in vitro*) despite CD20 density, likely related to the glycosylation pattern.[29]

2.3.2 *In Vivo* Activity

The antitumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models. Single agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in the FL xenograft at a dose of 100mg/kg, and a superior tumor growth delay (21 days) compared to rituximab. Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels.[28]

2.3.2.1 Toxicology

In single-dose and repeat dose toxicology studies performed under GLP, ublituximab displayed a safety profile similar to what might be expected for anti-CD20 monoclonal antibodies. Single administration of up to 100 mg/kg ublituximab in cynomolgus monkeys was well tolerated, with no local irritation with intravenous administration. Genotoxicity studies (Ames test) showed that ublituximab was not mutagenic. Monkeys that received a single injection of 0.3 mg/kg of ublituximab developed an anti-ublituximab response, whereas anti-ublituximab antibodies were not detected in the animals which received 10 or 100 mg/kg (see Ublituximab Investigator Brochure).

2.3.3 Clinical Development of Ublituximab

Ublituximab has been studied in a variety of patient populations, both as a single agent, and in combination with other agents, with over 1,000 patients having received ublituximab therapy to date across all studies. Two Single-Agent Phase I/Ib trials have been conducted with ublituximab treating both NHL and CLL patients. Further, following demonstration of safety and tolerability in these early single agent studies, Phase I and II combination studies were undertaken with a variety of agents. Given the number of patients who have received ublituximab in early-phase trials, the safety and side effect profile of the agent is well characterized. Summaries of the single-agent experience are provided below as well as data with use of ublituximab in combination with ibrutinib.

In a two part, first-in human dose escalation study (protocol CD20-0703), patients with relapsed or refractory CLL received one weekly infusion of single agent ublituximab for 4 doses in a 3+3 dose escalation design through 5 sequential dose levels. Part II of the study was a dose-confirmation component which used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg) – the clinical summary will focus on the Part II part of the study as the dose is more relevant to the clinical application used in current clinical studies. In Part II, 12 patients were enrolled at 9 centers in France and followed for 12 months. Demographic data for the 12 patients enrolled in the study were as follows. The median age was 69.5 years [62–77]; median time from diagnosis to inclusion was 10.4 years [4.0–23.6] and median prior therapies was 3 [1–8]. Seven patients (58%) received at least one prior rituximab-containing regimen. The median lymphocyte bone marrow infiltration was 85% [40–94].

Most frequent drug-related adverse events (AE's) reported were infusion related reactions (IRR) (75% of the patients, including 33% of patients with Grade 3 IRR). Other Grade 3/4 AE's > 10% included: neutropenia (67%) and increase ALT/AST (17%). All AEs were reversible spontaneously or with supportive care intervention. None of the reported adverse events were considered as a dose-limiting toxicity according the judgment of the study Safety Committee. Therefore, the maximum tolerated dose was not reached in this study. Significant blood lymphocyte depletion was observed in all patients: median lymphocyte count at baseline was 46.6 ($x10^9$/l); after 1 month (M1) = 1.5 (↓94%); M4=1.4 (↓91%) and M6=2.0 (↓89%). No cases of serum anti-ublituximab antibodies were detected at any time point.

Clinical response was based on the criteria established by the National Cancer Institute (NCI)-Working Group updated in 2008. All patients but one received the planned 8 infusions without any dose reduction--one patient was prematurely withdrawn due to a concomitant secondary leukemia unrelated to ublituximab therapy. Response was evaluated at month 4 for the 11 evaluable patients, with an initial response rate of 64% (7/11) with a confirmed response at month 6 in 5/11 patients (45%) patients (all PRs). Four of the 11 patients achieved stable disease. At the 1 year follow-up, no responders had progressed, demonstrating all confirmed responses were durable despite no ublituximab maintenance therapy. The median progression-free survival (PFS) was not reached at the 12 month follow-up.[30]

A phase I trial of ublituximab (Study TG-1101-101; NCT01647971) was subsequently undertaken in subjects with B-cell lymphoma or CLL who were relapsed or refractory to a prior rituximab containing regimen. This trial utilized a 3+3 design, assessing dose levels of 450, 600, 900, and 1200 mg. Patients with CLL/SLL received treatment on days 1, 8 and 15 during cycles 1 and 2 (28-day cycles) followed by maintenance ublituximab on day 1 of cycles 3–6, then every 3 months for a maximum of 2 years. Patients with NHL were treated with the same schedule except for the omission of the Cycle 2 doses. For CLL subjects, Cycle 1 Day 1 infusions were split (up to 150 mg administered on Day 1 and up to 750 mg administered on Day 2). No dose-limiting toxicities (DLTs) were observed, hence no MTD was identified. There was no significant difference in the overall number of AEs among the four dose cohorts. There appeared to be no difference in ORR between 900 and 1200 mg, with a slightly higher incidence of hematological AEs observed (grade 3 neutropenia, anemia, and thrombocytopenia) at the 1200-mg dose level. Hence, 900 mg was selected as the recommended phase 2 dose.

All 35 subjects enrolled were evaluable for safety. IRRs occurred in 14 (40%) subjects and were more prevalent among subjects with CLL. The majority of IRRs occurred on C1D1, with only 5 occurring on subsequent cycles. No episodes of grade ≥ 3 IRR were reported. All IRRs were manageable with infusion interruptions, and all subjects recovered without repercussion. Other common AEs included fatigue (37%), pyrexia (29%) and diarrhea 26%, which were all grade 1 or 2 except for 1 subject with grade 3 fatigue. Laboratory abnormalities included neutropenia (14%; grade 3/4, 14%), thrombocytopenia (6%; grade 3/4, 6%) and anemia (11%; grade 3/4, 6%). No infections were associated with grade 3/4 neutropenia, and no bleeding accompanied thrombocytopenia. See the ublituximab investigator's brochure for a complete overview of the ublituximab side effect profile.

Among response evaluable subjects, the ORR was 44% (11/25) and 50% (3/6) in subjects with NHL and CLL, respectively. Of 6 evaluable CLL subjects, 5 (83%) had an absolute lymphocyte count (ALC) > 4.0 x 10^9/l at study entry (range 3.055–165.996 x 10^9/l). A rapid depletion in circulating lymphocytes was observed in all 6 CLL subjects, with most subjects achieving a > 50% reduction within 7 days of the first infusion, and all 6 CLL subjects achieved an ALC < 4.0 x 10^9/l within the first cycle. Among 12 follicular lymphoma subjects, 5 subjects responded (42%) including 2 CRs (17%) and 3 PRs (25%). Of 7 MZL subjects, there were 5 responders (71%) including 2 CRs (29%) and 3 PRs (43%).

2.3.3.1 Pharmacokinetics

After infusion of ublituximab (previously known as LFB-R603) at a 150 mg dose followed by seven weekly injection infusions at 450 mg, results suggested non-linear pharmacokinetics with respect to dose (450 mg vs. 150 mg) and time (week 4 vs. week 8) and more than proportional increase of C_{max} and AUC_{∞} due to a clearance decrease. The volume of distribution at steady state was small (~5 L), approximately equal to blood volume. These non-linear pharmacokinetics may be explained by binding of ublituximab to its target, with a large component of target-mediated elimination after the first dose that is decreased after subsequent infusions due to a reduction in the available target. However, limited data for each dose level cohort and considerable variability in baseline patient characteristics, particularly in terms of tumor burden, make firm conclusions difficult.

A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of ublituximab are presented in the table below.

Table 3: PK results after the 1st (150 mg), 4th (450 mg) & 8th (450 mg) ublituximab infusion

PK Parameters [a]	1st Infusion 150 mg (Day 1)	4th Infusion 450mg (Day 22)	8th Infusion 450 mg (Day 50)
N	12	11	11
C_{max} (mg/L)	23.4 ± 11.2	168.6 ± 61.8	220.5 ± 141.9
t_{max} (h)	9.0 (5.0-30.3)	5.00 (3.1-52.0)	5.1 (3.1-23.5)
AUC∞ (mg.h/L)	732.1 ± 590	17890 ± 17730*	50760 ± 74460
$t_{1/2term}$ (h)	13.43± 10.2	80.7 ± 58.5*	147.8 ± 133.8
CL (mL/h)	424.2 ± 389.3	57.69 ± 42.91	38.62 ± 26.63
V_d/V_{dss}, (L)	4.8 ± 2.1	4.9 ± 2.3*	5.7 ± 3.3

[a] mean ± SD, $t_{max:}$ median (range) , with respect to the start of infusion
*Accurate determination not possible
Concentration was still measurable in at least one patient of the cohort up to day 169. Values for C_{max} and AUC_{∞} increased from the first to the eighth infusion whereas $t_{1/2}$ term decreased.

2.3.3.2 Ublituximab in Combination with Umbralisib

The combination of ublituximab and umbralisib (TGR-1202) is currently under evaluation in registration trials in CLL and various B cell NHL histologies. Preliminary results of an ongoing Phase I/Ib study in patients with relapsed or refractory NHL and CLL have been reported.[31] In early cohorts, patients received ublituximab on days 1, 8 and 15 of Cycles 1 & 2, then on day 1 of Cycles 4, 6, 9, and 12. In later cohorts, the ublituximab administration schedule was amended to infusions on days 1, 8, and 15 of Cycle 1, followed by Day 1 of Cycles 2 through 6. CLL patients receive Cycle 1, Day 1 infusions split over Days 1 and 2. TGR-1202 is taken once daily until patients are removed from study as per the protocol. A 3+3 dose-escalation design is being utilized to evaluate sequentially higher doses of the combination agents.

As of December 1, 2015, 71 patients have been enrolled and are evaluable for safety, with 58 patients evaluable for efficacy. The median age was 65 years (range 26 – 86), 47 Male/24 Female, with histologies as follows: 24 DLBCL, 19 CLL/SLL, 19 FL, 6 MZL, 2 MCL, and 1 patient with Richter's Transformation. Patients had a median of 3 prior therapies, and 58% were refractory to prior therapy.

Among the 71 patients evaluable for safety, nausea was the most prevalent adverse event (46%), followed by diarrhea (44%), fatigue (41%), neutropenia (30%), and infusion related reaction (25%). Seven patients had their dose of TGR-1202 reduced due to various adverse events. IRR and neutropenia were managed through dose delays, with 1 CLL patient having a neutropenia related dose delay which met the criteria for a DLT, necessitating enrollment of additional CLL patients into Cohort 1. Overall 8% of patients have discontinued TGR-1202 due to an adverse event.

Sixteen DLBCL patients treated with ublituximab + TGR-1202 were treated with therapeutic doses, amongst whom, the overall response rate was 31% with three patients experiencing a complete remission as confirmed by independent review. Amongst the five patients who responded, three had GCB subtype, while the other two patients subtype was not known.

Overall, the preliminary data suggests the combination of ublituximab and TGR-1202 is well tolerated and active in patients with relapsed or refractory hematologic malignancies. The combination of ublituximab and umbralisib is in registration directed trials in CLL (Study UTX-TGR-304 [UNITY-CLL]; NCT02612311), and various NHL subtypes, (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583). See the latest Investigator's Brochure for updated information regarding the clinical development of ublituximab and umbralisib as single-agents or in combination.

2.4 **Acalabrutinib (CALQUENCE®, ACP-196)**

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 non-clinical studies, acalabrutinib inhibited BTK mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

Acalabrutinib first received FDA approval in 2017 for the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy. Please refer to the FDA package insert and acalabrutinib Investigator's Brochure (IB) for full background information.

2.4.1 Key Risks Associated with Acalabrutinib Include the Following

2.4.1.1 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.

2.4.1.2 Infection

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.

2.4.1.3 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.

2.4.1.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer. Advise protection from sun exposure.

2.4.1.5 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.

2.5 **Umbralisib and Ibrutinib ± Ublituximab**

Our group studied the doublet combination of umbralisib and ibrutinib in a phase 1 study of patients with relapsed or refractory CLL or mantle cell lymphoma (NCT02268851).[12] A total of 42 participants were analyzed for safety and efficacy, 21 of whom had CLL. CLL participants enrolled to the dose escalation received treatment with ibrutinib at 420 mg and umbralisib at 400, 600, or 800 mg. No DLTs were observed and an MTD was not reached. An expansion cohort of 12 CLL patients received treatment with ibrutinib at 420 mg and umbralisib at 800 mg. Toxicities were manageable and consistent with expected adverse events for both agents. The most common adverse events of any grade among all participants were diarrhea (n = 22, 52%), infection (n = 21, 50%), nausea (n = 18, 43%), neutropenia (n = 17, 40%), fatigue (n = 16, 38%), thrombocytopenia (n = 10, 33%), hyperglycemia (n = 12, 29%), anemia (n = 8, 27%), transaminitis (n = 10, 24%), and dizziness (n = 9, 21%). Nineteen CLL participants (90%) experienced a response, defined as CR, PR, or PR with lymphocytosis. Six (29%) participants achieved CR and 13 (62%) PR. Median PFS and OS were not reached, with 2-year OS 95% and 2-year PFS 90%.[12]

The triplet combination of ublituximab, umbralisib and ibrutinib was previously evaluated as part of a phase 1 trial in participants with advanced B-cell malignancies (NCT02006485).[16] Umbralisib, ublituximab and ibrutinib were administered to a total of 46 participants. The recommended dose for the combination was umbralisib at 800 mg orally once daily, ibrutinib orally once daily at either 420 mg for CLL participants or 560 mg for non-Hodgkin lymphoma participants (the FDA recommended dose for the respective diagnoses), and ublituximab at 900 mg IV on days 1, 8, and 15 of cycle 1, day 1 of cycles 2 – 6, and day 1 of cycles 9 and 12. The regimen was well tolerated, an MTD was not reached. The most common adverse events of any grade were diarrhea (n = 27, 37%), fatigue (n = 23, 50%), infusion-related reaction (n = 20, 43%), dizziness (n = 17, 37%), nausea (n = 17, 37%), cough (n = 16, 35%), insomnia (n = 15, 33%), neutropenia (n = 15, 33%), pyrexia (n = 15, 33%), thrombocytopenia (n = 13, 28%), and peripheral edema (n = 12, 26%). Grade 3/4 adverse events were infrequent, the most common being neutropenia (n = 10, 22%) and cellulitis (n = 6, 13%). Four patients (9%) experienced grade 3 diarrhea, no grade 4 diarrhea was reported. No deaths due to treatment-related adverse events were reported.[16]

A total of 44 participants were evaluable for response, including 18 CLL participants. Among those 18, 8 (44%) achieved a CR and 10 (56%) achieved a PR. Nine CLL participants were analyzed for MRD, 7 (78%) had no MRD, 3 (33%) achieved CR, and 4 (44%) achieved PR. The median duration of response for CLL or small lymphocytic leukemia participants was 22.7

months (IQR 8.6 – 25.9), median PFS in all participants was 38.2 months, and median PFS in CLL participants was not reached.[16]

2.6 **Correlative Studies Background**

2.6.1 BH3 Profiling

This study will incorporate a laboratory technique known as BH3 profiling, which is a functional assay we previously developed that detects the proximity of malignant cells to the threshold of apoptosis (what we call 'priming') through physiologic interrogation of BCL-2 family members.[32] To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized primary CLL cells and use fluorescence activated cell sorting (FACS) to determine the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release. We previously found that in a small, heterogeneously treated cohort of CLL patients, increased priming was associated with improved clinical response.[33] Building on these initial studies, we will incorporate BH3 profiling into this clinical trial to determine whether priming predicts degree of clinical response in this larger, homogeneously treated patient population.

