Official Title: Phase 2/3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Umbralisib and Venetoclax (U2-V) Compared to Ublituximab and Umbralisib (U2) in Subjects with Chronic Lymphocytic Leukemia (CLL)

NCT Number: NCT03801525

Document Date: Protocol version 4: 5-October-2021

Local Protocol #: Protocol U2-VEN-207

TITLE: ULTRA-V: Phase 2/3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Umbralisib and Venetoclax (U2-V) Compared to Ublituximab and Umbralisib (U2) in Subjects with Chronic Lymphocytic Leukemia (CLL)

Sponsor: TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
Tel: (212) 554-4484

IND Number: 114,779

Study Drugs: **Ublituximab, umbralisib, venetoclax**

Study Chair:
[redacted] MD
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Medical Monitor: [redacted] MD
[redacted]
TG Therapeutics
Tel: [redacted]

Study Coordination: TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
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Version: 1.0	**Date:** 15 August 2018
Version: 1.1	**Date:** 01 November 2018
Version: 2.0	Date: 07 October 2019
Version: 3.0	Date: 04 January 2021
Version: 4.0	**Date: 05 October 2021**

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol U2-VEN-207 for issuance.

Protocol Title:	**ULTRA-V: Phase 2/3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Umbralisib and Venetoclax (U2-V) Compared to Ublituximab and Umbralisib (U2) in Subjects with Chronic Lymphocytic Leukemia (CLL)**
Protocol Number:	U2-VEN-207
Study Drugs:	Ublituximab Umbralisib Venetoclax
IND Number:	114,779
Date FINAL:	05 October 2021

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted] MD

Print Name | Signature | Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 01-Nov-2021 | 3:34:28 PM EDT
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STUDY CHAIR, [redacted]

[redacted] MD

Print Name | Signature | Date

DocuSigned by:
[redacted]
Signer Name: Dr. [redacted] MD
Signing Reason: I approve this document
Signing Time: 01-Nov-2021 | 12:38:35 PM PDT
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SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted]

Print Name | Signature | Date

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[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 01-Nov-2021 | 3:54:52 PM EDT
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[redacted] RN PhD

Print Name | Signature | Date

DocuSigned by:
[redacted]
Signer Name: [redacted] PhD,RN
Signing Reason: I approve this document
Signing Time: 01-Nov-2021 | 3:37:34 PM EDT
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PROTOCOL ACCEPTANCE FORM

Protocol Title:	**ULTRA-V: Phase 2/3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Umbralisib and Venetoclax (U2-V) Compared to Ublituximab and Umbralisib (U2) in Subjects with Chronic Lymphocytic Leukemia (CLL)**
Protocol Number:	U2-VEN-207
Date FINAL:	05 October 2021

I have read the attached protocol and agree that it contains all the necessary details for performing U2-VEN-207.

I will provide copies of the protocol and of the ublituximab and umbralisib Investigator's Brochures, which were given to me by TG Therapeutics (Sponsor), to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding venetoclax, ublituximab, and umbralisib, and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB), I will not modify this protocol without obtaining the prior approval of TG Therapeutics and of the IRB. I will submit the protocol modifications and/or any informed consent modifications to TG Therapeutics and the IRB, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964).

Print Name	Signature	Date

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SUMMARY OF AMENDMENTS

Version 1.1 (Dated 1 November 2018) of this protocol contains the following modifications:

- Typographical and administrative errors and inconsistencies were corrected throughout, including:
  - The response assessment schedule by CT and/or MRI was clarified throughout to be "within 14 days prior to Cycles 4 & 13, and at least once every 12 cycles thereafter";
  - The footnotes in the study assessment table in Section 5 were corrected for misalignment. Serum pregnancy test was added within 3 days prior to Day 1 of Cycle 1.
- Sections 1.5 and 1.6 were added to provide background information on venetoclax and rationale for the study;
- Section 6.2.3.3 was revised to allow dose delays of any study medication for durations longer than 28 days to recover from toxicity. All dose modifications should now be reported in the IWRS, with questions regarding dose modifications referred to TG Therapeutics;
- Section 6.2.1.3.1 was amended to provide dilution infusions for both the 25 mg/mL and 10 mg/mL concentration vials of ublituximab;
- The sample size was adjusted from 60 patients to 90 patients and divided into 2 cohorts of approximately 60 non-BTK-refractory patients and approximately 30 BTK-refractory patients.

Version 2.0 (Dated 07 October 2019) of this protocol contains the following modifications:

- Language was modified throughout to effect addition of 60 subject cohort of treatment naïve CLL;
- Synopsis and Section 3 Eligibility Criteria:
  - Inclusion #1 updated to allow patients with treatment naïve CLL;
  - Inclusion #2 updated to specify that adequate organ system function must be independent of growth-factor or transfusion support, and creatinine clearance requirement was lowered from >50 mL/min to >30 mL/min;
  - Exclusion #1 was updated to lower the washout period for prior BTK inhibitors from 21 days to 7 days;
  - Exclusion #3 was reworded for clarity, and to suggest antiviral prophylaxis for HBV reactivation for subjects that are HBc antibody positive at Investigator discretion;
  - Exclusion # 8 added to ensure patients with known barriers to obtaining access to commercially available venetoclax are not enrolled;
- Updated to clarify adverse events will be assessed and reported using the most up to date NCI Common Terminology Criteria for Adverse Events (CTCAE) V5.0;
- Reference to 10 mg/mL formulation of ublituximab removed throughout as this formulation is not available;
- Study Assessment Tables:
  - Updated for clarity;
  - End of Study visit added;
  - The window for baseline bone marrow was extended to within 90 days of C1D1;
  - The window for baseline FISH and *TP53* was extended to within 60 days of C1D1;
  - If IGHV status is found within the medical history, it does not need to be repeated;

  - Schedule of response assessment updated to align with study visits;
  - The schedule for MRD testing clarified;
- Efficacy Endpoints updated for consistency in wording throughout the protocol. Time to response was added as an efficacy endpoint;
- Statistical Considerations updated in synopsis and body to remove reference to multi-arm comparisons and to clarify statistical testing;
- Section 5.1 Laboratory Assessment:
  - Updated to clarify local labs required per the protocol. Updated to reflect CLL mutation panel to be done at local labs rather than at the central lab;
  - [redacted]
- Section 11 – Adverse Event Reporting Criteria updated to clarify criteria for event reporting and proper forms for reporting safety events. Typographical errors corrected throughout.

Version 3.0 (Dated 04 January 2021) of this protocol contains the following modifications:

- Study title updated to reflect new study design;
- Study cover page updated with new medical monitor name and contact information;
- Introduction, overview of study drugs, and rationale for study drug combinations and study design updated;
- Phase 3 Study Objectives added;
- Eligibility criteria updated as follows:
  - Inclusion #1 removed qualifier that initial absolute lymphocyte count (ALC) was to be ≥30,000/μL; updated to clarify exclusion for prior steroid use;
  - Inclusion #6 updated to reflect requirement for contraception for 4 months after last dose of ublituximab, umbralisib or venetoclax;
  - Exclusion #3 updated to clarify virology testing;
  - Exclusion #8 updated to clarify that known barriers to commercially available venetoclax are exclusionary;
  - Exclusion #14 updated to clarify unacceptable previous malignancies;
- Study Design updated to include a randomized Phase 3 component;
- Registration and Randomization updated to reflect a randomized Phase 3 design;
- Study Assessment and Treatment Schedule for subjects enrolled to V3.0, randomized Phase 3 stage of the trial added;
- Local laboratory assessments updated to reflect CLL mutation panel is no longer required to be sent to the local lab and will be sent to the central laboratory;
- Central Laboratory assessments – updated to reflect central laboratories are required for subjects enrolled to the Phase 2 and Phase 3 stages;
- Treatment Summary updated to reflect the schedule for subjects enrolled to the Phase 3 stage of the trial for both the U2-V and U2 regimens;
- Agent administration - ublituximab section updated to include information on monitoring for hepatitis b reactivation and treatment for suspected hepatitis b reactivation;
- Ublituximab medication overview updated with all applicable information related to the addition of ublituximab 36mL vials (900 mg);
- Statistical considerations added for the Phase 3 randomized stage of the study;
- Typographical and grammatical errors corrected throughout.

Version 4.0 (Dated 05 October 2021) of this protocol contains the following modifications:

- Editorial and consistency fixes throughout the document;

- The Phase 3 portion of the study was amended to include SLL patients
- Section 1.5 was amended to include clarification that venetoclax is FDA approved for the treatment of adult patients with CLL or SLL;
- Section 2.2 was amended to remove definitive disease progression as an efficacy endpoint;
- Section 2.2 was amended to add overall survival as an efficacy endpoint;
- Section 3.1 was amended to include additional language clarifying contraception timelines;
- Section 3.2 was amended to include the most updated TG language regarding severe and/or uncontrolled medical conditions that could exclude the patient from the trial;
- Section 4.1 was amended to include language that Phase 2 was closed to enrollment and additional language added to reinforce need for use of central lab results when randomizing subjects;
- Section 4.1 was amended to include language regarding CT and/or MRI evaluation to determine disease progression;
- Section 4.5 was amended to include additional clarification on the type of situations that warrants a patient to be discontinued from the study and confirmation that PFS and/or OS would continue to be followed per the schedule of assessments;
- Section 5 and 6 were amended to include additional footnote verbiage regarding CMV screening and evaluation;
- Section 5 and 6 was updated to include additional clarification of study in the Phase 3 schedule to include the addition of 30-Day and 90-Day Safety Follow-Up column for clarity;
- Section 6 was amended to include urine pregnancy, sparse PK, immunogenicity, and authorization for venetoclax in the study assessment table;
- Section 6 was amended to include an additional footnote regarding the dosing of umbralisib in Arm B;
- Section 7.1 was amended to include additional verbiage regarding urine pregnancy;
- Section 7.2 was amended to include updated verbiage regarding the MRD assessment for the Phase 3 portion trial;
- Section 7.2.1 was added to include verbiage and guidance for sparse PK;
- Section 7.2.3 was added to include verbiage and guidance related to the immunogenicity assessment;
- Section 8.3 Table 11 was amended to remove C16-24 from the dosing schema;
- Section 8.5.1 was amended to include the most updated verbiage regarding the administration of ublituximab;
- Section 8.5.1 was amended to include the most updated verbiage regarding the management of patients with hepatitis B;
- Section 8.5.1.3 was amended to include the most updated verbiage regarding the dispensation of ublituximab;
- Section 8.5.2 amended to include dosing for timing of dosing of umbralisib on Cycle 1 Days 1 and 2. When ublituximab will be administered, umbralisib should be administered prior to ublituximab pre-medication
- Section 8.5.2.2 was amended to include the most updated verbiage regarding the dose hold or modification of umbralisib;
- Section 8.5.3.3 was amended to include the most updated verbiage regarding the dose hold and modification of venetoclax;
- Section 8.5.4 was added to include a table displaying the study drug modifications for all IPs, and include verbiage regarding anaphylaxis, drug-related toxicity, and cytopenias/non-hematologic toxicities;
- Section 9.1 was updated to include additional ublituximab storage information;

- Section 10.1 was amended to include updated verbiage regarding Phase 3 disease progression and how the site should appropriately handle its possible occurrence;
- Section 11.1 was updated to include additional verbiage regarding the interim analysis and the sensitivity analyses;
- Section 11.11.1.1. was amended to include the most updated language regarding analyses of PFS for Phase 3;
- Section 11.11.2.4 was added to include the most updated verbiage for analyses of CR;
- Section 11.11.2.5 was added to include the most updated verbiage for analyses of ORR;
- Section 11.11.3 was added to discuss, in depth, the interim analysis;
- Section 11.11.4 was added to include the most updated verbiage for multiplicity of the Phase 3 cohort;
- Section 11.11.5 was added to include the most updated verbiage on stopping rules;
- Section 12.2.3 was updated to include additional clarification regarding SAE/AE recording;
- Section 12.8 Language regarding pregnancy reporting added to this section;
- Section 13.1 Language regarding timing of the DSMB added to this section;
- Section 13.4 was amended to update language regarding data ownership and publication;
- Section 14 was amended to include most updated TG language;
- Section 15 was amended to include most updated TG language;
- Section 17 (Appendix A) was updated with additional guidance regarding contraception practices for fertile males and females.