2.6.2 Genomic Markers

We will perform whole exome sequencing (WES) on CLL cells and normal tissue from patients at baseline to evaluate for somatic mutations that may confer drug sensitivity and resistance. Our group and others have recently identified recurrent somatic mutations in the CLL genome which appear to associate with prognosis; these include *NOTCH1* and *SF3B1*.[34] At present, whether other recurrent mutations associate with prognosis is less clear. Our group has also recently found that the presence of subclonal driver mutations was associated in retrospective analysis with time to next treatment.[35] In this trial, we will assess all of these recently described mutations as well as the presence of a subclonal driver mutation as potential predictors of response and PFS. We will also bank samples at time of relapse for repeat analysis by WES to assess for the acquisition of resistance mutations and evaluate established CLL prognostic markers such as cytogenetics by FISH, *TP53* mutation presence, *IGHV* status, and ZAP-70 status, and will determine whether these factors are associated with response.

2.6.3 Single Cell Sequencing Studies

Next generation sequencing (NGS) techniques have the potential for revolutionizing the treatment of CLL by allowing the detection of minimal residual disease or resistance mutations at levels below the sensitivity of current assays. We have previously explored the utility of measuring undetectable MRD using a targeted deep sequencing panel. Here we will again evaluate that technology and will consider using single cell DNA sequencing and RNA sequencing to identify the presence of oncogenic mutations, resistance mutations, and transcriptomic profiles of circulating CLL cells at various time points during the course of therapy. We will also retain plasma samples collected at the same time to explore the utility of cell-free DNA (cfDNA) analysis, making use of an orthogonal assay to verify or expand upon

results obtained from single cell sequencing.

2.6.4 ClonoSEQ NGS

In addition to our prior work exploring the utility of targeted sequencing for somatic mutations, we have also explored the utility of NGS targeting the B cell receptor. Specifically, Adaptive, Inc. has an assay known as ClonoSEQ, in which a baseline sample of genomic DNA is extracted from tumor cells, amplified using locus-specific primer sets for IGH and IGK rearrangements, and sequenced. This sequence is then used to assess for undetectable MRD with a sensitivity as high as 10^{-6}. Once a patient achieves an undetectable MRD state, a peripheral blood sample can be examined to determine whether tumor DNA again becomes detectable.

PARTICIPANT SELECTION

2.7 **Eligibility Criteria**

2.7.1 Confirmed diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) per International Workshop on CLL (iwCLL) 2018 criteria.[1]

2.7.2 Participants must have an indication for treatment as defined by iwCLL 2018 criteria.[1]

2.7.3 Participants must have measurable disease, defined as lymphocytosis > 5,000 / µL, or palpable or CT measurable lymphadenopathy ≥ 1.5 cm, or bone marrow involvement ≥ 30%.

2.7.4 For enrollment to **Cohort 1**: Participants must have relapsed or refractory disease as per iwCLL 2018 criteria,[1] and must have received no more than 2 prior lines of anti-cancer therapy.

2.7.5 For enrollment to **Cohort 2**: Participants must have previously untreated disease (i.e. must not have received any prior systemic therapy for CLL or SLL).

2.7.6 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of umbralisib, acalabrutinib, and ublituximab in participants < 18 years of age and CLL is extremely rare in this population, children are excluded from this study.

2.7.7 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see **Appendix A**).

2.7.8 Participants must have adequate organ and marrow function as defined below:

Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN) (unless due to hemolysis or Gilbert's disease, in which ≤ 3 × institutional ULN is acceptable)
AST (SGOT) and ALT (SGPT)	≤ 2.5 × institutional ULN, **OR**
AST (SGOT) and ALT (SGPT)	≤ 5 × institutional ULN if there is hemolysis or documented disease involvement in the liver
Calculated creatinine clearance	≥ 30 mL/min (as calculated by the Cockcroft-Gault formula)
Platelet count	≥ 50,000/mcL, unless there is bone marrow involvement with disease
PT-INR or aPTT	≤ 2 × institutional ULN
Absolute neutrophil count (ANC)	≥ 750 mm^3
Hemoglobin (Hgb)	> 8 g/dL

2.7.9 Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants should be class 2B or better.

2.7.10 The effects of umbralisib, acalabrutinib, or ublituximab on the developing human fetus are unknown. For this reason and because anti-cancer agents are known to be teratogenic, women of child-bearing potential and men must agree to use highly effective methods of contraception (see **Section 5.4**). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated on this protocol must agree to use highly effective contraception prior to the study, for the duration of study participation, and 4 months after completion of umbralisib, acalabrutinib, or ublituximab administration.

2.7.11 Ability to understand and the willingness to sign a written informed consent document.

2.7.12 Ability to swallow and retain oral medication.

2.7.13 Participants must be able to receive prophylactic anti-pneumocystis jiroveci pneumonia (PJP) and anti-viral therapy, see **Section 5.4**.

2.8 Exclusion Criteria

2.8.1 Participants with progressive or refractory disease while receiving either a BTK inhibitor or PI3K inhibitor. Prior exposure to either a BTK inhibitor, PI3K inhibitor, or both is acceptable as long as the participant's disease did not progress during active therapy with the agent(s).

2.8.2 Participants who have undergone a major surgical procedure within 28 days of the first dose of study drug. If a participant had major surgery greater than 28 days prior to the first dose of study drug, they must have recovered adequately from any adverse event and/or complications from the intervention prior to the first dose (as judged by the treating investigator).

2.8.3 For enrollment to **Cohort 1**: For enrollment to Cohort 1: receipt of prior BTK inhibitor treatment or any other anti-cancer therapy (e.g. chemotherapy, immunotherapy, radiation, biologic therapy or any investigational agent) within five half-lives or 21 days, whichever is shorter, of the first dose of study drug.

2.8.4 Participants who are receiving any other investigational agents.

2.8.5 History of prior allogeneic stem cell transplant.

2.8.6 History of autologous hematologic stem cell transplant within 6 months of the first dose of study drug.

2.8.7 Participants with known Richter's transformation, or histological transformation from CLL to large cell lymphoma.

2.8.8 Participants with known CNS involvement, because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Participants with no known history of CNS leukemia are not required to undergo CT scan or lumbar puncture (LP) for trial eligibility unless the participant is symptomatic as judged by the treating investigator.

2.8.9 Participants with uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).

2.8.10 Participants with active clinically significant bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease).

2.8.11 Participants requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (other anticoagulants are permitted).

2.8.12 Participants with a history of significant cerebrovascular disease/event within 6 months before the first dose of study drug, including stroke or intracranial hemorrhage.

2.8.13 Participants with uncontrolled intercurrent illness, including but not limited to: unstable angina pectoris, cardiac arrhythmia, or poorly controlled and clinically significant atherosclerotic vascular disease (including patients who required angioplasty, cardiac or vascular stenting within 6 months prior to the first dose of study agent), myocardial infarction within 6 months of screening, congestive heart failure, or patients with Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix D). Note: participants with controlled, asymptomatic atrial fibrillation are permitted to enroll on study. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.

2.8.14 Individuals with a history of a different malignancy are ineligible with the following exceptions: individuals who have been treated and are disease-free for a minimum of 2 years prior to study enrollment, or individuals who are deemed by the treating investigator to be at low risk for disease recurrence. Additionally, individuals with the following cancers are eligible if diagnosed and curatively treated within the past 2 years: basal or squamous cell carcinomas of the skin, and breast or cervical carcinomas *in situ*. Prostate cancer on observation, with stable PSA for 6 months, is also eligible.

2.8.15 Participants who require ongoing immunosuppressive therapy including systemic corticosteroids (prednisone or equivalent ≤ 10 mg daily is permitted). Topical, inhaled, and ophthalmologic steroids are permitted.

2.8.16 Participants with a history of inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis).

2.8.17 Participants with irritable bowel syndrome (IBS) with greater than 3 loose stools per day at baseline.

2.8.18 Participants with evidence of ongoing systemic bacterial, fungal, or viral infection, except localized fungal infections of the skin or nails. NOTE: participants may be receiving prophylactic antiviral or antibacterial therapies at the treating investigator's discretion. Use of anti-pneumocystis and antiviral prophylaxis is required, see **Section 5.4**.

2.8.19 Participants with a known history of progressive multifocal leukoencephalopathy (PML).

2.8.20 Participants with evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination or positive serum Hepatitis B antibody), chronic active Hepatitis C infection (HCV), active cytomegalovirus (CMV), or known history of human immunodeficiency virus (HIV):

- If HBc antibody is positive or the patient has a known history of hepatitis B, the subject must be evaluated for the presence of HBV DNA by PCR (see **Appendix B**). Subjects with a known history of hepatitis B and a positive HBc antibody but a negative HBV DNA by PCR are eligible if on suppressive therapy. Subjects with no known history of hepatitis B, with positive HBc antibody and negative HBV DNA by PCR, are eligible but serial monitoring of HBV DNA by PCR is required, see **Section 5.4**. Subjects with positive HBV DNA by PCR are not eligible.
- Participants with positive HBsAg are to be excluded.
- If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible. Subjects with positive HCV RNA by PCR are not eligible.
- If the subject is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible, anti-viral prophylaxis should be considered per treating investigator discretion.

2.8.21 History of allergic reactions attributed to study drugs including active product or excipients, or compounds of similar chemical or biologic composition to acalabrutinib, umbralisib, or ublituximab, including participants with a history of anaphylaxis (excluding infusion-related reactions) in association with previous anti-CD20 administration.

2.8.22 Participants requiring concomitant treatment with any medications or substances that are strong inhibitors or inducers of CYP3A4 at the time of study enrollment. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

2.8.23 Participants requiring concomitant treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) at the time of study enrollment. Note: participants receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids prior to the first dose of study medication are eligible.

2.8.24 Participants with psychiatric illness/social situations that would limit compliance with study requirements.

2.8.25 Pregnant women are excluded from this study because acalabrutinib, umbralisib, and ublituximab are anti-cancer agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with acalabrutinib, umbralisib, or ublituximab, breastfeeding must be discontinued prior to the initiation of study treatment. A negative serum pregnancy test is required for women of childbearing potential within 3 days prior to Cycle 1 Day 1.

2.9 **Inclusion of Women and Minorities**

Both men and women of all races and ethnic groups are eligible for this trial.

3. REGISTRATION PROCEDURES

3.1 **General Guidelines for DF/HCC Institutions**

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following

registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

3.2 **Registration Process for DF/HCC Institutions**

Applicable DF/HCC policy (REGIST-101) must be followed.

3.3 **General Guidelines for Other Investigative Sites**

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator or Project Manager. The required forms can be found in **Section 4.4**.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

3.4 **Registration Process for Other Investigative Sites**

To register a participant, the following documents should be completed by the participating site and e-mailed to the Study Coordinator/Project Manager:

- Signed participant consent form
- HIPAA authorization form
- DFCI eligibility checklist
- Screening provider note including the medical/surgical history, ECOG performance status, vital signs, and physical exam findings
- Copies of laboratory reports and clinical information confirming satisfaction of eligibility criteria.

The participating site will then e-mail the Study Coordinator or Project Manager to verify eligibility. The Study Coordinator/Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator/Project Manager will e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator/Project Manager may also contact the participating site and verbally confirm registration

NOTE: Registration can only be conducted during the regular business hours of 8:30 AM to 4:30 PM Eastern Standard Time Monday through Friday, holidays excluded. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager or Study Coordinator.

4. TREATMENT PLAN

4.1 Treatment Regimen

A treatment cycle is defined as 28 consecutive days. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6.**

Participants will receive acalabrutinib at the FDA approved dose of 100 mg by mouth twice daily and umbralisib at 800 mg by mouth once daily continuously throughout each treatment cycle. Ublituximab will be given IV starting with cycle 7 on days 1, 2, 8, and 15 and cycles 8-12 on day 1.

Participants who are in bone marrow and CT confirmed CR at the end of cycle 12 will stop dosing with acalabrutinib and umbralisib.. Participants not in CR will continue to cycles 13-24.

Participants will have peripheral blood monitoring for MRD as described in the **Study Calendar** in **Section 10**. If early relapse or recurrence is detected, the patient will undergo restaging with a CT scan and a bone marrow biopsy / aspirate. At the discretion of the treating investigator, patients with early relapse not meeting iwCLL criteria for retreatment may resume dosing with acalabrutinib and umbralisib until further disease progression, unacceptable toxicity, or other criteria are met as described in **Section 5.5**. The study agents will be resumed at the dose levels the participant was receiving prior to discontinuation. Dosing will resume for a maximum of 12 additional treatment cycles, such that participants may receive a maximum total of 36 cycles of study therapy.

Table 4: Regimen Description

Agent	Premedications; Precautions	Dose	Route	Schedule[1]	Cycle Length
Acalabrutinib	May be taken with or without food.	100 mg	By mouth	Twice Daily	28 days
Umbralisib	Take within 30 minutes of a meal. Participants are required to receive prophylactic anti-viral and anti-pneumocystis jiroveci pneumonia (PJP) treatment, refer to **Section 5.4.**	800 mg	By mouth	Once Daily	

Table 4: Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule[1]**	**Cycle Length**
Ublituximab	Pre-medicate with an antihistamine (diphenhydramine 50 mg or equivalent) and a corticosteroid (dexamethasone 10 – 20 mg or methylprednisolone 80 mg or equivalent).[2,3,4] • If oral pre-medication: start the ublituximab infusion 45 – 60 minutes after the ingestion of the oral pre-medications • If IV pre-medication: start the ublituximab infusion 30 – 35 minutes after the completion of the last pre-medication infusion	See **Section 5.3.3**	IV	Cycle 7: Days 1, 2, 8, 15 Cycles 8 – 12: Day 1	
1. Order of administration of the study agents does not matter. 2. Diphenhydramine must be 50 mg IV on Cycle 7 day 1 and 2, but may be reduced to 25 mg on subsequent infusions in the absence of infusion related reactions and at treating physician discretion. After the completion of cycle 8, use of corticosteroid pre-medication may be discontinued with approval from the sponsor-investigator if the participant has not experienced any infusion-related or hypersensitivity reactions. 3. Administration of oral acetaminophen 650 mg (or equivalent) may be as clinically warranted, or in participants who experience fever/pyrexia after the first infusion. 4. Infusion-related hypotension may occur, investigators should consider holding anti-hypertensive medications 12-24 hours prior to and throughout the infusion. Decision to withhold anti-hypertensive medication is at the treating investigator's discretion.					

4.2 **Pre-Treatment Criteria**

4.2.1 Cycle 1, Day 1

If screening laboratory assessments were completed ≤ 72 hours prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values. If cycle 1 day 1 laboratories are performed, the values do not need to re-meet eligibility criteria, participants will be allowed to initiate treatment at the treating investigator's discretion.

4.2.2 Subsequent Cycles

Management guidelines for toxicities associated with study treatment are located in **Section 6**.

4.3 **Agent Administration**

4.3.1 Acalabrutinib

Acalabrutinib administration instructions:

- Acalabrutinib should be administered orally twice daily, approximately every 12 hours.
- If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 3 hours, the dose should not be taken and the participant should take the next dose at the scheduled time.
- The tablets should be swallowed intact with water. Participants should not attempt to open, crush, chew, or dissolve the tablets.
- Acalabrutinib can be taken with or without food.
- If the participant vomits following a dose, the dose should not be re-taken. Instead, the participant should proceed with their next scheduled dose as clinically appropriate.
- Order of administration of the study agents does not matter.

4.3.2 Umbralisib

Umbralisib administration instructions:

- Umbralisib should be administered orally once daily, approximately every 24 hours.
- If a dose is missed, it can be taken up to 12 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 12 hours, the dose should not be taken and the participant should take the next dose at the scheduled time.
- The tablets should be swallowed intact. Participants should not attempt to crush, chew, or dissolve the tablets.
- Umbralisib should be taken within 30 minutes of a meal.
- If the participant vomits following a dose, the dose should not be re-taken. Instead, the participant should proceed with their next scheduled dose as clinically appropriate.
- See **Section 4.4** for information regarding required anti-viral and anti-PJP prophylaxis.
- Order of administration of the study agents does not matter.

4.3.3 Ublituximab

Ublituximab administration instructions:

- Ublituximab will be administered as an intravenous (IV) infusion through a dedicated infusion line.
- Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions. See hypersensitivity and infusion reaction guidance below.
- Ublituximab should not be administered as an IV push or bolus.
- Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if it does not conform to the specifications.

- It is recommended that ublituximab be administered immediately after dilution. It should NOT be mixed the day before and mixing should only occur once confirmed that the patient is eligible for therapy on the day of treatment.
- Ublituximab should not be mixed with other medicinal products.
- Ublituximab should only be diluted in 0.9% NaCl before use.
- Participants must be pre-medicated with an antihistamine (diphenhydramine 25-50 mg or equivalent) and a corticosteroid (dexamethasone 10 – 20 mg or equivalent). Decision of using oral or IV pre-medication is at the treating investigator's discretion except for cycle 1 days 1 and 2, when IV pre-medication and diphenhydramine 50 mg are required:
    - If oral pre-medication: start the ublituximab infusion 45 – 60 minutes after the ingestion of the oral pre-medications.
    - If IV pre-medication: start the ublituximab infusion 30 minutes (+ 5 minute window) after the completion of the last pre-medication infusion.
    - Adjusting antihistamine and corticosteroid doses, adjusting the timing of administration and/or additional pre-medications may be used at investigator discretion for additional prophylaxis against infusion related reactions.
    - Administration of oral acetaminophen 650 mg (or equivalent) may be as clinically warranted, or in participants who experience fever/pyrexia after the first infusion.
- Infusion-related hypotension may occur, investigators should consider holding anti-hypertensive medications 12 – 24 hours prior to and throughout the infusion. Decision to withhold anti-hypertensive medication is at the treating investigator's discretion.
- For patients at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or similar per recommended institutional standards should be considered.
- Order of administration of the study agents does not matter.
- Ublituximab should be administered at the dose, rate, and schedule indicated in the tables below.

Table 5: Ublituximab Infusion Rate Cycle 7 Days 1 and 2

Cycle 7	Ublituximab Dose	Total Volume to be Infused	Infusion Rate[1]			
			Start – 30 min	30 min – 1 hr	1 hr – 2 hrs	2 hrs – 4 hrs
Day 1	150 mg	250 mL	10 mL/hr	20 mL/hr	35 mL/hr	100 mL/hr
Day 2	750 mg	500 mL	10 mL/hr	20 mL/hr	85 mL/hr	200 mL/hr

1: A ± 2 minute window is allowable for adjustment of the infusion rate.

Table 6: Ublituximab Infusion Rate Cycle 7 Days 8 and 15					
Cycle 7	**Ublituximab Dose**	**Total Volume to be Infused**	**Infusion Rate[1]**		
			Start – 1 hr	**1 hr – 2 hrs**	**2 hrs – 3 hrs**
Day 8, 15	900 mg	500 mL	50 mL/hr	150 mL/hr	300 mL/hr
1: A ± 2 minute window is allowable for adjustment of the infusion rate.					

Table 7: Ublituximab Infusion Rate Cycles 8 – 12 Day 1				
Cycle Day	**Ublituximab Dose**	**Total Volume to be Infused**	**Infusion Rate[1]**	
			Start – 30 min	**30 min – 90 min**
1	900 mg	500 mL	200 mL/hr	400 mL/hr
1: A ± 2 minute window is allowable for adjustment of the infusion rate.				

4.3.4 Infusion-Related Reaction Guidelines – Ublituximab

Infusion-related reactions (including severe reactions) have been reported with ublituximab administration. Guidelines are provided for patients who experience such reactions. Symptomatic infusion reactions may be treated at the discretion of the treating investigator and as per institutional standards of practice, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen, and bronchodilators.

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

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

If grade 4 anaphylaxis is observed at any point during ublituximab treatment, permanently discontinue ublituximab treatment and intervene as per treating investigator discretion and institutional standards of practice.

1st or 2nd Infusion Interruption (same day):

- Hold infusion and closely monitor patient, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the treating investigator, and provided the patient is stable, the infusion may be resumed at no more than half the previous rate.
- If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

3rd Infusion Interruption (same day):

- Discontinue infusion for that day – monitor patient for resolution of all symptoms. Patient should have all vital signs completed as well as any other standard of care procedures completed as warranted by the treating investigator prior to release of patient from study site.
- Any remaining diluted investigational product should be discarded.

If an ublituximab infusion is discontinued, the next scheduled dose should be administered according to the protocol dosing schedule.

4.4 General Concomitant Medication and Supportive Care Guidelines

No investigational or commercial agents or therapies other than acalabrutinib, umbralisib, or ublituximab may be administered with the intent to treat the participant's malignancy.

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to anti-emetics, anti-diarrheals, hematopoietic growth factors and blood product transfusion.

4.4.1 Umbralisib Prophylactic Anti-Viral Treatment

Participants receiving umbralisib are required to start prophylactic treatment with anti-PJP and anti-viral therapy prior to day 1 of treatment. Choice of PJP and anti-viral prophylaxis is per investigator discretion and institutional standard of care, with the following as recommendations:

- Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
- PJP Prophylaxis: Sulfamethoxazole/trimethoprim 800 mg / 160 mg three times per week, or 400 mg / 80 mg daily, or if allergic, atovaquone 750 mg twice daily. Dapsone 100 mg daily may also be used if other agents are contraindicated or unavailable but is not recommended. If dapsone is used, be aware that methemoglobinemia is not uncommon in CLL patients treated with dapsone.
- Final choice of PJP and anti-viral prophylactic therapy is per treating investigator discretion.

Participants should continue prophylactic treatment for at least one year after stopping protocol therapy.

If anti-viral or anti-bacterial prophylaxis is not tolerated, alternate to a different prophylactic agent, reduce the dose or modify the schedule for the prophylactic agent, or discontinue prophylaxis at the treating investigator’s discretion.

4.4.2 Hepatitis B Monitoring and Anti-Viral Prophylaxis

All participants are required to have testing for hepatitis B surface antigen (HBsAg) and

hepatitis B core (HBc) antibody at screening. If HBc antibody is positive, the subject must also be evaluated for the presence of hepatitis B viral (HBV) DNA by PCR (see **Appendix B**). Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible, but serial monitoring of HBV DNA is required monthly.

> Subjects with a prior history of hepatitis must be closely monitored as clinically indicated based on liver tests and any observed signs/symptoms such as jaundice, abdominal pain, dyspepsia, dark-colored urine often accompanied by lighter-than-normal colored stools, nausea, vomiting or fatigue.

For patients with a prior history of hepatitis B who experience an increase in liver enzymes while on study, hold ublituximab immediately and assess for active hepatitis B infection. If negative for hepatitis B by viral load testing, ublituximab may be resumed. If reactivation of hepatitis B is confirmed, institute hepatitis B antiviral treatment. Ublituximab may be resumed at investigator discretion once hepatitis B infection has resolved, with continued monitoring as described above.

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with acalabrutinib or ublituximab. Use of anti-viral prophylaxis will be permitted at the treating investigator's discretion. Entecavir is the preferred agent for pharmacologic prophylaxis. Use of an agent other than entecavir must be discussed with the sponsor-investigator. HBV DNA should be monitored every 1-2 months while a patient is receiving pharmacologic prophylaxis. If the HBV DNA level becomes detectable, all study medications must be discontinued and infectious disease consultation should be obtained. If a patient completes study therapy while taking entecavir, they should remain on entecavir for at least one year after completion of all therapy. If discontinuation of entecavir is considered, patients should have their LFTs and HBV DNA level monitored weekly for the first two months.

4.4.3 CYP Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, acalabrutinib is metabolized by CYP3A. Participants who are known to require the concomitant administration of strong inhibitors or inducers of CYP3A4 at the time of study entry are excluded from trial participation. The concomitant use of strong or moderate inhibitors of CYP3A4, or strong inducers of CYP3A4, should be avoided when possible while the participant is receiving treatment with acalabrutinib. If it is medically necessary to administer while on study, monitor the participant closely for potential toxicities and refer to dose adjustment table below.

Table 8: Acalabrutinib Dose Adjustments for Concomitant Administration of CYP Agents[1]		
CYP3A	**Co-Administered Drug**	**Recommended Acalabrutinib Adjustment**
Inhibition	Strong CYP3A4 Inhibitor	Avoid concomitant use when possible. If used short-term (e.g. anti-infectives for up to 7 days), hold dosing of acalabrutinib.
Inhibition	Moderate CYP3A4 Inhibitor	100 mg once daily.
Induction	Strong CYP3A4 Inducer	Avoid concomitant use when possible. If these inducers cannot be avoided, increase dose to 200 mg twice daily.
1. To be made in accordance with institutional standards of practice, treating investigator judgement, and FDA prescribing information.		

The *in vitro* ability of umbralisib acting as a substrate, inhibitor, or inducer of cytochrome P450 enzymes (CYPs), conjugating enzymes, and transporters was evaluated as per FDA Guidance. Except for a P-gp inhibitory potential, the results demonstrated no drug-drug interaction effects against major CYPs, conjugating enzymes, and transporters evaluated.

Ublituximab is a protein and is expected to be metabolically degraded through peptide hydrolysis. Based on this expectation, ublituximab is an unlikely candidate for cytochrome P450-mediated drug-drug interactions.

4.4.4 Agents that Reduce Gastric Acidity

The effect of agents that reduce gastric acidity (e.g., proton pump inhibitors or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study. Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the treating investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

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

4.4.5 Acceptable Forms of Contraception and Pregnancy Guidelines

4.4.5.1 Definition of Females Not of Childbearing Potential

Females are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4.4.5.2 Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring, must use a condom during treatment and for 4 months after the last dose of study treatment. They should also not father a child during this period.

4.4.5.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported and followed as per the guidelines in **Section 7**.

4.4.5.4 Acceptable Contraception

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

Such methods include:

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

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

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for subjects participating at sites in the relevant region.

The following are **unacceptable** forms of contraception for females of childbearing potential:

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

4.4.6 Live Virus Vaccines

Live virus vaccines are prohibited beginning 4 weeks prior to the first dose of ublituximab and for the duration of ublituximab treatment.