STUDY SYNOPSIS

Protocol no.	U2-VEN-207
Study Title	ULTRA-V: Phase 2/3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Umbralisib and Venetoclax (U2-V) Compared to Ublituximab and Umbralisib (U2) in Subjects with Chronic Lymphocytic Leukemia (CLL)
Sponsor	TG Therapeutics, Inc.
Study Sites & Enrollment	• This study may be conducted in up to 125 clinical trial sites • Enrollment is expected to take approximately 24 months
Study Rationale	During the past 5 years, an unprecedented array of highly active therapies has emerged for the treatment of patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL). Despite the availability of these targeted therapies, CLL remains an incurable disease. The recently approved agents have shown significant clinical activity, but they still render a low rate of complete responses and even lower rate of undetectable minimal residual disease (uMRD), and often require undefined treatment durations with continuous treatment until progression. Ultimately, it is important to develop combination regimens that achieve deeper, more durable remissions with defined treatment periods. For these reasons, this trial will examine a novel triplet treatment regimen with the combination of an anti-CD20 antibody (ublituximab), a next generation phosphatidylinositol-3-kinase delta (PI3Kδ) inhibitor (umbralisib), and a BCL-2 inhibitor (venetoclax). Ublituximab (TG-1101, LFB-R603) is a glycoengineered monoclonal antibody under clinical investigation that binds to the trans-membrane antigen CD20 found on B lymphocytes. The binding of ublituximab induces an immune response that results in the lysis of B cells. Umbralisib (TGR-1202) is a novel oral, once daily dual inhibitor of PI3K-δ and casein kinase-1ε (CK1ε) that is pharmacologically distinct from currently approved PI3K inhibitors, with improved delta isoform selectivity. The delta isoform of PI3K is highly expressed and strongly upregulated in CLL/SLL. Given the non-overlapping mechanisms of action of each of these agents, the combination of ublituximab and umbralisib was explored in Phase I-III trials in subjects with CLL/SLL. The combination regimen is well tolerated with ublituximab administered at doses up to 900 mg per infusion, and umbralisib administered at doses up through 800 mg QD. Preliminary clinical activity and potentially differentiated safety profile was noted in a variety of hematologic malignancies, with responses reported in subjects with a broad range of non-Hodgkin lymphomas and CLL/SLL. Venetoclax (Venclexta®) is an orally administered BCL-2 inhibitor approved for the treatment of patients with CLL/SLL (https://www.rxabbvie.com/pdf/venclexta.pdf). Treatment with venetoclax can cause rapid reduction in tumor burden that poses a risk for severe tumor lysis syndrome (TLS). Fatal events and renal failure requiring dialysis have occurred

	in patients with previously treated CLL/SLL with high tumor burden when treated with venetoclax. Thus, an initial 5-week dose ramp-up phase has been developed to achieve the recommended dose of venetoclax. This 5-week dose ramp-up along with a TLS risk mitigation which has shown to ameliorate TLS, leading to a safe effective orally administered therapy for CLL/SLL. Venetoclax has been previously studied both as monotherapy and in combination with other targeted agents such as rituximab, obinutuzumab, and ibrutinib (Seymour et al., 2018, Fischer et al., 2017, and Jain et al., 2017). Initially, this trial will explore the use of ublituximab and umbralisib (U2) as induction therapy prior to addition of venetoclax (U2-V), with umbralisib monotherapy maintenance in subjects receiving the triplet who do not achieve uMRD. Based on the initial results from this Phase 2 stage of the study and another Phase 1 study with U2-V (NCT03379051), a randomized Phase 3 study design will commence to evaluate the efficacy and safety of U2-V regimen versus the U2 regimen.

Study Objectives	PHASE 2 STUDY OBJECTIVES
	
	• PRIMARY OBJECTIVES
	  ○ To determine the complete response (CR) rate of the combination of ublituximab + umbralisib + venetoclax (U2-V)
	  ○ To determine the overall response rate (ORR) of the combination of ublituximab + umbralisib + venetoclax (U2-V)
	• SECONDARY OBJECTIVES
	  ○ To determine the rate of undetectable MRD
	  ○ To determine time to response (TTR) and duration of response (DOR)
	  ○ To characterize the safety of the combination regimens
	 
	
	PHASE 3 STUDY OBJECTIVES
	
	• PRIMARY OBJECTIVES
	  ○ To evaluate the efficacy of the combination of ublituximab + umbralisib + venetoclax (U2-V) compared to the combination of ublituximab + umbralisib (U2) in patients with either treatment naïve or previously treated CLL/SLL as measured by progression-free survival (PFS)
	• SECONDARY OBJECTIVES
	  ○ To evaluate the CR rate and ORR of the combination of ublituximab + umbralisib + venetoclax (U2-V) compared to ublituximab + umbralisib (U2) as assessed by an independent review committee (IRC);
	  ○ To compare the rate of undetectable MRD;
	  ○ To compare OS;

	○ To characterize the safety of the combination regimens
Inclusion Criteria	Subjects must meet all the following inclusion criteria to be eligible for participation in this study: 1. B-cell CLL/SLL that warrants treatment consistent with iwCLL 2018 criteria for initiation of therapy with diagnosis established according to iwCLL 2018 criteria and documented within medical records. At least one of the following criteria should be met: a. Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia; or b. Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly; or c. Massive (i.e., ≥ 10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy; or d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months; or e. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection: i. Unintentional weight loss of ≥10% within the previous 6 months; or ii. Significant fatigue (≥ Grade 2); or iii. Fevers >100.5°F or 38.0°C for ≥2 weeks; or iv. Night sweats for >1 month. 2. Adequate organ system function, independent of growth-factor or transfusion support, defined as follows: a. Absolute neutrophil count (ANC) ≥ 750/mm³ (µL) / platelet count ≥ 40,000/mm³ (µL); b. Total bilirubin ≤1.5 times the upper limit of normal (ULN). Subjects with Gilbert's syndrome with bilirubin > 1.5 × ULN allowed per discussion with the Medical Monitor; c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement, or ≤5 x the ULN if known liver involvement; d. Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault formula). 3. ECOG performance status ≤ 2. 4. Male or female ≥ 18 years of age. 5. Ability to swallow and retain oral medication. 6. Female subjects who are not of child-bearing potential, and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female subjects of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of ublituximab and for at least 30 days after the last dose of umbralisib or venetoclax. Men of reproductive potential may not participate unless they agree to use medically acceptable contraception.

	7. Willingness and ability to comply with trial and follow-up procedures and provide written informed consent.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1, Day 1 (within 7 days of Cycle 1, Day 1 for prior BTK inhibitor). a. Corticosteroid use within 1 week prior to first dose of study drug are excluded, with the exception of steroid use for adrenal replacement, inhaled steroid for asthma, topical steroid use or other locally administered corticosteroids. Patients requiring systemic steroids for leukemia control or white blood cell (WBC)-count lowering are excluded. 2. Autologous hematologic stem cell transplant within 6 months of study entry. 3. Prior allogeneic hematologic stem cell transplant. 4. Evidence of chronic active hepatitis B (HBV) infection as evidenced by a detectable hepatitis B surface antigen (HBsAg); or chronic hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of human immunodeficiency virus (HIV). Subjects with positive hepatitis B core antibody (HBc Ab) or hepatitis C virus antibody (HCV AB) or positive CMV by IgM or IgG are eligible only if PCR is negative for HBV DNA, HCV RNA or CMV. 5. Known histological transformation from CLL/SLL to an aggressive lymphoma (e.g., Richter's Transformation, prolymphocytic leukemia, or DLBCL). 6. History of CNS involvement with CLL/SLL. 7. Prior exposure to any PI3K inhibitor (e.g. idelalisib, duvelisib, umbralisib [TGR-1202], etc.) or venetoclax (ABT-199, GDC-0199). 8. Known barriers to obtain access to commercially available venetoclax. 9. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. 10. Live virus vaccines within 4 weeks prior to or during study therapy. 11. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 monoclonal antibody administration. 12. Any severe and/or uncontrolled medical conditions or other conditions that could adversely affect the safety of the subject or their participation in the study such as: a. Ongoing alcoholic liver disease, nonalcoholic steatohepatitis, cirrhosis of the liver, primary biliary cirrhosis, portal hypertension b. Splenomegaly from causes other than CLL/SLL c. Symptomatic, or history of documented congestive heart failure (New York Heart Association [NYHA] functional classification III-IV). Class 3 is defined as cardiac disease in which patients are comfortable at rest but marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain;

	d. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization; e. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at Investigator discretion; f. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of randomization. 13. Requirement for use of strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-glycoprotein (P-gp) inhibitors, or narrow therapeutic index P-gp substrates (See Appendix D). 14. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or *in situ* carcinomas, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer with a PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry. 15. Women who are pregnant or lactating.
Efficacy Endpoints	**Progression-free survival (PFS)** PFS is defined as the interval from enrollment (Phase 2) or randomization (Phase 3) to the earlier of the first documentation of definitive disease progression or death from any cause. **Overall response rate (ORR)** ORR is defined as the proportion of subjects who achieve a CR, CRi, PR or PR-L. **Complete Response (CR) Rate** CR rate is defined as the proportion of subjects who achieve a CR or CRi. **Rate of Undetectable Minimal Residual Disease (uMRD)** uMRD is defined as the proportion of subjects who are MRD negative, defined as a quantitative detection of less than one CLL/SLL cell in 10000 leukocytes by flow cytometry (MRD level $<10^{-4}$) in the blood or bone marrow. **Time to response (TTR)** TTR is defined as the interval from enrollment to first documentation of CR, CRi, PR, or PR-L. **Duration of response (DOR)** DOR is defined as the interval from the first documentation of CR, CRi, PR, or PR-L to the earlier of the first documentation of definitive disease progression or death from any cause. **Overall Survival (OS)** OS is defined as the interval from randomization (Phase 3 subjects only) to the first documentation of death from any cause.