4.5 **Criteria for Taking a Participant Off Protocol Therapy**

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for a maximum of 24 cycles or until one of the following criteria applies:

- Disease progression, with the exception of participants who relapse following confirmed CR and treatment discontinuation who are permitted to be re-treated as described in **Section 5.1**
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant becomes pregnant or plans to become pregnant
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

4.6 **Duration of Follow Up**

Participants will be followed for 30 days after removal from protocol therapy or until death, whichever occurs first, for adverse events. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Following the 30 day follow up period, participants will be followed for a maximum of 5 years after treatment discontinuation to observe treatment response and survival status.

4.7 **Criteria for Taking a Participant Off Study**

Participants will be removed from study when any of the following criteria apply:

- Completion of the 5 year follow-up period
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

5. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications of non-hematologic toxicity. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The iwCLL 2018 criteria will be used for grading and assessment of hematologic toxicity (**Appendix E**).[1]

5.1 **Dose Delays**

Umbralisib may be held for a maximum of 56 days to allow for recovery of toxicity, and acalabrutinib may be held for a maximum of 28 days. Ublituximab may be delayed for a maximum of 2 cycles (56 days). Participants requiring a longer delay should be removed from

protocol therapy. Participants who are deriving clinical benefit who require a longer hold of any of the study agents may be allowed to continue treatment following discussion and agreement with the sponsor-investigator.
If attribution of the toxicity is known, study medications may be held independently of each other. For example, a participant may continue dosing with acalabrutinib and umbralisib while holding ublituximab at the treating investigator's discretion. If attribution of the toxicity is unknown or the combination of study agents may be contributing to the toxicity, all study agents must be held. Refer to **Section 6.3** for toxicity management guidelines.

In the event of a dose hold due to toxicity, the counting of cycle days and protocol assessment schedule will continue without interruption. For example, a participant who holds dosing of umbralisib and acalabrutinib on Cycle 4 Day 15 to Cycle 4 Day 18 for toxicity will resume dosing on Cycle 4 Day 19 and proceed with their next scheduled clinic visit as previously planned (Cycle 5 Day 1). Interim visits may be conducted as clinically necessary to manage toxicity; however, the cycle will not restart and doses will not be "made up" in the event of dosing delays.

5.2 **Dose Modifications**

Permitted dose reductions of acalabrutinib and umbralisib are detailed below. Once a participant's dose has been reduced due to toxicity, it may not be re-escalated. If a subject requires a dose reduction of umbralisib and further evaluation of the toxicity reveals the event was not related to umbralisib, this should be recorded in the medical record and dose re-escalation to the previous umbralisib dose may be considered at the discretion of the treating investigator after consultation with the sponsor-investigator. No dose reductions of ublituximab are permitted. If the participant cannot tolerate the dose of ublituximab, ublituximab should be discontinued.

If attribution of the toxicity is known, dose reductions may occur independently of each other. For example, the dose of umbralisib may be reduced while maintaining the dose of acalabrutinib. If toxicity attribution is unknown or the combination of study agents may contribute to the toxicity, both agents must be dose reduced.

Table 9: Umbralisib Dose Reductions	
Dose Reduction Level	**Umbralisib Dose (Once Daily)**
-1	600 mg
-2	400 mg
-3	Discontinue

Table 10: Acalabrutinib Dose Reductions[1,2]	
Dose Reduction Level	**Acalabrutinib Dose**
-1	100 mg once daily
-2	Discontinue
1. Dose modifications of acalabrutinib may be made in	

Table 10: Acalabrutinib Dose Reductions[1,2]	
Dose Reduction Level	**Acalabrutinib Dose**
accordance with the FDA prescribing information. 2. Refer to **Section 5.4** for dose modifications for co-administered CYP3A drugs.	

If attribution of the toxicity is known, discontinuation of study medications may also occur independently of each other with agreement from the sponsor-investigator. For example, participants who cannot tolerate ublituximab may be allowed to continue to receive umbralisib and acalabrutinib if the sponsor-investigator provides approval.

5.3 **Toxicity Management**

Management of toxicity considered at least possibly related to the study agents is detailed in the tables below.

Table 11: Hematologic Toxicity Management[1]		
Event Term	**Grade**	**Study Agent Management Guidelines[2]**
Neutrophil count decreased	Grade 3	Provide supportive care as warranted. Maintain current dose of umbralisib and acalabrutinib. For recurrent or persistent Grade 3 neutropenia unresponsive to supportive care, reduce umbralisib by one dose level. Maintain full dose and schedule of ublituximab, if applicable.
Neutrophil count decreased	Grade 4	Provide supportive care as warranted. Hold dosing of study agents until resolution to ≤ Grade 3. First and second occurrence: resume umbralisib and acalabrutinib at the same dose level. Recurrence after second re-challenge: resume umbralisib and acalabrutinib with one dose level reduction. If applicable, resume ublituximab at full dose and schedule.
Febrile neutropenia	≥ Grade 3	Provide supportive care as warranted. Hold study agents until resolution. First occurrence: resume umbralisib and acalabrutinib at the same dose level. Recurrence after re-challenge despite supportive care: reduce dose of umbralisib by one dose level. If applicable, resume ublituximab at full dose and schedule upon resolution.

Table 11: Hematologic Toxicity Management[1]		
Event Term	**Grade**	**Study Agent Management Guidelines[2]**
Platelet count decreased[3]	Grade 3 with clinically significant bleeding **-OR-** Grade 4	Provide supportive care as warranted. First occurrence: delay umbralisib and acalabrutinib until Grade ≤ 3 without clinically significant bleeding; thereafter, resume umbralisib and acalabrutinib at the same dose level. Second occurrence: delay umbralisib and acalabrutinib until Grade ≤ 3 without clinically significant bleeding; thereafter, resume umbralisib and acalabrutinib at next lower dose level unless there is a clear alternative explanation for the event. Delay ublituximab until Grade ≤ 3 without clinically significant bleeding; thereafter, resume ublituximab at full dose and schedule.
1. Grading of hematologic toxicity will be per iwCLL 2018 criteria (**Appendix E**).[1] 2. Management of acalabrutinib may be made in accordance with the FDA prescribing information. 3. If participant receives a platelet transfusion, they will be considered to have grade 4 toxicity for that day and the next 2 calendar days regardless of actual platelet count.		

Table 12: Non-Hematologic Toxicity Management		
Event Terms	**CTCAE Grade**	**Study Agent Management Guidelines[1]**
Pulmonary & Related Infections[2]	Grade 3	Provide supportive care as warranted. Maintain acalabrutinib dosing. Hold dosing of umbralisib and ublituximab (if applicable) until complete resolution. Acalabrutinib may also be held at the treating investigator's discretion and SHOULD be held for any suspected fungal or opportunistic infections until resolution of infection to grade 1 or less. Resume acalabrutinib at the same dose level. If suspicious for a possible drug-related pneumonitis, resume umbralisib at next lower dose level. If recurrence after re-challenge, permanently discontinue umbralisib. Upon complete resolution, resume ublituximab at full dose and schedule. If recurrence after re-challenge, permanently discontinue ublituximab.
Pulmonary & Related Infections[2]	Grade 4	Provide supportive care as warranted. Permanently discontinue umbralisib and ublituximab (if applicable).

Table 12: Non-Hematologic Toxicity Management		
Event Terms	**CTCAE Grade**	**Study Agent Management Guidelines[1]**
Colitis	ANY	Provide supportive care as warranted. Hold dosing of umbralisib and ublituximab (if applicable) until resolution. Acalabrutinib may also be held at the treating investigator's discretion. Upon resolution, resume umbralisib at the next lower dose level. Acalabrutinib may be resumed at the same dose level or reduced at the treating investigator's discretion. Resume ublituximab at the same dose and schedule.
Liver Toxicity Includes: ALT (SGPT), AST (SGOT), Bilirubin increased	Grade 1	Maintain current dose and schedule of umbralisib, acalabrutinib, and ublituximab (if applicable). Assess concomitant medications and risk factors.[3] Monitor liver function laboratories every 1 – 2 weeks until resolution to baseline.
Liver Toxicity Includes: ALT (SGPT), AST (SGOT), Bilirubin increased	Grade 2	Assess concomitant medications and risk factors.[3] First Occurrence: Maintain current dose and schedule of umbralisib, acalabrutinib, and ublituximab (if applicable). Begin supportive care (prednisone 0.5 – 1.0 mg/kg/day or equivalent per treating investigator's discretion).[4] Monitor liver function laboratories at least weekly until Grade 1 or baseline. Once resolved to Grade 1 or baseline, taper prednisone by 10 mg per week until off. If liver toxicity recurs: • Re-initiate steroids. • Delay umbralisib and ublituximab dosing. • Monitor liver function labs at least weekly until resolution to Grade 1 or baseline. • Once resolved to Grade 1 or baseline, restart umbralisib at current dose and resume ublituximab at full dose and schedule. • Taper prednisone by 10 mg per week until off.

Table 12: Non-Hematologic Toxicity Management		
Event Terms	**CTCAE Grade**	**Study Agent Management Guidelines[1]**
Liver Toxicity Includes: ALT (SGPT), AST (SGOT), Bilirubin increased	Grade ≥ 3	Assess concomitant medications and risk factors.[3] Hold dosing of umbralisib, ublituximab, and acalabrutinib. Begin supportive care (prednisone 0.5 – 1.0 mg/kg/day or equivalent per treating investigator's discretion).[4] Monitor liver function labs at least weekly until Grade 1 or resolution to baseline. Once resolved to Grade 1 or baseline, resume dosing with study agents, beginning with acalabrutinib and adding umbralisib and ublituximab (as applicable) one week later if the liver toxicity does not return upon re-introduction of acalabrutinib. Reduce dose of umbralisib by one dose level, resume full dose and schedule of acalabrutinib and ublituximab. Taper prednisone by 10 mg per week until off.
Any other non-hematologic toxicity	≤ Grade 2	No change in study agent dosing or schedule.[5] Implement supportive care as appropriate. **NOTE**: If persistent grade 2 diarrhea despite supportive care, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at next lower dose level.

Table 12: Non-Hematologic Toxicity Management		
Event Terms	**CTCAE Grade**	**Study Agent Management Guidelines[1]**
Any other non-hematologic toxicity	≥ Grade 3	Implement supportive care as appropriate. First occurrence: hold dosing of study agents until resolution to ≤ Grade 2 or baseline. Upon resolution, may resume dosing with umbralisib and acalabrutinib at the same dose level, or at the treating investigator's discretion, may reduce dose by one dose level. Resume ublituximab at the full dose and schedule. Recurrence: hold dosing of study agents until resolution to ≤ Grade 2 or baseline. Upon resolution, resume dosing with umbralisib and acalabrutinib with one dose level reduction. Resume ublituximab at the full dose and schedule. Exceptions: • Asymptomatic laboratory abnormalities considered non-clinically significant: participants may continue dosing at the treating investigator's discretion. • Asymptomatic laboratory abnormalities that resolve to ≤ Grade 2 or baseline within 48 hours of repletion or treatment: study medication should be held until resolution to Grade 2 and may be resumed at the same dose level or with one dose level reduction at the treating investigator's discretion. Treatment and resumption of study medication dosing may occur on the same day.

1. Management of acalabrutinib may be made in accordance with the FDA prescribing information.
2. For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at the treating investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required prior to the start of therapy, refer to **Section 5.4**.
3. Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc.
4. Supportive Care may include aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc. **Important:** Before initiating steroids, check for viral hepatitis or CMV infection.
5. At the treating investigator's discretion, dosing of the study agent(s) may be held and/or dose reduced for intolerable Grade 2 toxicity.

5.4 **Overdose**

There are currently no specific treatments in the event of overdose with acalabrutinib, umbralisib or ublituximab and possible symptoms of overdose are not established. In the event of an overdose, the participant should be monitored as clinically appropriate (e.g. vital signs, hematologic parameters, etc.) and adverse reactions associated with the overdose should be treated symptomatically. Please refer to **Section 7.4** for adverse event reporting requirements.

In the event of an overdose ingestion of acalabrutinib that is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered at the treating investigator's discretion and in accordance with local institutional guidelines.

5.5 **Withdrawal of Umbralisib and Ublituximab**

As of March 2023, TG therapeutics has decided to no longer provide umbralisib, ublituximab and funding for this study. Study participants still on treatment will still have the option to continue taking acalabrutinib.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (**Section 7.1**) and the characteristics of an observed AE (**Sections 7.2, 7.3, 7.4** and **7.5**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

6.1 **Expected Toxicities**

6.1.1 Expected Toxicities for Acalabrutinib

For the purposes of suspected unexpected serious adverse reaction (SUSAR) reporting, the toxicities in the table below will be considered expected for acalabrutinib. Events that are fatal or life-threatening (i.e. posing an immediate risk of dying) must always be reported according to expedited timelines. Please also refer to the acalabrutinib IB.

Table 13: Acalabrutinib Expected Toxicities

System Organ Class	Event
Gastrointestinal disorders	Abdominal pain
	Diarrhea
	Vomiting
Nervous system disorders	Headache
Vascular disorders	Hematoma

6.1.2 Expected Toxicities for Umbralisib

For the purposes of SUSAR reporting, the toxicities in the table below will be considered expected for umbralisib. Events that are fatal or life-threatening (i.e. posing an immediate risk of dying) must always be reported according to expedited timelines. Please also refer to the umbralisib IB.

Table 14: Umbralisib Expected Toxicities

System Organ Class	Event	Frequency (n=number of occurrences)	Serious
Blood and Lymphatic System Disorders	Febrile Neutropenia	8	Yes
	Anemia	4	Yes
	Neutropenia	2	Yes
	Thrombocytopenia*		
	Leukopenia*		
	Leukocytosis*		
Cardiac Disorders	Cardiac Failure Congestive	2	Yes
	Heart Palpitations	1	Yes
	Pulmonary Edema	1	Yes
Congenital, Familial and Genetic Disorders	Congestive Heart Failure	1	Yes
Gastrointestinal Disorders	Diarrhea	9	Yes
	Small Intestinal Obstruction	2	Yes
	Nausea	2	Yes
	Vomiting	2	Yes
	Colitis	3	Yes
	Anorectal Fistula	1	Yes
	Acute Pancreatitis	1	Yes
	Ileus	1	Yes
	Abdominal Pain*		
	Gastrointestinal Hemorrhage*		
General Disorders and Administrative Site Conditions	Pyrexia	6	Yes
	Fatigue	3	Yes
	Pyrexia*		
Immune System Disorders	Uveitis	1	Yes
	Allergic Reaction	1	Yes
Infections and Infestations	Pneumonia	18	Yes
	Cellulitis	3*	Yes
	Cytomegalovirus Colitis	2	Yes
	Lung Infection	2	Yes

Table 14: Umbralisib Expected Toxicities			
System Organ Class	**Event**	**Frequency (n=number of occurrences)**	**Serious**
	Sepsis	12	Yes
	Septic Shock	1	Yes
	Upper Respiratory Tract Infection	2	Yes
	Neutropenic Sepsis	2	Yes
	Bacteremia	2	Yes
	Pulmonary Infection		
Investigations	Transaminases Increased	2	Yes
	Elevated Liver Enzymes*		
Metabolism & Nutrition Disorders	Dehydration	5	Yes
	Hypophosphatemia	2	Yes
	Tumor Lysis Syndrome*	2	Yes
Nervous System Disorders	Headache	3	Yes
	Syncope	2	Yes
	PML*	1	Yes
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Malignant Melanoma*	1	Yes
Respiratory, Thoracic and Mediastinal Disorders	Pneumonitis	4	Yes
	Pleural Effusion	2	Yes
	Hypoxia	2	Yes
	Shortness of Breath*		
Skin and Subcutaneous Tissue Disorders	Rash	4	Yes
	Eczema	2	Yes
	Erythrodermic Eczematous Rash*	1	Yes
*: these events have not been seen as a serious adverse reaction ≥ 2 however are still considered to be of special interest for umbralisib			

6.1.3 Expected Toxicities for Ublituximab

For the purposes of SUSAR reporting, the toxicities in the table below will be considered expected for ublituximab. Events that are fatal or life-threatening (i.e. posing an immediate risk of dying) must always be reported within expedited timelines. Please also refer to the ublituximab IB.

Table 15: Ublituximab Expected Toxicities			
System Organ Class	**Event**	**Frequency (n=number of occurrences)**	**Serious**
Blood and Lymphatic System Disorders	Febrile Neutropenia	8	Yes
	Anemia	2	Yes
	Thrombocytopenia	2	Yes
	Pancytopenia*		
Gastrointestinal Disorders	Diarrhea	3	Yes
General Disorders and Administrative Site Conditions	Pyrexia	5	Yes
	Fatigue	3	Yes
Immune System Disorders	Serum Sickness-Like Reaction	1	Yes
	Hypersensitivity/Anaphylaxis*		
Infections and Infestations	Pneumonia	14	Yes
	Sepsis	6	Yes
	Neutropenic Sepsis	2	Yes
	Cellulitis	2	Yes
	Bacteremia	2	Yes
	Septic Shock	2	Yes
Injury, Poisoning and Procedural Complications	Infusion-Related Reactions	9	Yes
Metabolism & Nutrition Disorders	Hypercalcemia	1	Yes
	Insulin Dependent Diabetes	1	Yes
	Tumor Lysis Syndrome	4	Yes
Nervous System Disorders	PML	1	Yes
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Malignant Melanoma	1	Yes
Skin and Subcutaneous Tissue Disorders	Rash	3	Yes
	Erythrodermic Eczematous Rash	2	Yes
*: these events have not been seen as a serious adverse reaction ≥ 2 however are still considered to be of special interest for ublituximab			

6.2 Adverse Event Characteristics

- **Term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting for non-hematologic toxicity. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The iwCLL 2018 criteria will be used for grading and assessment of hematologic toxicity (**Appendix E**).[1]

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3 Serious Adverse Event Reporting

A serious adverse event (SAE) is any adverse event that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment that results in one of the following outcomes or meets at least one of the following criteria:

- Death
- Hospitalization for greater than 24 hours
- Prolonging an existing inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Any suspected transmission of an infectious agent via a study agent (e.g. Prion Protein Transmitting Transmissible Spongiform Encephalopathy)
- Any confirmed occurrence of Hy's Law, defined as an ALT or AST ≥ 3 × institutional ULN **AND** concurrent total bilirubin ≥ 2 × institutional ULN without findings of cholestasis
- Considered significant by the investigator for any other reason

If an investigator becomes aware of an SAE that is considered related to acalabrutinib after completion of the 30-day period following the last dose of acalabrutinib, the event should also be reported as an SAE to Acerta Pharma at the contact information given below.

Previously planned (prior to signing the informed consent form) surgeries, and non-disease related elective surgeries planned during the course of the study, should not be reported as SAEs unless the underlying medical condition has worsened or appeared during the course of the study. Events that occur prior to the first administration of study medication should not be reported as SAEs.

Preplanned hospitalizations or procedures for pre-existing conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (e.g., for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Death due to disease progression should not be reported as an SAE unless the investigator deems it to be related to the use of study drug. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as SAEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an SAE being due only to the disease under study, it should be reported as an SAE.

Study site personnel must alert the sponsor-investigator of any SAE as soon as possible and no later than 1 business day of the treating investigator receiving notification of the SAE experienced by a patient participating in the study. Study site personnel must alert TG Therapeutics, Inc. of any SAE within 24 hours of the first knowledge of the event by the treating physician or research personnel. Study site personnel must alert Acerta Pharma within 15 calendar days of awareness of any SAEs. The SAE reports should be on a standard reporting form (e.g. CIOMS, local institutional SAE form, MedWatch 3500a, or similar) and are to be sent via email to TG Therapeutics, Inc.: safety@tgtxinc.com and Acerta Pharma: AEMailboxClinicalTrialTCS@astrazeneca.com.

6.4 **Adverse Events of Special Interest (AESI)**

6.4.1 Pregnancy

During the course of the study, all female participants of childbearing potential must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator). If an investigator suspects that a participant may be pregnant, the study drugs must be withheld until a pregnancy test has been administered and the result has been confirmed. If a pregnancy is confirmed, the patient must be permanently discontinued from the study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Any pregnancy that occurs with the subject or with the partner of a treated subject during the study intervention period, or that occurs within 30 days following the last dose of study medication, will be reported, followed to conclusion, and the outcome reported. Abortions (spontaneous, accidental, or therapeutic) must also be reported.

Study site personnel must alert the sponsor-investigator and submit an SAE form (CIOMS, local institutional SAE form, or similar) within 15 calendar days to Acerta Pharma at AEMailboxClinicalTrialTCS@astrazeneca.com.

Confirmed pregnancies, subject's partner pregnancies, and abortions (spontaneous, accidental, or therapeutic) must be reported to TG Therapeutics, Inc. at safety@tgtxinc.com within 24 hours of the first knowledge of the event by the treating physician or research personnel on a Pregnancy Report Form. For subject's partner pregnancies, the partner will be requested to consent to access to medical records. After the subject's partner provides consent, the pregnant partner and baby will be followed to see what effect the drug(s) under study may have on the outcome of the pregnancy or the health of the newborn.

Congenital anomalies/birth defects **always** meet SAE criteria and should therefore be expeditiously reported as an SAE to TG Therapeutics, Inc. at safety@tgtxinc.com within 24 hours of the first knowledge of the event by the treating physician or research personnel.

6.4.2 Study Drug Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF. Any accidental or intentional overdose with the study treatment, even if not fulfilling a seriousness criterion, is to be reported to the sponsor-investigator within 1 business day, to TG Therapeutics, Inc. at safety@tgtxinc.com within 24 hours, and to Acerta Pharma at AEMailboxClinicalTrialTCS@astrazeneca.com within 15 calendar days on an SAE form (CIOMS, local institutional SAE form, or similar).

6.4.3 Secondary and Second Primary Malignancy

Secondary and second primary malignancies are considered AESIs for acalabrutinib. Any malignancy possibly related to cancer treatment, and any secondary (occurring as a direct result as study drug administered, including but not limited to MDS) or second primary (unrelated, new cancer, including but not limited to MDS and MPD) malignancy event must be reported to the sponsor-investigator and to Acerta Pharma at: AEMailboxClinicalTrialTCS@astrazeneca.com via the SAE form (CIOMS, local institutional SAE form, or similar) within 1 business day of awareness.

AEs for malignant tumors reported during a study should generally be assessed as serious AEs (refer to **Section 7.3**). If no other seriousness criteria apply, the "considered significant by the investigator for any other reason" 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.

6.4.4 Ventricular Arrhythmias

Ventricular arrhythmias (e.g. ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.) are considered AESIs for acalabrutinib. Any occurrence of a ventricular arrhythmia must be reported to the sponsor-investigator and Acerta Pharma irrespective of regulatory seriousness criteria or event causality. Report on an SAE form (CIOMS, local institutional SAE form, or similar) within 15 calendar days of awareness, email form to Acerta Pharma at: AEMailboxClinicalTrialTCS@astrazeneca.com

6.5 **Adverse Event Reporting**

6.5.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

6.5.2 Investigators **must** report to the PI any serious adverse event (SAE) or adverse event of special interest (AESI) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

6.5.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Sponsor-Investigator within the timeframes detailed below:

- **Grade 2 and Grade 3 Events:** Report events that are **unexpected** and there is a reasonable possibility the event is related to the study intervention (i.e. possible, probable, or definite attribution). Report to the sponsor-investigator within 5 calendar days of the treating investigator or research site personnel learning of the event.
- **Grade 4 Events:** Report all events that are **unexpected**. Report to the sponsor-investigator within 5 calendar days of the treating investigator or research site personnel learning of the event.
- **Grade 5 Events:** Report **ALL** grade 5 events. Report to the sponsor-investigator within 1 business day of the treating investigator or research site personnel learning of the event.

The Sponsor-Investigator will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

6.6 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

Any adverse events meeting criteria for FDA reporting must also be reported to Acerta Pharma in parallel with FDA submission: AEMailboxClinicalTrialTCS@astrazeneca.com.

6.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

6.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA,**

etc.) must also be reported in routine study data submissions.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in **Section 7.1**.

7.1 **Acalabrutinib maleate**

7.1.1 Description

Other Names: CALQUENCE®, ACP-196 Maleate
Molecular Formula: $C_{26}H_{23}N_7O_2.C_4H_4O_4$
Molecular Weight: 581.58
Appearance: Orange film-coated tablet

7.1.2 Form

The investigational product, acalabrutinib maleate tablet, is presented as an orange film-coated tablet containing 129 mg of acalabrutinib maleate (equivalent to 100 mg of acalabrutinib) drug substance.

Each tablet also contains the following compendial inactive ingredients: mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. The tablet coating contains: hypromellose, copovidone, titanium dioxide, polyethylene glycol, caprylic/capric triglyceride, yellow iron oxide and red iron oxide.

7.1.3 Storage

Acalabrutinib maleate tablets are packed in white, high-density polyethylene (HDPE) bottles containing a silica gel desiccant and should be stored according to the storage conditions as indicated on the label. The recommended storage condition for acalabrutinib maleate tablets is below 30°C (86°F)

7.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.5 Availability

Acalabrutinib is a commercially available agent that will be supplied by Acerta Pharma.

7.1.6 Administration

See **Section 5.3.**

7.1.7 Ordering

Acalabrutinib should be ordered from Acerta Pharma by site pharmacy personnel.

7.1.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.1.9 Destruction and Return

Expired, returned, or unused supplies of acalabrutinib should be destroyed according to local institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 **Umbralisib**

7.2.1 Description

Classification: Phosphatidylinositol-3-Kinase (PI3K) Delta Inhibitor
Other Names: TGR-1202
Appearance: off-white to brown colored powder
Solubility: Freely soluble in dimethyl sulfoxide and soluble in methanol

7.2.2 Form

Umbralisib is supplied as 200 mg light green, oval tablets with "L474" debossed on one side. It is supplied in HDPE bottles, each containing 30 tablets and a silica gel canister as a desiccant.

Table 16: Composition of Umbralisib Drug Product

Ingredients	%w/w
Umbralisib Tosylate	36.09
Microcrystalline Cellulose (Avicel PH 101)	9.96
Hydroxy Propyl Betadex (Kleptose HPB)	37.45
Croscarmellose Sodium (Ac-Di-Sol)	2.77
Hydroxypropyl Cellulose (Klucel LF)	0.83
Croscarmellose Sodium (Ac-Di-Sol)	9.71

Table 16: Composition of Umbralisib Drug Product	
Ingredients	**%w/w**
Magnesium Stearate (Vegetable Source)	0.28
Opadry II Green 40L510005	2.91
Total Weight	**100.00**

7.2.3 Storage

Store umbralisib at 20˚C to 25˚C. Excursions permitted to 15˚C to 30˚C. Do not freeze. For questions about product expiry email productquality@tgtxinc.com.

7.2.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.2.5 Availability

Umbralisib is an investigational agent that will be supplied by TG Therapeutics, Inc.

7.2.6 Administration

Refer to **Section 5.3**.

7.2.7 Ordering

Umbralisib is available from TG Therapeutics, Inc. and will be ordered by site pharmacy personnel. Ensure staff will be available to unpack shipment immediately upon arrival. Allow 5 to 7 business days between drug ordering and drug arrival. Direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following:

- Requested quantity of TG Therapeutics, Inc. study drug(s)
- Date needed
- Sponsor-investigator name
- Study title
- TG Therapeutics, Inc. Tracking Number (U2-NTG-013)
- Investigational drug pharmacy shipping address

Upon receipt of the shipment, the pharmacist or appropriate person at the site should update the accountability forms for umbralisib. If there is any abnormality in the supplied bottles, the pharmacist or the appropriate person must document it during the acknowledgement of receipt and contact TG Therapeutics, Inc. at productquality@tgtxinc.com.

7.2.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.2.9 Destruction and Return

Expired, returned, or unused supplies of umbralisib should be destroyed according to local institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.3 **Ublituximab**

7.3.1 Description

Chemical Name: Ublituximab
Other Names: TG-1101
Classification: Recombinant chimeric anti-CD20 monoclonal antibody

Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.