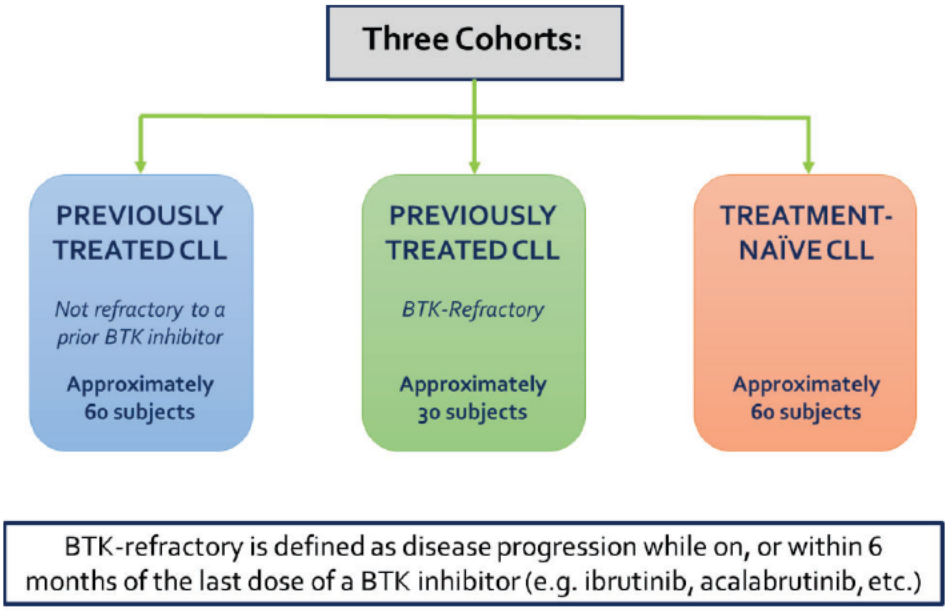
Safety Endpoints	All Adverse Events (AEs) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (NCI CTCAE) v5.0.
DSMB	For the Phase 3 stage of the trial, an independent Data Safety Monitoring Board (DSMB) will be established to advise the Sponsor on safety and provide benefit/risk oversight of the study as described in the DSMB Charter. The independent DSMB will review the primary efficacy data and safety data.
Independent Review Committee	For the efficacy objectives of the study, an IRC will provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation and confirmation of changes in disease status.

Study Design

This is an open-label, multicenter, Phase 2/3 trial to investigate the efficacy and safety of ublituximab and umbralisib combined with venetoclax (U2-V) in subjects with CLL/SLL. Subjects with treatment naïve and previously treated CLL/SLL are eligible for enrollment. Based on preliminary results from ongoing ublituximab and umbralisib trials and the changing landscape of approved CLL/SLL treatments, single-arm or randomized cohorts may be added for both safety and efficacy.

In the Phase 2 stage of the trial, 3 separate cohorts will be enrolled (Figure 1): a cohort of approximately 60 subjects with treatment naïve CLL; a cohort of approximately 60 subjects with previously treated CLL, which includes relapsed subjects who are not refractory to a prior BTK inhibitor; and a separate cohort of approximately 30 subjects with BTK-refractory CLL. BTK-refractory subjects are defined as those with disease progression while on or within 6 months of the last dose of a BTK inhibitor (e.g., ibrutinib, acalabrutinib, etc.).

FIGURE 1: PHASE 2 STUDY DESIGN



The Phase 3 stage of the trial will include 2 independent randomized cohorts of CLL/SLL subjects (Figure 2): a treatment naïve cohort and a previously treated cohort. Following screening, qualified subjects in each cohort will be randomized 1:1 to 1 of 2 arms:

- Arm A: Ublituximab + Umbralisib + Venetoclax (U2-V)
- Arm B: Ublituximab + Umbralisib (U2)

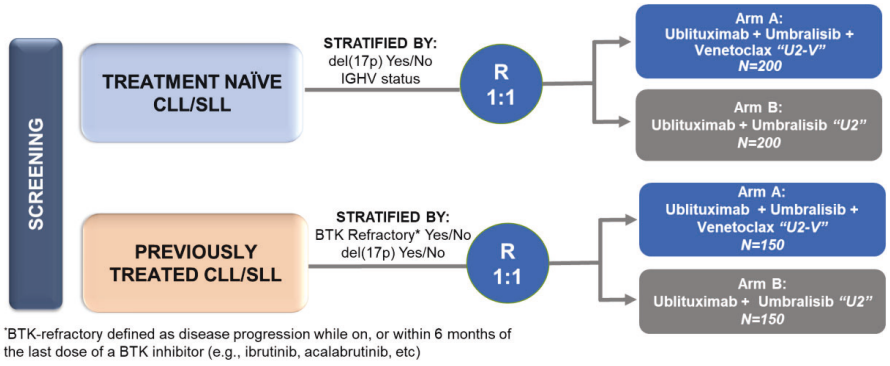
Approximately 400 (200 per treatment arm) subjects will be enrolled to the treatment naïve cohort and approximately 300 (150 per treatment arm) subjects will be enrolled to the previously treated cohort. The treatment naïve cohort and

the previously treated cohort will be enrolled and evaluated independently of each other.

Patients will be stratified at randomization by the following factors:

- Treatment naïve cohort: del17p by central lab (deleted or not deleted) and IGHV status (mutated or not mutated)
- Previously treated cohort: del17p by central lab (deleted or not deleted) and BTK status (refractory to BTK: yes or no)

FIGURE 2: PHASE 3 STUDY DESIGN



During the study period, all subjects will be evaluated for response by CT and/or MRI. At each follow-up visit, subjects will be assessed for response/progression by physical examination and laboratory tests. The best clinical response as well as disease progression will be determined by an IRC. Subjects will remain on study treatment until the occurrence of definitive disease progression (subjects enrolled to the randomized Phase 3 stage must have PD confirmed by central radiology prior to discontinuing study drug), completion of treatment, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. Subjects who discontinue from study treatment (either for unacceptable toxicity or Investigator choice) and have not progressed will continue to be followed for progression until confirmed by IRC. All subjects enrolled to the Phase 3 portion of the study will be followed for overall survival.

Dosing Regimen & Treatment Study Visits

Phase 2: U2-V

Cycle 1

Ublituximab			Umbralisib
Day 1	**Day 2**	**Day 8 & 15**	**Day 1 – 28**
150 mg	750 mg	900 mg	800 mg daily

Cycles 2 – 3

Ublituximab	Umbralisib
Day 1	**Days 1 – 28**
900 mg	800 mg daily

Cycle 4

Ublituximab	Umbralisib	Venetoclax			
Day 1	**Days 1-28**	**Days 1 – 7 (wk 1)**	**Days 8 – 14 (wk 2)**	**Days 15 – 21 (wk 3)**	**Days 22 – 28 (wk 4)**
900 mg	800 mg daily	20 mg daily	50 mg daily	100 mg daily	200 mg daily

Cycles 5 – 6

Ublituximab	Umbralisib	Venetoclax
Day 1	**Days 1 – 28**	**Days 1 – 28**
900 mg	800 mg daily	400 mg daily

Cycles 7 – 24

Ublituximab	Umbralisib	Venetoclax
	Days 1 – 28	**Days 1 – 28**
	800 mg daily	400 mg daily

Cycle 25+ for MRD positive subjects ONLY

Ublituximab	Umbralisib	Venetoclax
	Days 1 – 28	
	800 mg daily	

Phase 3: Arm A (U2-V) Randomized Subjects

Cycle 1

Ublituximab			Umbralisib
Day 1	**Day 2**	**Day 8 & 15**	**Days 1 – 28**
150 mg	750 mg	900 mg	800 mg daily

Cycles 2 – 3

Ublituximab	Umbralisib
Day 1	**Days 1 – 28**
900 mg	800 mg daily

Cycle 4

Ublituximab	Umbralisib	Venetoclax			
Day 1	**Days 1 – 28**	**Days 1 – 7 (wk 1)**	**Days 8 – 14 (wk 2)**	**Days 15 – 21 (wk 3)**	**Days 22 – 28 (wk 4)**
900 mg	800 mg daily	20 mg daily	50 mg daily	100 mg daily	200 mg daily

Cycles 5 – 6

Ublituximab	Umbralisib	Venetoclax
Day 1	**Days 1 – 28**	**Days 1 – 28**
900 mg	800 mg daily	400 mg daily

Cycles 7 – 15		
Ublituximab	**Umbralisib**	**Venetoclax**
Day 1 of Cycle 9, Cycle 12, and Cycle 15	**Days 1 – 28**	**Days 1 – 28**
900 mg	800 mg daily	400 mg daily

Phase 3: Arm B (U2) Randomized Subjects			
Cycle 1			
Ublituximab			**Umbralisib**
Day 1	**Day 2**	**Day 8 & 15**	**Days 1 - 28**
150 mg	750 mg	900 mg	800 mg
Cycles 2 – 6			
Ublituximab			**Umbralisib**
Day 1			**Days 1 – 28**
900 mg			800 mg
Cycle 7+			
Ublituximab			**Umbralisib**
Day 1, every 3 cycles (9, 12, 15, 18, etc.)			**Days 1 – 28**
900 mg			800 mg

Study Drugs	Ublituximab is an investigational, recombinant chimeric monoclonal antibody against the CD20 antigen, available as a 25 mg/mL concentrate for solution for infusion, supplied by TG Therapeutics, Inc. Umbralisib is a novel investigational, once daily oral dual inhibitor of PI3Kδ and CK1ε available in 200 mg tablets, supplied by TG Therapeutics, Inc. Venetoclax is an orally administered BCL-2 inhibitor available in 10 mg, 50 mg, and 100 mg tablets, commercially available as VENCLEXTA™.

LIST OF ABBREVIATIONS

Abbreviations and Definitions of Terms	
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
AE(s)	adverse event(s)
AESI	adverse event of special interest
AKT	protein kinase B
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCG	Bacille Calmette Guerin
BCL-2	B-cell lymphoma 2
BH	BCL-2 homology
BM	bone marrow
BTK	bruton's tyrosine kinase
BUN	blood urea nitrogen
C, c	Cycle
Ca	calcium
CBC	complete blood cell count
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CK1ε	casein kinase 1 epsilon
CL	clearance
CLL	chronic lymphocytic leukemia
Cm	centimeter
Cmax	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRi	complete response incomplete
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
D, d	day/Day
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRG	data review group
DSMB	Data Safety Monitoring Board
EC	ethics committee

Abbreviations and Definitions of Terms	
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EKG	electrocardiogram
EOS	end of study
EOT	end of treatment
Fc	fragment crystallizable (region)
FCR	fludarabine, cyclophosphamide, rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
GTD	greatest transverse diameter
h/H	hour
HBc	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCL	hairy cell leukemia
HCV	hepatitis C vaccine
HCVcAB	hepatitis C virus core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	hodgkin lymphoma
HTRF	homogeneous time resolved fluorescence
IB	investigator brochure
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IgG	immunoglobulin G
IGHV	immunoglobulin heavy chain variable region
IL2	interleukin 2
INR	international normalized ratio
IRC	independent Review Committee
IRR	infusion related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
iwCLL	international workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response Systems
L	liter
LD	longest diameter
LDH	lactate dehydrogenase
LPD	longest perpendicular diameter

Abbreviations and Definitions of Terms	
LTFU	long term follow-up
LVD	longest vertical dimension
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MedDRA	Medical dictionary for Regulatory Activities
Mg	magnesium or milligram
Min	minute(s)
mL	milliliter
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute Working Group
NHL	non-hodgkin lymphoma
NK	natural killer
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic or progressive disease
PE	physical examination
PFS	progression-free survival
Phos	phosphorus
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PO	by mouth / polyolefin
PPD	perpendicular diameters
PPS	per protocol set
PR	partial response
PR-L	partial response with lymphocytosis
PSA	prostate specific antigen
PT	preferred term or prothrombin time
PVC	polyvinyl chloride
QD	once daily
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease or standard deviation
SDV	source document verification
SEER	Surveillance, Epidemiology, and End Results
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLL	small lymphocytic lymphoma

Abbreviations and Definitions of Terms	
SOC	system organ class / standard of care
SPD	sum of the product of the perpendicular diameters
SUV	standardized uptake value
q	every
t1/2	half-life of elimination
TCL	T-cell lymphoma/leukemia
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
Tmax	time to maximum concentration
TTR	time to response
U2	ublituximab-umbralisib
U2-V	ublituximab-umbralisib-venetoclax
ULN	upper limit of normal
uMRD	undetectable MRD
USPI	United States Prescribing Information
UTX	ublituximab
V	visit
Vd	volume of distribution
Vdss	volume of distribution at steady state
WHO	World Health Organization
Wk	week(s)
WM	waldenstroms macroglobulinemia

1 INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

In the United States, an estimated 21,040 new cases of chronic lymphocytic leukemia (CLL) and deaths due to CLL totaling 4,060 will be reported in 2020, according to National Cancer Institute (NCI) estimates (SEER Cancer Statistics Factsheets) (Howlander et al., 2020). During 2013-2017, the NCI estimated an age-adjusted incidence rate of 5.0 per 100,000 individuals. CLL mainly affects older adults with an onset typically around 70 years and is characterized by the accumulation of clonal mature B lymphocytes in the blood, bone marrow, and secondary lymphoid tissues (SEER Cancer Statistics Factsheets) (Howlander et al., 2020). CLL/small lymphocytic lymphoma (SLL) is a heterogeneous disease with several higher risk cytogenetic abnormalities which are generally more difficult to treat including 17p deletion, *TP53* gene mutation, and 11q deletion which have been associated with marked lymphadenopathy (Hallek et al., 2018; Lin et al., 2002). Patients with *TP53* gene mutations are associated with an adverse clinical outcome.