7.3.2 Form

Concentration of 25 mg/mL in:

- 6 mL (150 mg) single-use glass vials
  Or
- 36 mL (900mg) single-use glass vials

7.3.3 Storage and Stability

Ublituximab vials must be stored in a secured limited-access refrigerated area at a temperature ranging from 2-8°C (36-46°F). Once a vial of ublituximab has been diluted, it should be used immediately. If not used immediately, diluted solutions must be stored refrigerated. The storage duration of ublituximab diluted in poly vinyl chloride (PVC) or non-PVC polyolefin (PO) material is up to 24 hours when refrigerated at 2-8°C (36-46°F). After allowing the diluted bag to come to room temperature, use immediately.

Ublituximab has a shelf-life of 36 months if stored between +2°C to +8°C, based on stability data. For questions about product expiry email productquality@tgtxinc.com.

7.3.4 Compatibility

Ublituximab should not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. The compatibility of ublituximab with medical devices was investigated using a standard PVC bag containing 0.9% NaCl and standard PVC tubing, however dilution into non-PVC bags and use of non-PVC tubing is acceptable.

7.3.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.3.6 Availability

Ublituximab is an investigational agent that will be supplied by TG Therapeutics, Inc.

7.3.7 Preparation

Ublituximab should not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. No data are available for other solutions such as 5% dextrose and 5% mannitol.

Ublituximab is available in 150 mg (6 mL quantity vial) or 900mg (36 mL quantity vial) single use vials as a 25 mg/mL concentrate for dilution. Dilutions for ublituximab are as indicated in the tables below.

Ublituximab preparation instructions for 900mg Single use vial C7D1 & C7D2

- Withdraw appropriate volume of ublituximab from the vial as per table
- For day 1 infusion, dilute 6 mL ublituximab into a 250 mL 0.9% sodium chloride infusion bag for administration on day 1. If not used immediately, diluted solutions must be refrigerated. After allowing the diluted bag to come to room temperature, use immediately.
- For day 2 infusion, dilute the remaining 30 mL into a 500 mL 0.9% sodium chloride infusion bag at the same time, and store at 2-8°C (36-46°F) for up to 24 hours for use on Day 2. After allowing the diluted bag to come to room temperature, use immediately.
- Label each infusion bag clearly.
    - Day 1 = 150 mg bag

- Day 2 = 750 mg bag
- Mix diluted solution by gentle inversion prior to use. Do not shake or freeze.

Table 17: Ublituximab Dilutions for Cycle 7 Day 1 & Day 2			
Dose of ublituximab for infusion	**Volume of ublituximab (25 mg/mL)**	**Volume of NaCl 0.9% to be removed**	**Final volume in perfusion bag**
Day 1: 150 mg	6 mL	6 mL	250 mL
Day 2: 750 mg	30 mL	30 mL	500 mL

Table 18: Ublituximab Dilutions for Cycle 7 Day 8 & Beyond			
Dose of ublituximab for infusion	**Volume of ublituximab (25 mg/mL)**	**Volume of NaCl 0.9% to be removed**	**Final volume in perfusion bag**
900 mg	36 mL	36 mL	500 mL

Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if does not conform to the specifications. Immediately inform TG Therapeutics, Inc. at productquality@tgtxinc.com with any product quality concerns or questions.

7.3.8 Administration

Refer to **Section 5.3**.

7.3.9 Ordering

Ublituximab is available from TG Therapeutics, Inc. and will be ordered by site pharmacy personnel. Order ublituximab Monday through Wednesday to ensure shipment arrives Monday through Friday. Ensure staff will be available to unpack shipment immediately upon arrival. Allow 5 to 7 business days between drug ordering and drug arrival. Direct drug orders to ISTdrugorder@tgtxinc.com. The email should include the following:

- Requested quantity of TG Therapeutics, Inc. study drug(s)
- Data needed
- Sponsor- investigator name
- Study title
- TG Therapeutics, Inc. Tracking Number (U2-NTG-013)
- Investigational drug pharmacy shipping address

Upon receipt of this shipment, the pharmacist or the appropriate person at the site should update the accountability forms for ublituximab. If there is any abnormality in

the supplied boxes, the pharmacist or the appropriate person must document it during the acknowledgement of receipt and contact TG Therapeutics, Inc. at productquality@tgtxinc.com.

7.3.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.3.11 Destruction and Return

Expired or unused supplies of ublituximab should be destroyed according to local institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

8.1 BH3 Profiling

BH3 profiling is a functional assay we previously developed that detects the proximity of CLL cells to the threshold of apoptosis (what we call 'priming') through interrogation of BCL-2 family members. To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized malignant cells and use FACS to measure the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release.

Assessments will be made on circulating CLL cells from the peripheral blood drawn from patients at baseline. We will attempt to identify potential resistance mechanisms by looking at whether patients who do not achieve CR have different upfront BH3 profiles from those who do. Additionally, another sample of peripheral blood will be collected from subjects at the time of relapse or disease progression, and the BH3 profile of these samples will be compared to subjects' baseline samples to help identify whether a change in anti-apoptotic protein dependence is observed as a possible mechanism of resistance.

If we have bone marrow aspirates and fresh lymph node tissue available, we may also perform BH3 profiling to see whether the level of priming in CLL cells from these tissues is a better predictor of response than peripheral blood CLL cells.

Dynamic BH3 profiling, a technique that allows us to measure "delta priming," defined as the difference in mitochondrial response to a BH3 peptide in a drug-treated sample versus an untreated control may also be performed. We will compare the dynamic BH3 profile of serially collected samples to a baseline sample, which will allow us to assess *in vivo* the short-term

change in apoptotic priming induced by the study agents. We will correlate this with clinical response.

All peripheral blood samples will promptly be delivered to the laboratory of Dr. Jennifer Brown at Dana-Farber Cancer Institute (DFCI), where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be batched and stored, and the BH3 profiling assays will be performed in Dr. Matthew Davids' lab at DFCI.

8.2 **Genomic Analyses**

We plan to perform whole exome sequencing (WES) on CLL cells and normal tissue from patients at baseline to evaluate for somatic mutations such as *TP53*, *NOTCH1* and *SF3B1* that may confer drug sensitivity and resistance. If the patient does not have significant circulating CLL cells, we will pursue sequencing of bone marrow aspirate samples in patients who require a new bone marrow biopsy for screening. In addition, saliva as a source of germline will be collected prior to study drug initiation and may be collected more than once if inadequate specimen is obtained.

All samples will promptly be delivered to the laboratory of Dr. Jennifer Brown at DFCI, where DNA will be extracted and then sent to the Broad Institute (Cambridge, MA) for WES. In an exploratory analysis, we will assess novel mutations as potential predictors of response and PFS. We will also collect a sample from each patient at time of relapse or progression for repeat analysis by WES to assess for acquired resistance mutations.

8.3 **Adaptive ClonoSEQ Assay**

To assess whether the presence of minimal residual CLL cells in the peripheral blood as measured by a novel sequencing platform is predictive of OS and PFS, peripheral blood and/or bone marrow samples will be serially collected for analysis. Samples will be sent to the Brown Lab at DFCI where they will be stored initially prior to batch shipping to Adaptive for analysis.

Using Adaptive's ClonoSEQ platform, rearranged immunoreceptor loci from genomic DNA will be extracted, amplified, and sequenced using V and J segment primers for each immunoreceptor gene. Tumor-specific clonotypes will be identified for each patient based on their high prevalence in peripheral blood or bone marrow. Sequences will be analyzed using standardized algorithms for clonotype determination. Adaptive MRD levels will be quantified using spiked-in reference sequences.

8.4 **T Cell Profiling**

Cells will be banked serially for the determination of T cell subsets by flow cytometry and/or CyTOF, in order to determine the effects of umbralisib and acalabrutinib on T cell populations, particularly CD8s, Tregs and Th17s. Samples will be banked in the laboratory of Dr. Jennifer

Brown at DFCI. T cell functional studies, including proliferation and T reg suppression studies among others, will be performed on *ex vivo* PBMC samples when possible given cell numbers.

8.5 **Additional Prognostic Tests**

Patients who have not had ZAP-70, *IGHV, TP53* and *NOTCH1* testing done locally will have baseline samples sent for testing to Genzyme/LabCorp. These samples will be shipped alongside the Integrated Oncology/LabCorp requisition form ambient priority overnight to:

Genzyme/LabCorp Specialty Testing Group
521 West 57th Street
New York, NY 10000

8.6 **Correlative Study Sample Collection Summary**

Correlative samples will be collected as indicated in the table below.

Table 19: Correlative Sample Collection Schedule

Sample Time Point*	Container[1]	Sample Type[2]	Shipping Method	Recipient
Screening or Pre-dose Day 1	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profiling, WES, T cell profiling, Adaptive Clonoseq)
	2 × 6 mL Green Top	Bone Marrow Aspirate		
	1 × Oragene Kit	Saliva[3]	Ambient overnight	
	2 × 6mL Green Top[4]	Peripheral blood	Fridge pack overnight	Genzyme/LabCorp[4,5]
Cycle 1, Day 8	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (T cell profiling, BH3 profile)
Cycle 2, Day 1	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profile)
Cycle 4, Day 1	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (T cell profiling, BH3 profile)
Cycle 7, Day 1 (prior to initiation of ublituximab)	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profile, T cell profiling, Adaptive Clonoseq)
	2 × 6 mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Brown Laboratory, DFCI (Adaptive Clonoseq)
	1 × 6 mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Mayo Clinic (MRD Assessment)
Cycle 13, Day 1	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profile, T cell profiling, Adaptive Clonoseq)

Table 19: Correlative Sample Collection Schedule

Sample Time Point*	Container[1]	Sample Type[2]	Shipping Method	Recipient
	2 × 6mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Brown Laboratory, DFCI (Adaptive Clonoseq)
	1 × 6mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Mayo Clinic (MRD Assessment)
Every 6 Months after Cycle 13	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral blood	Fridge pack overnight	Brown Laboratory, DFCI (T cell profiling, BH3 profile)
Cycle 25 Day 1 AND Re-Treatment Cycle 13 Day 1 (as applicable)	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral Blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profile, Adaptive Clonoseq)
	2 × 6 mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Brown Laboratory, DFCI (Adaptive Clonoseq)
	1 × 6 mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	Mayo Clinic (MRD Assessment)
Treatment Discontinuation	6 × 6 mL Green Top 1 × 6 mL Red Top	Peripheral Blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profile, T cell profiling, Adaptive Clonoseq)
	2 × 6mL Green Top	Bone Marrow Aspirate	Fridge pack overnight	
Relapse/Disease Progression	1 × 6 mL Red Top	Peripheral Blood	Fridge pack overnight	Brown Laboratory, DFCI (BH3 profiling, whole exome sequencing, T cell profiling, Adaptive Clonoseq)
	6 × 6 mL Green Top	Peripheral Blood	Fridge pack overnight	
	2 × 6 mL Green Top	Bone Marrow Aspirate		

1. Green top = sodium heparin tube; Red top = no additive
2. For time points that mention blood and/or aspirate: If patient has few circulating CLL cells in peripheral blood, send additional aspirate (1 × 6 mL green top tube) in addition to blood.
3. Oragene kits require approximately 2 mLs of saliva.
4. Samples required for all patients at baseline unless previously tested for ZAP-70, *IGHV*, *TP53*, and *NOTCH1*.
5. Genzyme/LabCorp only provides requisition form.

*: All sample time points have a ± 7 day scheduling window. Cycle 7 Day 1 samples must be collected prior to initiation of ublituximab.

Correlative studies note: While the goal of the correlative studies is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to either practical reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results
obtained during the study, sample collection/analysis may be omitted at the discretion of the PI. Additional correlative samples may be collected after the 24-cycle time point at the discretion of the investigators.

9. STUDY CALENDAR

Screening evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of screening radiologic scans which may be conducted within 30 days prior

to the start of protocol therapy and the bone marrow biopsy / aspirate which may be obtained up to 90 days prior to the start of protocol therapy as long as no intervening therapy has occurred. Assessments must be performed prior to administration of any study agent.