With the advent of novel targeted therapies, the paradigm of treatment for CLL/SLL is rapidly evolving away from standard chemotherapy-based regimens, which while active, result in considerable toxicity to patients (Burger, 2020). Novel non-chemotherapy-based therapies have demonstrated greater clinical benefit than current standard of care regimens with the added advantage of significantly greater tolerability (Burger, 2020). Despite advancements in available therapies, CLL/SLL remains incurable with progressive disease and CLL/SLL-related complications accounting for 73% of deaths in CLL/SLL patients (Strati et al., 2017). Additionally, 5-year survival rates are lower than the general population in age and sex-matched comparisons (Howlander et al., 2020), and 10-year survival rates even lower than 5-year rates (Weide et al., 2020); thus, highlighting the life-threatening nature of this malignancy. Furthermore, patients with higher risk cytogenetic abnormalities still present with a less than optimal response to approved therapies and a shorter duration of response and progression-free survival (PFS) (Roberts et al., 2019; Woyach et al., 2019). As such, there is a pressing need for new, innovative, combinations of targeted therapies to produce deep and durable responses for patients with CLL/SLL, especially those with cytogenetic abnormalities.

1.2 UBLITUXIMAB

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD20, ublituximab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

FDA-approved anti-CD20 antibodies, such as rituximab and obinutuzumab, have proven clinical benefit in CLL/SLL. Ublituximab has been glycoengineered for reduced fucose content, which increases its affinity for FcγRIII compared to rituximab (De Romeuf et al., 2008). Ublituximab has demonstrated enhanced ADCC compared to rituximab and ofatumumab in human cancer cell lines with low CD20 expression and in CLL/SLL patient-derived peripheral blood mononuclear cells

(Bellon et al., 2011). Ublituximab exhibits complement-dependent cytotoxicity (CDC) on par with rituximab and has also been demonstrated to induce programmed cell death upon binding to the CD20 antigen on B lymphocytes in pre-clinical studies (De Romeuf et al., 2008). Additionally, ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies (Esteves et al., 2011). Clinically, ublituximab possesses activity in CLL patients previously treated with rituximab including those who are rituximab-refractory (Sawas et al., 2017).

1.2.1 PRE-CLINICAL EVALUATIONS OF UBLITUXIMAB

1.2.1.1 IN VITRO ACTIVITY

In an in vitro assay using B-CLL/SLL cells from patient donors, ublituximab demonstrated an enhanced ability to kill CLL/SLL 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/SLL cells, and a higher FcγRIIIA mediated interleukin-2 (IL2) production by FcγRIIIA+ Jurkat cells (De Romeuf et al., 2008). Ublituximab demonstrated high ADCC against both patient-derived CLL/SLL cells and NHL cell lines. Ublituximab's engagement to FcγRIIIA triggers a stronger NK cell cytotoxicity against CLL/SLL as compared to rituximab (in vitro) despite CD20 density, likely related to the glycosylation pattern (De Romeuf et al., 2008).

1.2.1.2 IN VIVO ACTIVITY

The anti-tumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models (Esteves et al., 2011). Single-agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in the FL xenograft at a dose of 100 mg/kg, and a superior tumor growth delay (21 days) compared to rituximab (Esteves et al., 2011). Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels (Esteves et al., 2011).

1.2.1.3 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 the latest ublituximab Investigator's Brochure for detailed results.

1.2.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB

As of mid-2018, approximately over 1000 subjects (both treatment naïve and previously treated subjects with CLL/SLL) have been exposed to ublituximab across 9 Phase I or II clinical trials and 2 Phase III clinical trials (UTX-IB-301 and UTX-TGR-304), either as a single-agent or in combination with a variety of anti-cancer agents, including ibrutinib, umbralisib, bendamustine, pembrolizumab, and/or lenalidomide. Two single-agent Phase I/Ib trials (CD20-0703 and TG-1101-101) have been

conducted evaluating ublituximab in both NHL and CLL/SLL subjects which includes a total of 41 subjects with relapsed or refractory CLL/SLL. 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 subjects exposed to ublituximab in early-phase trials, the safety profile of the agent is well characterized.

Summaries of the single-agent clinical experience are provided below.

Study CD20-0703 is a 2-part, first-in human dose escalation study, subjects with relapsed or refractory CLL/SLL. In Part I, subjects received a 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 study has completed. In Part II, 12 subjects were enrolled at 9 centers in France and followed for 12 months. Demographic data for the 12 subjects 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 [range, 1–8] (Bruno Cazin et al., 2011). Seven subjects (58%) received at least one prior rituximab containing regimen (Bruno Cazin et al., 2011). The median lymphocyte BM infiltration was 85% [range, 40–94%] (Bruno Cazin et al., 2011).

Most frequent drug-related AEs reported were infusion related reactions (IRR) (75% of the subjects, including 33% of subjects with Grade 3 IRRs) (Bruno Cazin et al., 2011). Other Grade 3/4 AEs observed in >10% subjects included: neutropenia (67%) and increases in ALT/AST (17%) (Bruno Cazin et al., 2011). All AEs were reversible spontaneously or with supportive care intervention. None of the reported AEs were considered as a dose limiting toxicity (DLT) according to the judgement of the study Safety Committee. Therefore, the maximum tolerated dose (MTD) was not reached in this study. Significant blood lymphocyte depletion was observed in all subjects: median lymphocyte count at baseline was 46.6 (x 10^9/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 (Bruno Cazin et al., 2011).

Clinical response was based on the criteria established by the NCI-Working Group (NCI-WG) updated in 2008 (Hallek et al., 2008). All subjects but one received the planned 8 infusions without any dose reduction; one subject was prematurely withdrawn due to a concomitant secondary leukemia unrelated to ublituximab therapy. Response was evaluated at month 4 for the 11 evaluable subjects, with an initial response rate of 64% (7/11) with a confirmed response at month 6 in 5/11 subjects (45%) subjects (all PRs). Four of the 11 subjects achieved stable disease (SD). At the 1-year follow-up, no responders had progressed, demonstrating all confirmed responses were durable despite no ublituximab maintenance therapy. The median PFS was not reached at the 12-month follow-up (B Cazin et al., 2013).

Study TG-1101-101 is a Phase I trial of ublituximab (NCT01647971) subsequently undertaken in subjects with B-cell lymphoma who were relapsed or refractory to a prior rituximab containing regimen. This trial utilized a 3+3 design, assessing dose levels of 450 mg, 600 mg, 900 mg, and 1200 mg. The trial is complete, and enrolled a total of 35 subjects, including 8 subjects with CLL. No DLTs were observed amongst the 12 subjects enrolled into the dose escalation part, and expansion cohorts were subsequently undertaken at 600 mg, 900 mg, and 1200 mg. Subjects with CLL were eligible to enroll into the expansion cohorts at 600 mg and 900 mg, receiving ublituximab on days 1, 8, and 15 of Cycles 1 and 2, with monthly maintenance infusions starting in Cycle 3, followed by every 3 months starting in Cycle 6.

Of the 8 CLL subjects enrolled, 4 had IRRs that were manageable with infusion interruptions only and all subjects received all schedule doses. Other observed AEs which were considered at least possibly related to study drug included neutropenia Grade 1/2 (n=1) and Grade 3/4 (n=3), as well as thrombocytopenia Grade 1/2 (n=1) and Grade 3/4 (n=1). Among the 6 CLL subjects evaluable for efficacy, 3 (50%) responded (all PRs) (Sawas et al., 2017). Rapid and profound circulating lymphocyte depletion (> 50% reduction) was noted with median time to peripheral response of 1 day (O'Connor et al., 2014).

1.2.2.1 PHARMACOKINETICS

After infusion of ublituximab (TG-1101, LFB-R603) at a 150 mg dose followed by 7 weekly injection infusions at 450 mg, results suggested non-linear pharmacokinetics (PK) with respect to dose (450 mg vs. 150 mg) and time (week 4 vs. week 8), and more than proportional increase of Cmax and AUC∞ due to a clearance decrease. The volume of distribution (Vd) at steady state was small (~5 L), approximately equal to blood volume. The non-linear PK 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 subject characteristics, particularly in terms of tumor burden, make firm conclusions difficult.

The linear mean serum concentration-times profile after the first, the fourth and the eighth infusion of ublituximab are presented in Figure 3. A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of ublituximab are presented in Table 1.

FIGURE 3: LINEAR MEAN SERUM CONCENTRATION-TIMES PROFILE AFTER THE FIRST, THE FOURTH AND THE EIGHTH INFUSION OF UBLITUXIMAB

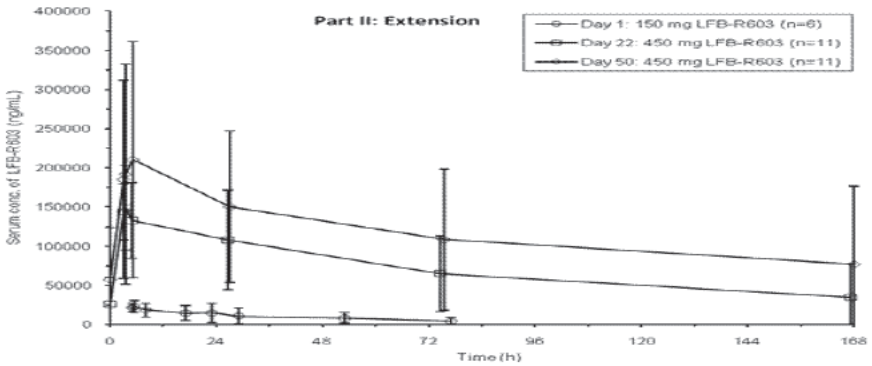


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150 MG), THE 4TH (450 MG) AND THE 8TH (450 MG) INFUSION OF UBLITUXIMAB

PK Parameters [a]	1st Infusion 150 mg (Day 1)	4th Infusion 450 mg (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 subject 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.

1.3 UMBRALISIB

Umbralisib (TGR-1202) is an orally available dual inhibitor of phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase 1 epsilon (CK1ε), with nanomolar inhibitory potency against both targets and exhibits enhanced selectivity for the delta isoform of PI3K over the alpha (α), beta (β), and gamma (γ) isoforms. 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 (δ) isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies.

The FDA-approved PI3K delta inhibitors idelalisib (Furman et al., 2014) and duvelisib (Flinn et al., 2018) have established the clinical potential of PI3K inhibition in CLL/SLL, however the use of these agents in treatment naïve CLL/SLL patients is not FDA-approved. Excess toxicity has been observed in the treatment naïve setting compared to the relapsed or refractory setting for these agents, and idelalisib specifically has a "Limitations of Use" statement in its USPI advising against first-line treatment of any patient (Gilead Sciences, 2018; Verastem, 2019). Preliminary clinical data suggests umbralisib exhibits a differentiated safety profile with lower rates of autoimmune-related toxicities (e.g., liver toxicity, severe diarrhea/colitis, and pneumonitis) (Davids et al., 2018). This difference may be attributable to a wider therapeutic window between the inhibition of PI3Kδ and the other PI3K isoforms and may also be augmented by the inhibition of CK1ε, which has been demonstrated to have a supportive effect on regulatory T-cells (Maharaj et al., 2020). Furthermore, umbralisib has limited drug-drug interaction liabilities, which facilitates its combination with other novel agents.

1.3.1 PRE-CLINICAL DEVELOPMENT OF UMBRALISIB

The potency of umbralisib binding 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) ([redacted], 2011d). Selectivity over the other 3 isoforms, namely, α, β, and γ was also determined (Figure 4) ([redacted], 2011a, 2011b, 2011c).

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.

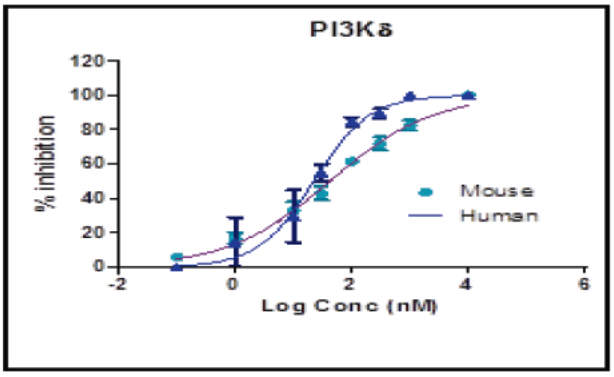


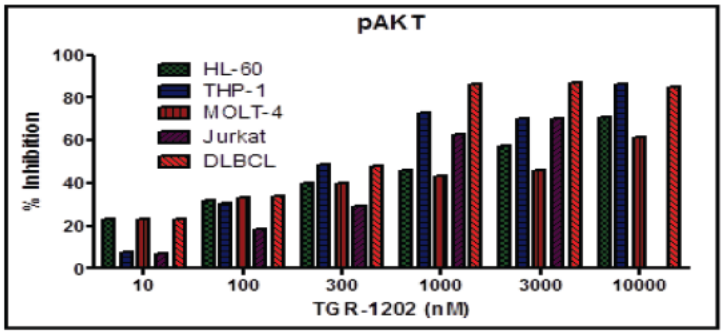
FIGURE 4: UMBRALISIB POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

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 ([redacted] 2012). 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 growth inhibition, the effect of umbralisib on AKT phosphorylation ([redacted] 2011e, 2011d, 2011a, 2011c, 2011b) 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 5).

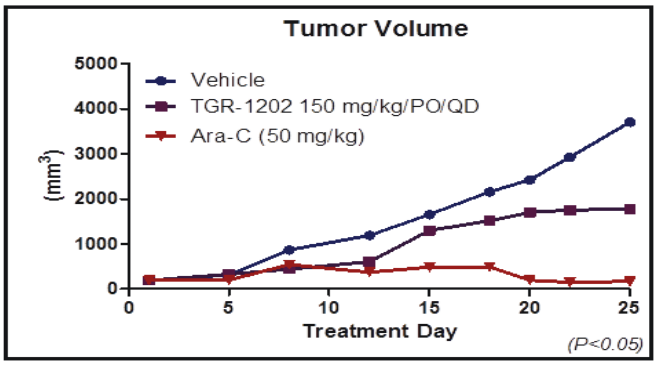
FIGURE 5: REDUCTION OF PAKT BY UMBRALISIB IN CELL LINES BY WESTERN BLOTTING



1.3.1.1 IN VIVO ACTIVITY

In vivo efficacy of umbralisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model. Oral administration of 150 mg/kg/day over a 25-day period resulted in a significant delay in tumor growth (Figure 6).

FIGURE 6: UMBRALISIB IN VIVO EFFICACY



1.3.1.2 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 PO 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 PO 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 latest umbralisib Investigator's Brochure for detailed information on toxicology studies conducted to date.

1.3.2 CLINICAL DEVELOPMENT OF UMBRALISIB

As of September 2018, approximately 1000 subjects have been exposed to umbralisib across multiple Phase I or II clinical trials and one Phase III clinical trial (UTX-TGR-304) either as a single-agent or in combination with other agents. Single-agent umbralisib has demonstrated safety and efficacy in a Phase I clinical trial in subjects with a wide variety of relapsed or refractory hematologic malignancies. Several Phase II clinical trials with umbralisib used as monotherapy and in doublet combinations with ublituximab and/or venetoclax in a wide variety of hematological malignancies are ongoing. A Phase III four-arm trial (UNITY-CLL) evaluating umbralisib combined with ublituximab and umbralisib monotherapy has completed enrollment and met its primary endpoint. Given the number of subjects who have received umbralisib in clinical trials, both as a single-agent and in doublet combination regimens and triplet combination regimens, the safety profile of umbralisib is well characterized.

1.3.2.1 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 (Burris et al., 2018). There were 90 subjects enrolled and eligible for safety evaluation, and 73 subjects evaluable for efficacy in the modified intention to treat population (ITT). 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 MTD was 1200 mg QD of the micronized formulation, with 800 mg of this formulation selected as the recommended Phase 2 dose (RP2D) 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 (TEAEs) 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 AEs were neutropenia (in 12 [13%] subjects), anemia (8 [9%]) and thrombocytopenia (6 [7%]). Serious adverse events (SAEs) considered at least possibly related to umbralisib occurred in 7 subjects: pneumonia in 3 (3%) subjects, lung infection in one (1%), febrile neutropenia in one (1%), and colitis in 2 (2%), one of whom also had febrile neutropenia. Both cases of colitis occurred above the RP2D. No time-related trends in toxicity were noted.

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 ITT, which included subjects who received at least 800 mg/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 3 (4%) were a CR and 30 (41%) were a PR. In subjects with relapsed or refractory CLL, 17 (85%) of 20 achieved an objective response, with 10 (50%) achieving an objective response per 2008 iwCLL criteria, 7 (35%) achieving a PR-L, and the remaining 3 (15%) achieving SD. Of 8 assessable subjects with CLL who had high risk cytogenetic features, 6 (75%) had a response, of whom 2 (25%) had a PR-L, and the remainder had SD. In subjects with FL, 9 (53%) of 17 subjects achieved an objective response, including 2 (12%) who achieved a CR; the remainder had PRs. In subjects with DLBCL, 4 (31%) of 13 achieved an objective response and 2 (15%) further subjects achieved SD. Responses for the other subject subgroups were HL: 1 CR, 4 SD, 4 PR; MZL: 1 PR, 4 SD; WM: 2 SD; and MCL: one PR, 4 SD, and 1 PD. 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 DOR 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 4 subjects in the DLBCL cohort, and 9.3 months (3.6–15.1) in 9 subjects in the FL cohort. In a post-hoc exploratory analysis of PFS, median PFS 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 NHL (FL, WM, MZL). Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts.

A distinct safety profile was noted with fewer than expected autoimmune toxicities based on experiences with other PI3K inhibitors such as duvelisib or idelalisib. These findings supported the rationale for further evaluation of umbralisib both as a single-agent and in novel doublet and triplet combinations. See the latest Investigator's Brochure for updated information regarding the clinical development of ublituximab and umbralisib as single -agents or in combination.

1.3.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

In parallel with the Phase 1 single-arm, dose -escalation study in subjects with relapsed or refractory hematologic malignancies, 2 healthy subject, crossover PK studies have been completed. The first PK 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 PK study evaluating the absorption, distribution, metabolism and excretion characteristics of 2 different oral formulations of 200 mg umbralisib (original formulation vs. micronized formulation) in healthy volunteers.

1.3.2.2.1 TGR-1202-PK101: 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 PK parameters under fasted and fed condition are shown in Table 2.

TABLE 2: PHARMACOKINETIC PARAMETERS OF UMBRALISIB UNDER FASTING AND FED CONDITIONS

Parameters	Geometric LS Means		% 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 (Cmax) 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-inf}.

1.3.2.2.2 TGR-1202-PK102: FORMULATION EFFECT

Study TGR-1202-PK 102 was a two-period, randomized, two-way cross over, relative bioavailability and PK bioequivalence study with 2 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.

The statistical comparison of the micronized 200 mg drug product formulation versus the original 200 mg drug product formulation are shown in Table 3.

TABLE 3 EFFECT OF UMBRALISIB FORMULATION ON PHARMACOKINETIC PARAMETERS

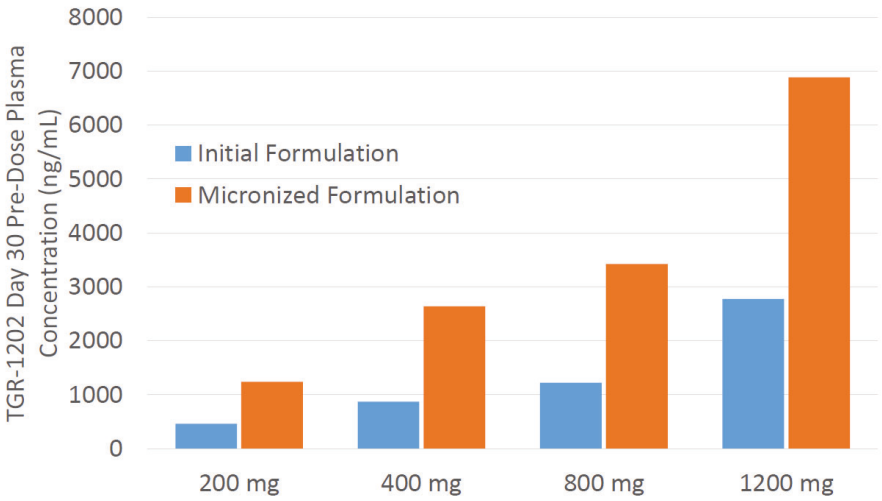
Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
AUC_{0-t} (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
AUC_{0-inf} (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

The micronized drug product formulation increased both the extent and rate of exposure of umbralisib under fasted conditions. The extent (AUC_{0-t}) and total extent (AUC_{0-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}) concentrations 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-inf}.

The improved exposure seen with the micronized formulation of umbralisib was confirmed in subjects in the Phase 1 dose escalation as well. Figure 7 below illustrates the pre-dose plasma concentrations of umbralisib on Day 1 of Cycle 2 in subjects administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state.

FIGURE 7. PRE-DOSE PLASMA CONCENTRATIONS OF UMBRALISIB BY FORMULATION



1.4 UBLITUXIMAB AND UMBRALISIB (U2) COMBINATION

A Phase I/Ib dose escalation study (Study UTX-TGR-103) was conducted in B-cell (CLL and NHL) malignancies to establish the MTD of the combination of ublituximab and umbralisib (U2) and characterize safety and efficacy (NCT02006485). The study Is completed. The MTD was not reached and the most common all grade, all causality AEs in > 20% of subjects were: diarrhea (57%), nausea (53%), fatigue (43%) and neutropenia (32%) (Davids et al., 2017). The ORR for the CLL/SLL cohort was 62% in the 21 evaluable subjects with a 10% CR rate (Lunning et al., 2019). U2 was well tolerated and the safety and efficacy profile supports further research with multi-drug regimens including novel targeted agents.