Table 20: Study Calendar for All Participants, Cycles 1 - 12

	Screening	Cycle 1 Day 1	Cycle 1 Day 8[a]	Cycle 1 Day 15[a]	Cycle 2 - 6 Day 1[b]	Cycle 7 Day 1[a]	Cycle 7 Day 2	Cycle 7 Day 8[c]	Cycle 7 Day 15[c]	Cycles 8 – 12 Day 1[a]	Off Treatment[d]	Long-term Follow-up[e]	EDC Timepoints[∞]
Demographics	X												Screening
Medical history	X												Screening
Physical exam	X	X	X	X	X	X		X	X	X	X		N/A
Vital signs	X	X	X	X	X	X	X	X	X	X	X		N/A
Height	X												N/A
Weight	X	X	X	X	X	X		X	X	X	X		N/A
ECOG performance status	X	X			X	X				X	X		Screening, Cycles 1 – 12 Day 1, Off Treatment
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X		All Visits
Serum chemistry[f]	X	X	X	X	X	X	X	X	X	X	X		N/A
PT-INR, aPTT	X												N/A
Serum β-HCG[g]	X												N/A
HCV, HBV, and CMV IgG or IgM serologies[h]	X												N/A
CMV surveillance by PCR[n]	X				X	X				X	X		
Echocardiogram[o]	X												Screening
EKG[i]	X	As clinically indicated											N/A
Adverse event evaluation		X----------									----------X	X	All Visits
Radiologic evaluation[j]	X	CT or MRI scans to be repeated as described in **Section 11.1**											Screening, Day 28 of Cycles 2, 6, and 12, Off Treatment, and to confirm CR
Bone marrow biopsy / aspirate / MRD assessment[k]	X	To be performed as described in **Sections 9.6 and 11.2**											Screening, Day 1 of Cycle 7, Off Treatment, and to confirm CR
Peripheral Blood MRD Analysis		To be performed on Day 1 of Cycles 3, 7, and 10 (±7 day scheduling window)									X		Day 1 of Cycles 3,7, and 10, Off Treatment

Table 20: Study Calendar for All Participants, Cycles 1 - 12

	Screening	Cycle 1 Day 1	Cycle 1 Day 8[a]	Cycle 1 Day 15[a]	Cycle 2 - 6 Day 1[b]	Cycle 7 Day 1[a]	Cycle 7 Day 2	Cycle 7 Day 8[c]	Cycle 7 Day 15[c]	Cycles 8 – 12 Day 1[a]	Off Treatment[d]	Long-term Follow-up[e]	EDC Timepoints[∞]
Correlative Analyses	As described in **Section 9**												N/A
Ublituximab[l]						X	X	X	X	X			Day 1 of Cycles 7 – 12
Acalabrutinib[m]		As described in **Section 5.3**											Day 1 of Cycles 1 - 12
Umbralisib[m]		As described in **Section 5.3**											Day 1 of Cycles 1 - 12
Medical Record Review / Care Provider Contact / Telephone Contact												X	Every 3 months following treatment discontinuation for a maximum of 5 years

∞: Column only relevant for CRF builders.

a. A ± 3 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
b. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
c. A ± 2 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
d. Off treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment.
e. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response following treatment discontinuation. To be completed every 3 months following the final dose of study drug (±1 month window) for a maximum of 5 years after treatment discontinuation or until death, whichever occurs first.

f. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid, LDH.
g. Serum pregnancy test within 3 days prior to Cycle 1 Day 1 only required for women of childbearing potential, as defined in **Section 5.4.**
h. Hepatitis B surface antigen (HBsAg) and antibody (HBsAb), hepatitis B core antibody (HBcAb), HBV DNA, hepatitis C antibody, hep C viral load and CMV IgG **or** IgM testing is required for all participants during the screening period. Refer to **Section 3.2.20** and **Section 5.4**.
i. Single EKG to be collected during the screening period. QTc to be calculated per institutional standards.
j. Screening chest/abdomen/pelvis CT or MRI required for all participants within 30 days prior to the start of protocol therapy. Refer to **Section 11.1**.
k. Screening bone marrow biopsy / aspirate may be performed up to 90 days prior to the start of protocol therapy as long as no intervening therapy has occurred. Refer to **Section 11.2.** Correlative analyses on collected aspirate specimens will be performed as described in **Section 9**. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both). MRD should be performed on the marrows to evaluate response at years 1 and 2.
l. Refer to **Section 5.3** for ublituximab administration and hypersensitivity reaction guidelines.
m. Adequate supply of the study agent should be dispensed to account for any pre-planned scheduling delays.
n. CMV surveillance by PCR approximately every 3 cycles during treatment with umbralisib and approximately 30 days after the last dose of umbralisib, aligned with scheduled visits.
o. Baseline 2D echocardiogram required prior to start of protocol therapy.

Table 21: Study Calendar for Participants in CR Cycles 13 - 37

	Cycles 13 Day 1[a]	Cycles 15, 18 Day 1[b]	Cycles 21, 25, 28, 31, 34, 37 Day 1[a]	Long-term Follow-up[c]	EDC Timepoints[∞]
Physical exam	X	X	X		N/A
Vital signs[d]	X	X	X		N/A
Weight	X	X	X		N/A
ECOG performance status	X	X	X		Day 1 of Cycles 13, 15, 18, 21, 25, 28, 31, 34, 37
CBC w/diff, plts	X	X	X		Day 1 of Cycles 13, 15, 18, 21, 25, 28, 31, 34, 37
Serum chemistry[e]	X	X	X		N/A
CMV surveillance by PCR[h]	X				
EKG	As Clinically Indicated				N/A
Adverse Event Evaluation	X----------X				All Visits
Radiologic evaluation	CT or MRI scans to be repeated as described in **Section 11.1**				Day 28 of Cycle 17 and 24, Off Treatment, and to confirm CR or Relapse
Bone marrow biopsy / aspirate / MRD assessment[f]	To be repeated as described in **Sections 9.6 and 11.2**				Day 1 of Cycle 25, and to confirm CR or Relapse
Peripheral Blood MRD Analysis	X	X	X		Day 1 of Cycles 13, 15, 18, 21, 25, 28, 31, 34, 37
Correlative Analyses	As described in **Section 9**.				N/A
Medical Record Review / Care Provider Contact / Telephone Contact				X	Every 3 months following the completion of Cycle 36 for a maximum of 2 years

∞: Column only relevant for CRF builders.

a. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
b. A ± 3 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
c. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response. To be completed every 3 months (±1 month window) following the completion of Cycle 36 for a maximum of 2 years or until death, whichever occurs first.
d. Heart rate, respiratory rate, temperature, blood pressure, and oxygen saturation.
e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid, LDH.
f. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both). MRD should be performed on the marrows to evaluate response at years 1 and 2.
g. CMV surveillance by PCR approximately every 3 cycles during treatment with umbralisib and approximately 30 days after the last dose of umbralisib, aligned with scheduled visits.

Table 22: Study Calendar for Participants with Recurrence/Relapse after Discontinuation of Therapy

	Retreatment Cycle 1 Day 1[a]	Retreatment Cycle 2 Day 1[b]	Retreatment Cycles 3, 7, 10, and 13 Day 1[b]	Off Treatment[c]	Long-term Follow-up[d]	EDC Timepoints[∞]
Physical exam	X	X	X	X		N/A
Vital signs	X	X	X	X		N/A
Weight	X	X	X	X		N/A
ECOG performance status	X	X	X	X		Day 1 of retreatment cycles 1 – 3, 7, 10, and 13, Off Treatment
CBC w/diff, plts	X	X	X	X		Day 1 of retreatment cycles 1 – 3, 7, 10, and 13, Off Treatment
Serum chemistry[e]	X	X	X	X		N/A
CMV surveillance by PCR[h]	X		X	X		
EKG	As Clinically Indicated					N/A
Adverse Event Evaluation	X----------			X		All Visits
Radiologic evaluation	CT or MRI scans to be repeated as described in **Section 11.1**					Day 28 of retreatment cycles 2, 6, and 12, Off Treatment
Bone marrow biopsy / aspirate / MRD assessment[f]	To be repeated as described in **Sections 9.6 and 11.2.**					Day 1 of Cycle 13
Peripheral Blood MRD Analysis			X	X		Day 1 of retreatment cycles 3, 7, 10, and 13, Off Treatment
Correlative Analyses	As described in **Section 9**.					N/A
Acalabrutinib[g]	As described in **Section 5.3**					Day 1 of Retreatment Cycles 1 - 12
Umbralisib[g]	As described in **Section 5.3**					Day 1 of Retreatment Cycles 1 - 12
Medical Record Review / Care Provider Contact / Telephone Contact					X	Every 3 months following treatment discontinuation for a maximum of 5 years

Table 22: Study Calendar for Participants with Recurrence/Relapse after Discontinuation of Therapy

	Retreatment Cycle 1 Day 1[a]	Retreatment Cycle 2 Day 1[b]	Retreatment Cycles 3, 7, 10, and 13 Day 1[b]	Off Treatment[c]	Long-term Follow-up[d]	EDC Timepoints[∞]

∞: Column only relevant for CRF builders.

a. Participants who relapse following confirmed CR will be required to undergo repeat radiologic scans (if not performed within the prior 3 months) and bone marrow biopsy / aspirate (if not performed within the prior 6 months) prior to re-treatment as described in **Section 11.1** and **Section 11.2**.

b. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.

c. Off treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment. Participants coming off treatment at the completion of retreatment cycle 13 will undergo a single visit/set of assessments to meet both the off treatment and C13D1 trial requirements (not two separate visits).

d. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response following treatment discontinuation. To be completed every 3 months following the final dose of study drug (±1 month window) for a maximum of 5 years after treatment discontinuation or until death, whichever occurs first.

e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid, LDH.

f. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both). MRD should be performed on the marrows to evaluate response at years 1 and 2.

g. Adequate supply of the study agent should be dispensed to account for any pre-planned scheduling delays.

h. CMV surveillance by PCR approximately every 3 cycles during treatment with umbralisib and approximately 30 days after the last dose of umbralisib, aligned with scheduled visits.

Table 23: Study Calendar for Participants NOT in CR Cycles 13 - 24

	Cycle 13 Day 1[a]	Cycles 15, 18 Day 1[b]	Cycles 21, 25 Day 1[a]	Off Treatment[c]	Long-term Follow-up[d]	EDC Timepoints[∞]
Physical exam	X	X	X	X		N/A
Vital signs[e]	X	X	X	X		N/A
Weight	X	X	X	X		N/A
ECOG performance status	X	X	X	X		Day 1 of cycle 13, 15, 18, 21, and 25, Off Treatment
CBC w/diff, plts	X	X	X	X		Day 1 of cycle 13, 15, 18, 21, and 25, Off Treatment
Serum chemistry[e]	X	X	X	X		N/A
CMV surveillance by PCR[i]	X	X	X	X		
EKG	As Clinically Indicated					N/A
Adverse Event Evaluation	X----------X			X		All Visits
Radiologic evaluation	CT or MRI scans to be repeated as described in **Section 11.1**					Day 28 of cycle 17 and 24, Off Treatment, and to confirm CR
Bone marrow biopsy / aspirate / MRD assessment[f]	To be repeated as described in **Sections 9.6 and 11.2.**					Day 1 of cycle 13 and 25 and to confirm CR
Peripheral Blood MRD Analysis	X	X	X	X		Day 1 of cycle 13, 15, 18, 21, and 25, Off Treatment
Correlative Analyses	As described in **Section 9**.					N/A
Acalabrutinib[h]	As described in **Section 5.3**					Day 1 of Cycles 13 - 24
Umbralisib[h]	As described in **Section 5.3**					Day 1 of Cycles 13 - 24
Medical Record Review / Care Provider Contact / Telephone Contact					X	Every 3 months following treatment discontinuation for a maximum of 5 years

Table 23: Study Calendar for Participants NOT in CR Cycles 13 - 24

	Cycle 13 Day 1[a]	Cycles 15, 18 Day 1[b]	Cycles 21, 25 Day 1[a]	Off Treatment[c]	Long-term Follow-up[d]	EDC Timepoints[∞]

∞: Column only relevant for CRF builders.

a. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
b. A ± 3 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
c. Off treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment. Participants coming off treatment at the completion of cycle 24 will undergo a single visit/set of assessments to meet both the off treatment and C25D1 trial requirements (not two separate visits).
d. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response following treatment discontinuation. To be completed every 3 months following the final dose of study drug (±1 month window) for a maximum of 5 years after treatment discontinuation or until death, whichever occurs first.
e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid, LDH.
f. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both). MRD should be performed on the marrows to evaluate response at years 1 and 2.
g. Adequate supply of the study agent should be dispensed to account for any pre-planned scheduling delays.
h. CMV surveillance by PCR approximately every 3 cycles during treatment with umbralisib and approximately 30 days after the last dose of umbralisib, aligned with scheduled visits.

10. MEASUREMENT OF EFFECT

Response and progression of CLL participants will be evaluated using the 2018 iwCLL criteria for CLL.[1]

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. All lymph node measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool.

10.1 **Imaging Evaluations**

All participants will have screening CT or MRI scans of the chest, abdomen, and pelvis within 30 days prior to the start of protocol therapy. Scans will be repeated on day 28 (± 7 day scheduling window) of cycles 2, 6, 12, 17, and 24, as well as at the off-treatment visit. Cycle 17 scan may be omitted for participants in confirmed CR at the treating investigator's discretion.

In addition, scans will be repeated at any point to confirm a CR and in any participant with suspected relapse following achievement of CR (if not done within the prior three months). Participants who undergo re-treatment will have scans on day 28 of re-treatment cycles 2, 6, and 12 as well as at the off-treatment visit (± 7 day scheduling window). Scans may also be repeated at any other time at the discretion of the treating investigator.

Conventional CT and MRI should be performed. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

10.2 **Bone Marrow Biopsy / Aspirate**

Screening bone marrow biopsy / aspirate is required for all participants and may be obtained up to 90 days prior to the start of protocol therapy as long as no intervening therapy has occurred. Repeat bone marrow biopsy / aspirate is required on day 1 of cycles 7, 13, and 25 (i.e. at the completion of 24 cycles of therapy), with an allowable ± 7 day window (cycle 7 day 1 bone marrow must be performed prior to the initiation of ublituximab therapy). Bone marrow biopsy / aspirate is also required at any point to confirm a CR, at the time of suspected relapse following achievement of CR (if not done within the prior 6 months), and on re-treatment cycle 13 day 1 for participants who undergo re-treatment (± 7 day window). Bone marrow biopsy / aspirate may also be done at any time at the treating investigator's discretion.

10.3 **Response Criteria**

Table 24: Response Definition Following Treatment of CLL Participants					
Group	**Parameter**	**Complete Remission (CR)[1]**	**Partial Remission (PR)[2]**	**Stable Disease (SD)[3]**	**Progressive Disease (PD)[4]**
A	Lymph nodes	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)[5]	Change of -49% to +49%	Increase ≥ 50% from baseline or from response
	Liver and/or spleen size[6]	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Change of -49% to +49%	Increase ≥ 50% from baseline or from response
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Change of -49% to +49%	Increase ≥ 50% from Baseline
B	Platelet count	≥ 100×10^9/L	≥ 100×10^9/L or increase ≥ 50% over baseline	Change of -49% to +49%	Decrease of ≥ 50% from baseline secondary to CLL
	Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 11 g/dL or increase ≥ 50% over baseline	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL	Decrease of ≥2 g/dL from baseline secondary to CLL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	No change in marrow infiltrate	Increase of CLL cells by ≥ 50% on successive biopsies

1. For CR, all criteria have to be met from groups A and B.
2. For 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.
3. For SD, all of the criteria have to be met.
4. For PD, at least 1 of the criteria of group A or group B has to be met.
5. 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).
6. Spleen size is considered normal if < 13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in accordance with local standard of care guidelines.

10.4 **Definitions**

Treatment Failure: Responses that should be considered clinically beneficial include CR and PR; all others (e.g., stable disease, non-response, PD, death from any cause) should be rated as a treatment failure.

Overall Survival (OS): Defined as the time from first treatment day to death due to any cause, or censored at date last known alive.

Progression-Free Survival (PFS): Defined as the time from first treatment day to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Event-Free Survival (EFS): Defined as the interval between the first treatment day to the first sign of disease progression or start of a new treatment or withdrawal from the trial because of toxicity or death (whichever occurs first).

Time to Next Treatment (TTNT): Defined as the interval between the first treatment day until the patient starts an alternative therapy for progressive CLL.

Relapse: Defined as evidence of disease progression in a patient who has previously achieved the above criteria of a CR or PR for ≥ 6 months.

Refractory Disease: Defined as treatment failure or as progression within 6 months from the last dose of therapy.

Minimal Residual Disease (MRD)-Negative: Blood or marrow with < 1 CLL cell per 10,000 leukocytes assessed by at least four color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay.

Complete Remission with incomplete marrow recovery (CRi): Some patients fulfill all the criteria for a CR, but have a persistent anemia, thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi). The marrow evaluation should be performed with scrutiny and not show any clonal disease infiltrate.

10.5 **Response Review**

Confirmation of scan results will be reviewed centrally by the Tumor Imaging Metrics Core (TIMC) at DF/HCC, however treatment decisions may be made based on local scan interpretation.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7.0** (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g., scans, laboratory values) will be provided upon request.

11.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in **Appendix C**.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

An open label, non-randomized phase 2 trial assessing the combination of acalabrutinib, umbralisib, and ublituximab in adult participants with chronic lymphocytic leukemia (CLL). Participants will be enrolled to one of two treatment cohorts:

- **Cohort 1:** Participants with relapsed disease
- **Cohort 2:** Participants who are treatment naïve

Each cohort will follow a one-stage enrollment design, accruing a maximum of 30 participants.

12.2 Sample Size, Accrual Rate and Study Duration

A total of 30 participants will be accrued to each cohort, for a maximum total of 60 participants. The anticipated overall accrual rate is approximately 4 patients per month, for a planned accrual duration of about 15 months. Participants will receive treatment for 24 cycles (2 years) and will continue to be followed for a maximum of 5 years following treatment discontinuation for survival, for a total study length of approximately 8 years.

Table 25: Accrual Targets

Ethnic Category	Sex/Gender					
	Females		Males		Total	
Hispanic or Latino	1	+	3	=	4	
Not Hispanic or Latino	20	+	36	=	56	
Ethnic Category: Total of all subjects	21 (A1)	+	39 (B1)	=	60	(C1)
Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	1	+	1	=	2	
Black or African American	1	+	3	=	4	
Native Hawaiian or other Pacific Islander	0	+	0	=	0	
White	19	+	35	=	54	
Racial Category: Total of all subjects	21 (A2)	+	39 (B2)	=	60	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

12.3 Interim Monitoring Plan

The triplet combination of umbralisib, ublituximab, and the BTK inhibitor ibrutinib has been previously tested in this patient population with an acceptable safety profile.[16] Acalabrutinib is a second-generation FDA approved BTK inhibitor that is typically better tolerated by patients and has fewer off-target side effects than ibrutinib (note that a direct head-to-head study has

not been performed).[22] This trial will substitute acalabrutinib for ibrutinib to test efficacy of the combination.

If in the first 10 participants who receive at least one cycle of triple therapy with acalabrutinib, umbralisib, and ublituximab, 3 or more develop serious toxicity, this will trigger a consultation with the DSMC about stopping accrual (see **Section 12.2**). Toxicities would include the following events that occur during the first cycle of triple therapy, unless they are clearly due to underlying disease or extraneous causes: grade 4 or higher infusion-related reaction, grade 4 or higher infection, or any other grade 3 or higher, clinically significant, non-hematologic toxicity, except asymptomatic laboratory abnormalities or nausea/vomiting/diarrhea that improves with supportive care. With this design, the probability of triggering a consultation is 0.07 if the true but unknown rate of serious toxicity is 10%, 0.18 if the rate is 15%, 0.74 if the rate is 35%, and 0.83 if the rate is 40%.

12.4 **Analysis of Primary Endpoints**

The primary endpoint is the rate of CR after 24 cycles of treatment with acalabrutinib, umbralisib, and ublituximab in previously untreated and relapsed CLL patients, assessed per 2018 IW-CLL criteria.[1]

Nastoupil et al. reported a CR rate of 44% in previously treated CLL participants who received ibrutinib, umbralisib, and ublituximab.[16] We hypothesize the CR rate will be 44% in **Cohort 1**; given that the depth of response for treatment naïve disease will likely be greater, we hypothesize a CR rate of 50% in **Cohort 2**.

For **Cohort 1**, if 10 or more patients achieve CR by the completion of 24 cycles, we will regard the treatment as efficacious. This sample size provides an α=0.06 (false positive type I error) and power β = 91% (one minus false negative type II error) using a one-sided one sample binomial test comparing to a null hypothesis of 20% complete response rate with one BCR inhibitor plus an antibody.

For **Cohort 2**, if 13 or more patients achieve CR by the completion of 24 cycles, we will regard the treatment as efficacious. This sample size provides an α=0.08 (false positive type I error) and power β = 82% (one minus false negative type II error) using a one-sided one sample binomial test comparing to a null hypothesis of 30% response rate for one BCR inhibitor plus an antibody.

12.5 **Analysis of Secondary and Exploratory Endpoints**

The analysis of secondary endpoints will be primarily descriptive, including rate of PR and CRi after 24 cycles of therapy, as well as best achieved rate of PR, CR, and CRi; PFS, time to new therapy (TTNT), and OS (including 2-year, 3-year, and 5-year landmark rates), rate of undetectable MRD in the bone marrow after 6, 12 and 24 cycles, rate of peripheral blood undetectable MRD after 6, 12, and 24 cycles, correlation between undetectable MRD in the

peripheral blood and bone marrow, time to MRD-positive disease recurrence in the peripheral blood, time to clinical disease progression, and safety/tolerability.

A descriptive analysis of rates of therapy discontinuation by cycle 12 will be performed, with subjects grouped by reasons for discontinuation (e.g. achievement of CR, progressive disease, or intolerability). Rates of discontinuation of individual components of the regimen will also be included in this analysis.

The Kaplan Meier method will be used to estimate the median PFS time, PFS, median OS time, TTNT, and OS.

Association between clinical response and established CLL prognostic factors (ZAP70, FISH cytogenetics, *IGHV* mutation status, *TP53* mutation status) will be tested using Fisher's exact test. A similar descriptive analysis will be performed for laboratory correlative studies of BH3 profiling and genomic markers such as *SF3B1, NOTCH1,* and *BCR/NFKB* pathway somatic mutations. If feasible, association between clinical response and correlative endpoints will be explored.

12.6 **Reporting and Exclusions**

Participants who never initiate protocol therapy will be excluded from all analyses.

12.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study medication.

12.6.2 Evaluation of the Primary Efficacy Endpoint

All participants who receive at least one dose of at least one of the study agents will be considered evaluable for the primary efficacy endpoint in an intent-to-treat analysis.

13. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

15. PROTOCOL AMENDMENTS

Proposed amendments to the protocol require review and approval by TG Therapeutics, Inc. prior to implementation.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: HEPATITIS B SEROLOGIC TEST RESULTS

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

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APPENDIX C: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA SAFETY MONITORING PLAN

INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB. For studies under a single IRB, the Coordinating Center with regulatory documents or source documents as requested.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.

- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to the Sponsor, Coordinating Center, and IRB of Record as applicable.
- Submit protocol deviations and violations to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions must be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance

Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites are to send their version of the informed consent document to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3 IRB Re-Approval

Verification of IRB re-approval from the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.4 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5 Participant Registration

3.5.1 Participant Registration

To register a participant, the following documents should be completed by the External Site and e-mailed to the Coordinating Center:

Kim E. Pena del Aguila
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
Email: kime_penadelaguila@dfci.harvard.edu
Phone: 857-215-1707

- Signed participant consent form
- HIPAA authorization form
- DFCI eligibility checklist
- Screening provider note including the medical/surgical history, ECOG performance status, vital signs, and physical exam findings
- Copies of laboratory reports and clinical information confirming satisfaction of eligibility criteria.

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.5.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.5.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.6 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web-based training for all eCRF users.

3.6.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within **14 calendar days**.

If study forms are not submitted on schedule, the External Site will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.7 Protocol Reporting Requirements

3.7.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

3.7.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.7.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4 MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to; source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in regular Coordinating Center initiated teleconferences.

Remote Monitoring: External Sites will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification.

and/or

On-Site Monitoring: Source documentation verification (SDV) will be conducted yearly by having access to participants' complete medical record and source documents.

4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Minimum site accrual expectations have been set to 3 subjects per year.

5 AUDITING: QUALITY ASSURANCE

5.1 DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

5.4 External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

APPENDIX E: IWCLL 2018 HEMATOLOGIC TOXICITY GUIDELINES

Table 26: Grading Scale For Hematological Toxicity in CLL Studies[1]		
Grade[2]	**Decrease in platelets[3] or hemoglobin[4] (nadir) from baseline value, %**	**Absolute neutrophil count (nadir)[5] × 10^9/L**
0	No change to 10	≥ 2
1	11 – 24	≥ 1 and < 2
2	25 – 49	≥ 1 and < 1
3	50 – 74	≥ 0.5 and < 1
4	≥ 75	< 0.5

1. Refer to iwCLL 2018 Criteria[1]
2. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.
3. Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20 × 10^9/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20 × 10^9/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
4. Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.
5. If the absolute neutrophil count (ANC) reaches <1 × 10^9/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 × 10^9/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity but should be documented.

APPENDIX F: ACALABRUTINIB DRUG DIARY

Study Participant Self-Administration Instructions

The study staff will explain how to take acalabrutinib, but these are points to remember:

1. Take the drug twice daily approximately 12 hours apart.
2. Take the drug with about 8 ounces of water. Acalabrutinib can be taken with or without meals.
3. You may **NOT** consume: Grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.
4. If you miss taking your dose at the scheduled time, it can be taken as soon as possible up to 3 hours after the scheduled time. If a dose is missed by more than 3 hours, it should be skipped, and the next dose should be taken at its regularly scheduled time. Please make sure to record the reason for missing the dose. If you vomit a dose, do not take it again unless you can see the capsule.
5. Please remember to bring your study drug supply, including empty bottles and remaining pills, and drug diary with you to your clinic appointment. Please do not throw away any empty bottles. On clinic days please take your study medication on your regular schedule.
6. If you are taking a H2 receptor antagonist, then it should be taken approximately 2 hours after an acalabrutinib dose.
7. The drug can be stored at room temperature.
8. Keep this drug out of the reach of children.

Please call your doctor or research nurse before taking any new prescription or over-the-counter medications/supplements other than the study drugs or if any other questions arise.

Study Participant Self-Administration Diary for Acalabrutinib

Please record how many tablets you take and the time you take them and bring the completed diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Participant Identifier: _____ Cycle Number: _____
Protocol #: _____
Study Doctor: _____
Study Nurse: _____
Contact Number: _____

You will take the following number of tablets each time (per dose) as listed in the table below:

Study Drug Name	# of tablets to take per dose	# of times each day
Acalabrutinib		

FOR STUDY TEAM USE ONLY	
Staff initials:	
Date dispensed:	Date returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Day	Date	Number of Acalabrutinib tablets	Time of First Dose each day	Number of Acalabrutinib tablets	Time of Second Dose each day
1			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
2			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
3			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
4			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
5			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
6			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
7			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
8			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
9			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
10			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
11			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
12			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
13			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
14			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
15			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
16			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____

Day	Date	Number of Acalabrutinib tablets	Time of First Dose each day	Number of Acalabrutinib tablets	Time of Second Dose each day
17			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
18			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
19			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
20			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
21			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
22			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
23			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
24			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
25			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
26			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
27			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
28			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____		_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____

Participant/Caregiver Signature: _____ Date: _____

APPENDIX G: UMBRALISIB DRUG DIARY

Study Participant Self-Administration Instructions

The study staff will explain how to take Umbralisib, but these are points to remember:

1. Take the drug once daily, approximately every 24 hours.
2. Take within 30 minutes of a meal.
3. The tablets should be swallowed whole. Do not attempt to crush, chew, or dissolve the tablets.
4. If you miss taking your dose at the scheduled time, it can be taken as soon as possible up to 12 hours after the scheduled time. If a dose is missed by more than 12 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Please make sure to record the reason for missing the dose. If you vomit a dose, the dose should not be re-taken. Instead wait until the next regularly scheduled dose.
5. Please remember to bring your study drug supply, including empty bottles and remaining pills, and drug diary with you to your clinic appointment. Please do not throw away any empty bottles. On clinic days please take your study medication on your regular schedule.
6. The drug can be stored at room temperature.
7. Keep this drug out of the reach of children.

Please call your doctor or research nurse before taking any new prescription or over-the-counter medications/supplements other than the study drugs or if any other questions arise.

Study Participant Self-Administration Diary for Umbralisib

Please record how many capsules you take and the time you take them and bring the completed diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Participant Identifier: _____ Cycle Number: _____
Protocol #: _____
Study Doctor: _____
Study Nurse: _____
Contact Number: _____

You will take the following number of capsules each time (per dose) as listed in the table below:

Study Drug Name	# of capsules (tablets) to take per dose	# of times each day
Umbralisib		

FOR STUDY TEAM USE ONLY	
Staff initials:	
Date dispensed:	Date returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Day	Date	Number of Umbralisib Capsules	Time of First Dose each day
1			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
2			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
3			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
4			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
5			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
6			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
7			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
8			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
9			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
10			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
11			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
12			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
13			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
14			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
15			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
16			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
17			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____

Day	Date	Number of Umbralisib Capsules	Time of First Dose each day
18			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
19			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
20			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
21			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
22			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
23			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
24			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
25			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
26			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
27			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____
28			_____:_____ □ AM / □ PM □ Dose Not Taken Why:_____

Participant/Caregiver Signature: _____ Date:_____