The Phase 3 UNITY-CLL trial (NCT02612311) demonstrated that ublituximab and umbralisib (U2) prolonged PFS compared to the chemoimmunotherapy combination of obinutuzumab and chlorambucil in both treatment naïve and previously treated CLL populations (Gribben et al., 2020). The safety profile of the U2 combination was consistent with the profiles seen with umbralisib and ublituximab as monotherapies, and no new safety signals were identified. An interim analysis evaluated the individual contribution of umbralisib and ublituximab as single agents to the U2 combination and confirmed U2 as superior compared to either agent as a monotherapy. These data establish U2 as superior to chemoimmunotherapy; thus, making U2 an appropriate control arm in both treatment naïve and previously treated CLL.

1.5 VENETOCLAX IN CLL

The BCL-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to 4 BCL-2 Homology (BH) domains. In CLL, microRNAs miR15a and miR16-1 that negatively regulate the transcription of BCL-2 are deleted or down regulated, resulting in increased expression of BCL-2 (Cimmino et al., 2005). Venetoclax is an orally administered BCL-2 inhibitor demonstrating in vitro activity against primary CLL cells and in lymphoid malignancy xenograft models (Souers et al., 2013). In a Phase I dose escalation study enrolling 116 relapsed/refractory CLL patients, tumor lysis syndrome (TLS) was initially observed but decreased after a dose escalation over 5 weeks was initiated. The terminal t1/2 of venetoclax was 19 hours, allowing daily dosing. With the 5-week dose escalation and TLS precautions, only 1 of 60

patients had laboratory evidence of TLS and no patients had clinical sequelae. Otherwise, Grade 1/2 diarrhea and nausea were observed in roughly 50% of patients as was neutropenia, reaching Grade 3/4 in 41% (Roberts et al., 2016). Of the 116 patients, the response rate was 79%, with 20% CRs. Of the 23 patients who had a CR, 17 underwent MRD testing and 6 (35%) had negative results per standard criteria. The median PFS for the 60 patients in the dose escalation was 25 months and not yet reached at 17 months in the expansion cohort (estimated to be 66% at 15 months).

Venetoclax is FDA-approved for treatment of adult patients with CLL or SLL(AbbVie, 2020). In treatment naïve CLL/SLL, the Phase 3 CLL-14 trial showed venetoclax plus obinutuzumab prolonged PFS compared to obinutuzumab-chlorambucil (Fischer et al., 2019). In the relapsed/refractory setting, the Phase 3 MURANO trial illustrated that the venetoclax plus rituximab combination improved PFS compared to bendamustine plus rituximab (Seymour et al., 2018). Furthermore, these trials highlighted the potential for time limited treatment using chemotherapy-free regimens with 12 months of venetoclax in treatment naïve CLL/SLL and 24 months of venetoclax in relapsed/refractory CLL/SLL. Both trials demonstrated that venetoclax based regimens can produce high rates of uMRD which is associated with prolonged PFS independent of radiographic response (Kater et al., 2019).

1.6 RATIONALE/HYPOTHESIS FOR U2 + VENETOCLAX COMBINATIONS

While venetoclax therapy is highly active in patients with CLL/SLL, relapses occur. Additionally, the majority of patients only achieve a PRs to currently available venetoclax combinations. Further, a practical limitation exists with the TLS risk mitigation strategy required for venetoclax administration, which requires intensive monitoring for patients at medium and high risk of TLS and makes administration challenging in the community setting. We hypothesize that the addition of venetoclax following U2 induction will provide deeper levels of remission than have been achieved with single-agent umbralisib, ublituximab, and venetoclax to date. Further, the sequential strategy has been designed to mitigate the risk of venetoclax related TLS by utilizing a debulking course of U2 prior to initiation of venetoclax. Lastly, sequential monitoring for rate of undetectable MRD will be used to potentially inform future time limited therapies based on the achievement of early optimal response.

Based on the above, we propose this Phase 2/3 trial to evaluate U2 with venetoclax (U2-V) and also to compare the U2 regimen in a randomized fashion to the triplet regimen of U2-V.

The combination of U2-V has been evaluated in an ongoing Phase 1 study (NCT03379051) in patients with relapsed or refractory CLL, which supports the dosing regimen used in this study U2-VEN-207. Of 43 patients treated to date, Grade ≥3 AEs were infrequent with neutropenia (21%), leukopenia (12%), and IRRs (7%) occurring in over 5% of patients (Barr et al., 2020). Discontinuations due to AEs were also uncommon with 9% and 4% discontinuing umbralisib and venetoclax respectively. No DLTs were observed during the Phase 1 portion, and the RP2D was found to be umbralisib 800 mg QD, ublituximab 900 mg, and venetoclax at standard dosing. The Phase 1 study utilized a 3 Cycle debulking schedule for U2, similar to this Protocol U2-VEN-207. After 3 cycles of U2 debulking, there was an 81% relative reduction in high- and medium-risk TLS, and no patients developed clinical or laboratory TLS during venetoclax administration. Of 27 patients evaluable at Cycle 12, the triple combination of U2 plus venetoclax produced a 100% ORR, 41% CR, and high rates of uMRD in the peripheral blood (96%) and BM (77%). The findings of the Phase 1 study support continued investigation in the current trial.

2 OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PHASE 2 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To determine the complete response (CR) rate of the combination of ublituximab + umbralisib + venetoclax (U2-V)
- To determine the overall response rate (ORR) of the combination of ublituximab + umbralisib + venetoclax (U2-V)

SECONDARY OBJECTIVES

- To determine the rate of undetectable MRD
- To determine time to response (TTR) and duration of response (DOR)
- To characterize the safety of the combination regimen

[redacted]

PHASE 3 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To evaluate the efficacy of the combination of ublituximab + umbralisib + venetoclax (U2-V) compared to the combination of ublituximab + umbralisib (U2) in patients with either treatment naïve or previously treated CLL/SLL as measured by PFS

SECONDARY OBJECTIVES

- To evaluate the CR rate and ORR of the combination of ublituximab + umbralisib + venetoclax (U2-V) compared to ublituximab + umbralisib (U2) as assessed by an independent review committee (IRC);
- To compare the rate of undetectable MRD;
- To compare OS;
- To characterize the safety of the combination regimens.

2.2 EFFICACY ENDPOINTS

Progression-free Survival (PFS)
PFS is defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression or death from any cause.

Overall response rate (ORR)
ORR is defined as the proportion of subjects who achieve a CR, CRi, PR or PR-L.

Complete Response (CR) Rate
CR rate is defined as the proportion of subjects who achieve a CR or CRi.

Rate of Undetectable Minimal Residual Disease (MRD)
Undetectable MRD is defined as the proportion of subjects who are MRD negative, defined as a quantitative detection of less than one CLL/SLL cell in 10000 leukocytes by flow cytometry (MRD level, 10^{-4}) in blood or BM.

Time to Response (TTR)
TTR is defined as the interval from enrollment to first documentation of CR, CRi, PR, or PR-L.

Duration of Response (DOR)
DOR is defined as the interval from the first documentation of CR, CRi, PR, or PR-L to the earlier of the first documentation of definitive disease progression or death from any cause.

Overall Survival (OS)
OS is defined as the interval from randomization (Phase 3 subjects only) to the first documentation of death from any cause.

3 ELIGIBILITY CRITERIA

3.1 INCLUSION CRITERIA

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

1. B-cell CLL/SLL that warrants treatment consistent with iwCLL 2018 criteria for initiation of therapy with diagnosis established according to iwCLL 2018 criteria and documented within medical records. At least one of the following criteria must be met:
    a. Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia; or
    b. Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly; or
    c. Massive (i.e., ≥ 10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy; or
    d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months; or
    e. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
        i. Unintentional weight loss of ≥10% within the previous 6 months; or
        ii. Significant fatigue (≥ Grade 2); or
        iii. Fevers >100.5°F or 38.0°C for ≥2 weeks; or
        iv. Night sweats for >1 month.
2. Adequate organ system function, independent of growth-factor or transfusion support, defined as follows:
    a. Absolute neutrophil count (ANC) ≥ 750/mm^3 (µL) / platelet count ≥ 40,000/mm^3 (µL);
    b. Total bilirubin ≤1.5 times the upper limit of normal (ULN). Subjects with Gilbert's syndrome with bilirubin > 1.5 × ULN allowed per discussion with the Medical Monitor;
    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement;
    d. Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault formula).
3. ECOG performance status ≤ 2.
4. Male or female ≥ 18 years of age.
5. Ability to swallow and retain oral medication.
6. Female subjects who are not of child-bearing potential, and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female subjects of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of ublituximab and for at least 30 days after the last dose of umbralisib or venetoclax. Men of reproductive potential may not participate unless they agree to use medically acceptable contraception.
7. Willingness and ability to comply with trial and follow-up procedures and provide written informed consent.

3.2 EXCLUSION CRITERIA

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

1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1, Day 1 (within 7 days of Cycle 1, Day 1 for prior BTK inhibitor).
   a. Corticosteroid use within 1 week prior to first dose of study drug are excluded, with the exception of steroid use for adrenal replacement, inhaled steroid for asthma, topical steroid use or other locally administered corticosteroids. Patients requiring systemic steroids for leukemia control or white blood cell (WBC)-count lowering are excluded.
2. Autologous hematologic stem cell transplant within 6 months of study entry.
3. Prior allogeneic hematologic stem cell transplant.
4. Evidence of chronic active hepatitis B (HBV) infection as evidenced by a detectable hepatitis B surface antigen (HBsAg); or chronic hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of human immunodeficiency virus (HIV). Subjects with positive hepatitis B core antibody (HBc Ab) or hepatitis C virus antibody (HCV AB) or positive CMV by IgM or IgG are eligible only if PCR is negative for HBV DNA, HCV RNA or CMV.
5. Known histological transformation from CLL/SLL to an aggressive lymphoma (e.g., Richter's Transformation, prolymphocytic leukemia, or DLBCL).
6. History of CNS involvement with CLL/SLL.
7. Prior exposure to any PI3K inhibitor (e.g. idelalisib, duvelisib, umbralisib (TGR-1202), etc.) or venetoclax (ABT-199, GDC-0199).
8. Known barriers to commercially available venetoclax.
9. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails.
10. Live virus vaccines within 4 weeks prior to or during study therapy.
11. History of anaphylaxis (excluding IRR) in association with previous anti-CD20 monoclonal antibody administration.
12. Any severe and/or uncontrolled medical conditions or other conditions that could adversely affect the safety of the subject or their participation in the study such as:
    a. Ongoing alcoholic liver disease, nonalcoholic steatohepatitis, cirrhosis of the liver, primary biliary cirrhosis, portal hypertension
    b. Splenomegaly from causes other than CLL/SLL
    c. Symptomatic, or history of documented congestive heart failure (New York Heart Association [NYHA] functional classification III-IV). Class 3 is defined as cardiac disease in which patients are comfortable at rest but marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain;
    d. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization;
    e. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at Investigator discretion;
    f. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of randomization.
13. Requirement for use of strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-glycoprotein (P-gp) inhibitors, or narrow therapeutic index P-gp substrates (See Appendix D).
14. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or in situ carcinomas, superficial bladder cancer not treated with intravesical

chemotherapy or BCG within 6 months, or localized prostate cancer with a PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry.

15. Women who are pregnant or lactating.

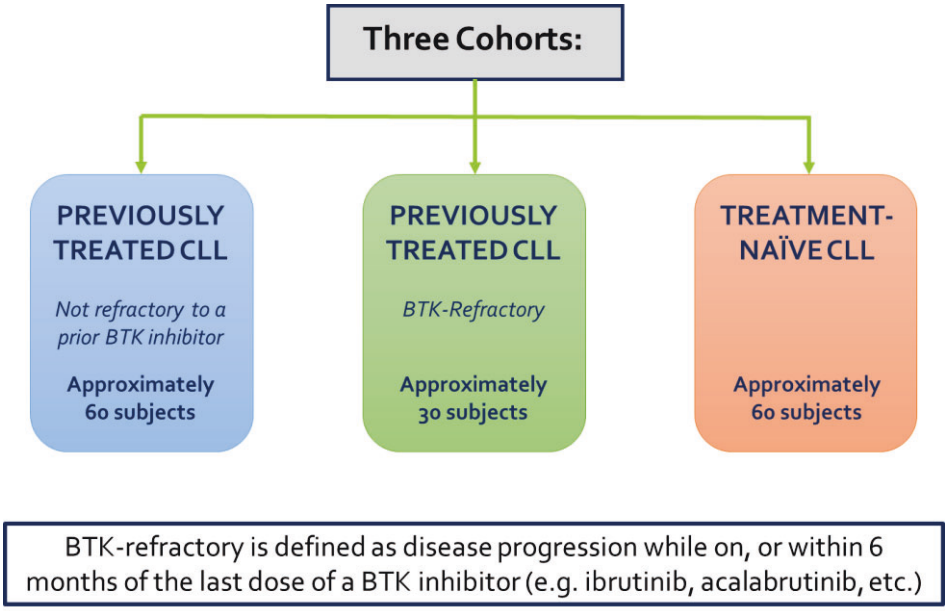
4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, Phase 2/3 study designed to investigate the efficacy and safety of U2 combined with venetoclax in subjects with CLL/SLL. Patients with treatment naïve and previously treated CLL/SLL are eligible for enrollment. Based on preliminary results from ongoing ublituximab and umbralisib trials and changing landscape of approved CLL/SLL treatments, single-arm or randomized cohorts may be added for both safety and efficacy.

In the Phase 2 stage of the study (see Figure 8 below), 3 separate cohorts will be enrolled: a cohort of approximately 60 subjects with treatment naïve CLL; a cohort of approximately 60 subjects with previously treated CLL, this includes relapsed subjects who are not refractory to a prior BTK inhibitor; and a cohort of approximately 30 subjects with BTK-refractory CLL will be enrolled in the study. BTK-refractory is defined as disease progression while on, or within 6 months of the last dose of, a BTK inhibitor (e.g. ibrutinib, acalabrutinib, etc.). See Section 8 for details on umbralisib administration based on MRD status. As of January 29, 2021, the Phase 2 portion of the study was closed to enrollment.

FIGURE 8: PHASE 2 STUDY DESIGN



The Phase 3 stage of the trial (Figure 9) includes 2 independent randomized cohorts of CLL/SLL patients; a treatment naïve cohort and a previously treated cohort. Following screening, qualified patients will be randomized 1:1 to 1 of the 2 arms:

- Arm A: Ublituximab + Umbralisib + Venetoclax (U2-V)
- Arm B: Ublituximab + Umbralisib (U2)

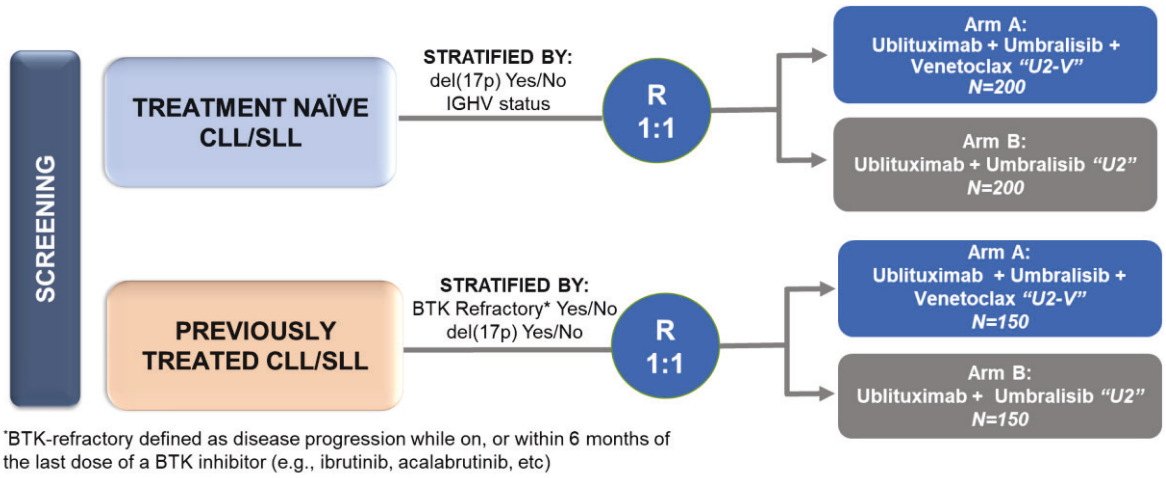
Approximately 400 (200 per treatment arm) patients will be enrolled to the treatment naïve CLL/SLL cohort and approximately 300 (150 per treatment arm) patients will be enrolled to the previously treated CLL/SLL cohort. The treatment naïve cohort and the previously treated cohorts will enroll independently of each other.

Patients will be randomized and stratified by the following factors:

Treatment Naïve Cohort: 17p status by central lab (deleted or not deleted) and IGHV status (mutated or not mutated)

Previously Treated Cohort: 17p status by central lab (deleted or not deleted) and BTK status (refractory to BTK; yes or no)

FIGURE 9: PHASE 3 STUDY DESIGN



During the study period, all subjects will be evaluated for response by CT and/or MRI. At each follow-up visit, subjects will be assessed for response/progression by physical examination and laboratory tests. The best clinical response as well as disease progression will be determined by an IRC. Subjects will remain on study treatment until the occurrence of definitive disease progression (subjects enrolled to the randomized Phase 3 stage must have PD confirmed by central radiology prior to discontinuing study drug), completion of treatment, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. Subjects who discontinue from study treatment (either for unacceptable toxicity or Investigator choice) and have not progressed will continue to be followed for progression until confirmed by IRC. All subjects enrolled to the Phase 3 portion of the study will be followed for overall survival.

4.2 EFFICACY AND SAFETY ANALYSES

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

Efficacy will be determined according to the iwCLL guidelines for the treatment of CLL/SLL (Hallek et al., 2018).

4.3 REGISTRATION AND RANDOMIZATION/BLINDING

Subjects who have signed an informed consent will be registered and receive a unique subject identifier. Subjects must be registered in the IRT system prior to dispensing any drug to the participant. Subjects enrolled to the Phase 3 randomized stage of the study will be randomized in the IRT system. Treatment arm will be assigned by the IRT system. Once randomized, subjects should start study treatment within 7 days of randomization. Further details about the subject registration and randomization process are available in the IRT Manual.

4.4 STUDY SITES

This study may be conducted in approximately 125 centers. Enrollment is expected to take approximately 24 months.

4.5 DISCONTINUATION FROM STUDY

Discontinuation from study treatment (discontinuation of all study drugs) and discontinuation from the study might be linked or might be separate events, depending on the triggering action, decision or outcome. Subjects will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Intolerable toxicity (all study drugs discontinued)
- Subject requests to withdraw consent for treatment
- Pregnancy
- Initiation of therapeutic intervention not permitted by the protocol
- Investigator discretion
- Discontinuation of the study by the Sponsor

Subjects will continue to be followed for PFS and/or OS per the schedule of assessments.

Subjects who discontinue from study treatment will continue to be followed for AEs and other protocol required procedures as per the study assessment table.

All subjects who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the Investigator, it is not likely that these values are to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for making this decision in the subject's medical records and as a comment on the eCRF.

5 STUDY ASSESSMENT AND TREATMENT SCHEDULE (PHASE 2)

The table below lists all the required assessments that should be performed at each study visit for subjects enrolled **to the Phase 2 stage of the trial .**

TABLE 4: STUDY ASSESSMENT AND TREATMENT SCHEDULE

Cycle = 28 days	Screening[1]	Cycle 1[2]				Cycles 2-3[3]	Cycle 4[3]				Cycles 5-6[3]	Cycles 9-24[4]	Cycles 30+[4]	EOT	30 and 90 day Safety FU[5]	LTFU[6]	EOS[7]
Procedure/Days	D-30 to D0	D1	D2	D8	D15	D1	D1	D8	D15	D22	D1	D1 Q3 Cycles	D1 Q6 Cycles				
Medical history	X																
Rai staging	X																
ECOG performance status	X	X				X	X				X	X	X	X			X
Physical examination	X	X				X	X				X	X	X	X			X
Weight	X	X				X	X				X	X	X				
Vital signs[8]	X	X	X	X		X	X				X	X	X	X			X
Hematology[9]	X	X	X	X	X	X	X				X	X	X	X			X
Chemistry, LDH, Mg, Phos, Uric acid[9,10]	X	X	X	X	X	X	X	X[11]	X	X	X	X	X	X			X
PT/INR[12]	X																
HBV/HCV serology, Coombs test, CMV[13]	X																
CMV screening[14]							X				X	X	X				
Quant IgG, IgA, IgM	X											X[15]					
β_2-microglobulin	X																
Serum pregnancy test[16]	X																

[1] Screening labs (hematology and chemistry only) must be conducted within 14 days prior to Cycle 1 Day 1. Patients must continue to meet eligibility criteria in respect to adequate organ system function as per Inclusion Criteria # 2 within the required screening timeframe, and importantly, on Cycle 1 Day 1. Hematology and chemistry results must be reviewed prior to dosing on Cycle 1 Day 1 to ensure subjects meet Inclusion #2 as per the protocol.

[2] Study visits have a ± 1 day window.

[3] Study visits have a ±3 day window.

[4] Study visits have a ± 7 day window.

[5] A 30-day (± 7 days) and a 90-day (± 7 days) safety follow up visit is required after the last dose of study drug. See Section 12.2.3 Adverse Event/Serious Adverse Event Recording.

[6] Subjects who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression or until a non-protocol line of therapy is initiated. Enter date of disease progression and/or death occurred in eCRF.

[7] End of Study (EOS) visit to be completed for subjects who are coming off study. Tumor Assessment should be performed if not done within previous 3 months. EOT and EOS may be the same visit if subject is discontinuing the study drugs and is not going into LTFU.

[8] Heart rate, blood pressure, temperature, respirations.

[9] Hematology and chemistry must be done prior to ublituximab administration.

[10] See Section 8.5.3: Guidelines for Administration of Venetoclax for dose ramp-up schedule and recommended blood chemistry monitoring based on tumor burden.

[11] Cycle 4, day 8, 15 and 22 only required for patients receiving venetoclax and during the venetoclax ramp up.

[12] PT/INR to be done at screening and as clinically indicated. INR should be monitored closely in subjects receiving venetoclax and warfarin.

[13] Serum virology to include HBsAg, HBc antibody, HCV AB, CMV IgG and CMV IgM or CMV by PCR if institutions SOC. If HBc antibody, HCV AB or CMV IgM or IgG is positive, subjects must be evaluated for the presence of active HBV, HCV, or CMV by PCR.

[14] CMV screening by PCR for all subjects while receiving umbralisib approximately Q3 months beginning C4D1, C6D1, C9D1 and approximately every 3 months up to Cycle 24, and Q6 months thereafter. If CMV IgM or IgG is positive, subjects must be evaluated for the presence of active CMV by PCR.

[15] To be completed at screening, during Cycle 12, and during Cycle 24 only.

[16] For females of childbearing potential, completed within 3 days prior to Day 1 of Cycle 1.

Cycle = 28 days	Screening[1]	Cycle 1[2]				Cycles 2-3[3]	Cycle 4[3]				Cycles 5-6[3]	Cycles 9-24[4]	Cycles 30+[4]	EOT	30 and 90 day Safety FU[5]	LTFU[6]	EOS[7]
Procedure/Days	**D-30 to D0**	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1 Q3 Cycles**	**D1 Q6 Cycles**				
BM biopsy/aspirate[17]	X																
CLL mutation panel [18]	X																
EKG	X																
[redacted]																	
T/B/NK Cell Subsets[20]	X						X					X					
TLS risk-assessment[21]	X						X										
Response assessment[22]	X						X					X	X			X	X
MRD (NeoGenomics)											X[23]	X	X			X	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Con Med Assessment		X	X	X	X	X	X				X	X	X	X			
Ublituximab[24]		X	X	X	X	X	X				X						
Umbralisib		Orally once daily with food[25]															
Venetoclax[26]							Orally daily *see ramp-up schedule										

[17] Baseline BM within 90 days of C1D1. A post-baseline BM biopsy is required to confirm potential CR and for MRD testing.
[18] For del(13q), del(11q), del(17p), and trisomy 12, IgHV and *TP53* gene mutation status in peripheral blood. This may be done within 60 days prior to C1D1. If IgHV status already documented in medical record it does not need to be repeated.
[redacted]
[20] To be drawn pre-dose C1D1, during Cycle 4, Cycle 12, and approximately every 6 cycles thereafter until Cycle 24. Subjects that end treatment prior to Cycle 24 should continue to have T/B/NK collected until month 24. See lab manual for sample collection procedures.
[21] TLS risk assessment according to Section 8.5.3.1 at baseline and on Day 1 of Cycle 4, prior to first dose of venetoclax.
[22] Response assessment at baseline (within 30 days prior to Cycle 1 Day 1), and within 14 days prior to Cycles 4 & 12, and at least every 12 cycles thereafter. Radiologic assessment should include CT with contrast or MRI imaging of neck, chest, abdomen, and pelvis. A post-baseline BM biopsy is required to confirm potential CR.
[23] MRD at Cycle 6 for all subjects without signs of clinical progression, perform MRD testing by PB; repeat every 6 cycles. At Cycle 12, MRD by PB will be performed. Subjects in a ≥PR and who are MRD negative by PB at Cycle 12, an MRD assessment by BM (central lab) is required. Any subject in a CR before Cycle 12 who are MRD negative by PB, perform MRD testing in BM (central lab). If MRD BM positive, repeat MRD by BM (central lab) at next response assessment. Regardless of MRD response in PB or BM, MRD by PB should continue every 6 cycles. Subjects that end treatment prior to Cycle 24 should continue to have MRD collected through cycle 24 and every 6 cycles thereafter in LTFU. See laboratory manual for collection, processing, and shipment instructions.
[24] Ublituximab to be administered C1 D1, 2, 8 & 15, then D1 C2-6. After C6 no further ublituximab will be administered.
[25] See Section 8.0 Treatment Plan for details on umbralisib administration based on treatment status and MRD status.
[26] Subject should have prior authorization for access to commercially available venetoclax.

6 STUDY ASSESSMENT AND TREATMENT SCHEDULE (PHASE 3)

The table below lists all of the required assessments that should be performed at each study visit for subjects enrolled **to the Phase 3 stage of the trial (version 3.0+).**

TABLE 5: STUDY ASSESSMENT AND TREATMENT SCHEDULE

Cycle = 28 days	Screening[1]	Cycle 1[2]				Cycles 2-3[3]	Cycle 4[4]				Cycles 5&6[3]	Cycles 9, 12, 15[5]	Cycle 18 and Q3 Cycle[5]	EOT	30- and 90-Day Safety FU[6]	LTFU[7]	EOS,[8]
Procedure/Days	**D-30 to D0**	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**				
Medical history	X																
Rai Staging	X																
ECOG Performance Status	X	X				X	X				X	X	X	X			X
Physical Examination	X	X				X	X				X	X	X	X			X
Weight	X	X				X	X				X	X	X				
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Hematology[10]	X	X	X	X	X	X	X				X	X	X	X			X
Chemistry, LDH, Mg, Phos, Uric acid[10]	X	X	X	X	X	X	X[11]	X[12]	X	X	X	X	X	X			X
PT/INR[13]	X																
Hep B/C[14]	X																
CMV[15]	X						X				X	X	X				

[1] Screening labs (hematology and chemistry only) must be conducted within 14 days prior to Cycle 1 Day 1. Patients must continue to meet eligibility criteria in respect to adequate organ system function as per Inclusion Criteria # 2 within the required screening timeframe, and importantly, on Cycle 1 Day 1. Hematology and chemistry results must be reviewed prior to dosing on Cycle 1 Day 1 to ensure subjects meet Inclusion #2 as per the protocol.

[2] Study visits have a ± 1 day window.

[3] Study visits have a ± 3 day window.

[4] Cycle 4 Day 8, 15, and 22 visits only for subject randomized to Arm A (U2-V). Study visits have a ± 3 day window.

[5] Study visits have a ± 7 day window.

[6] A 30-day (± 7 days) and a 90-day (± 7 days) safety follow up visit is required after the last dose of study drug. See Section 12.2.3 Adverse Event/Serious Adverse Event Recording.

[7] Subjects who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression until a non-protocol line of therapy is initiated. LTFU for PD and OS should be entered approximately every 6 months. Enter date of disease progression and/or death occurred in eCRF.

[8] End of Study (EOS) visit to be completed for subjects who are coming off study. Tumor Assessment should be performed if not done within previous 3 months. EOT and EOS may be the same visit if subject is discontinuing the study drugs and is not going into LTFU.

[9] Heart rate, blood pressure, temperature, respirations.

[10] Hematology and chemistry must be done prior to ublituximab administration.

[11] See Section 8.5.3: Guidelines for Administration of Venetoclax for dose ramp-up schedule and recommended blood chemistry monitoring based on tumor burden.

[12] Cycle 4, day 8, 15 and 22 only required for patients receiving venetoclax and during the venetoclax ramp-up.

[13] PT/INR to be done at screening and as clinically indicated. INR should be monitored closely in subjects receiving venetoclax and warfarin.

[14] Serum virology to include HBsAg, HBcAb and HCV AB. If HBcAb is positive subjects must be evaluated for the presence of active HBV by PCR. If HCV AB positive, subjects must be evaluated for the presence of HCV by PCR. See exclusion criteria.

[15] At baseline, CMV IgG and IgM or CMV by PCR (if institutions SOC). Thereafter, CMV by PCR for all subjects while receiving umbralisib beginning C4D1, then C6D1 and approximately every 3 cycles thereafter up to Cycle 24, then approximately every 6 cycles thereafter. If CMV IgM or IgG is positive, subjects must be evaluated for the presence of active CMV by PCR.

Cycle = 28 days	Screening[1]	Cycle 1[2]				Cycles 2-3[3]	Cycle 4[4]				Cycles 5&6[3]	Cycles 9, 12, 15[5]	Cycle 18 and Q3 Cycle[5]	EOT	30- and 90-Day Safety FU[6]	LTFU[7]	EOS,[8]
Procedure/Days	**D-30 to D0**	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**				
Quant IgG, IgA, IgM[16]	X											C12	C24				
β_2-microglobulin	X																
Serum Pregnancy Test[17]	X																
Urine Pregnancy[18]						X	X				X	X					
BM biopsy/aspirate	X[19]																
EKG	X																
IGHV	X[20]																
FISH and NGS[21]	X																
MRD[22]	X										C6	C12 and C15	C24			X	
Sparse PK[23]							X										
Immunogenicity[24]		X			X	C3					C6	C12					
Response Assessment[25]	X						X					X[25]	X[25]			X	X
TLS Risk-Assessment[26]	X						X										
AE Assessment[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Con Med Assessment		X	X	X	X	X	X				X	X	X	X			X

[16] To be completed at baseline, during Cycle 12, and during Cycle 24 only.
[17] For females of childbearing potential, serum pregnancy test completed within 3 days prior to Day 1 of Cycle 1.
[18] For females of childbearing potential. This is only required if patients are receiving drug.
[19] Baseline BM as clinically indicated as per standard of care. Post-baseline BM biopsy to confirm potential CR required.
[20] IgHV to be done at screening if mutation status is not already known.
[21] FISH central lab results required for randomization. Samples for FISH, and NGS to be sent to the Central Lab, see lab manual for sample collection and shipment procedures.
[22] MRD in peripheral blood at baseline and Cycle 6, Cycle12, Cycle 15 and Cycle 24 (MRD drawn only if subject is in PR or better). One MRD by bone marrow aspirate sample should be completed for all patients MRD negative by peripheral blood. Thereafter, all subjects without signs of clinical progression, repeat MRD every 6 cycles (peripheral blood). Subjects that end treatment prior to Cycle 15 should continue to have MRD collected until month 15. See laboratory manual for collection, processing, and shipment instructions.
[23] A total of 2 serum samples should be collected from each subject for sparse population PK analyses (Pre-dose on Cycle 4, Day 1, and one randomly assigned post-baseline sample). See Section7.2.1 Sparse Sampling Pharmacokinetics.
[24] Samples to be collected pre-dose of ublituximab
[25] Response assessment at baseline (within 30 days prior to Cycle 1 Day 1), and within 14 days prior to Cycles 4 & 12, and at least every 6 cycles thereafter. Radiologic assessment should include CT with contrast or MRI imaging of neck, chest, abdomen, and pelvis. BM biopsy to confirm potential CR required. If PD is suspected, scans and relevant clinical data should be sent to central radiology for expedited PD review. This PD confirmation should be obtained prior to subject being removed for PD (except in rare cases where it is in the patients best interest to be discontinued immediately.
[26] Venetoclax Cohort Only: TLS risk assessment according to Section 8.5.3.1 at baseline and on Day 1 of Cycle 4, prior to first dose of venetoclax.
[27] AEs are to be reported from Cycle 1 Day 1 and SAEs are to be reported from signing of informed consent. A 30-day (± 7 days) and a 90-day (± 7 days) safety follow up visit is required after the last dose of study drug. See Section 12.2.3Adverse Event/Serious Adverse Event Recording

Cycle = 28 days	Screening[1]	Cycle 1[2]				Cycles 2-3[3]	Cycle 4[4]				Cycles 5&6[3]	Cycles 9, 12, 15[5]	Cycle 18 and Q3 Cycle[5]	EOT	30- and 90-Day Safety FU[6]	LTFU[7]	EOS,[8]
Procedure/Days	**D-30 to D0**	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**				
Pre-authorization for venetoclax (if applicable)	X																
Randomize	D-7 to D1																
Arm A																	
Venetoclax							Orally daily *see ramp-up schedule										
Ublituximab		X	X	X	X	X	X				X	X					
Umbralisib		X[28]	X	Orally once daily with food													
Arm B																	
Ublituximab		X	X	X	X	X	X				X	X	X				
Umbralisib		X[28]	X	Orally once daily with food													

[28] Umbralisib will be self-administered (by the subject). On Cycle 1 Days 1 and 2, when ublituximab will be administered, umbralisib should be administered prior to ublituximab pre-medication.

7 LABORATORY ASSESSMENTS

Laboratory assessments will be collected as specified in the study assessments tables. Please see Section 8.5.3.1 for details regarding recommended blood chemistry monitoring based on tumor burden.

7.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include:

TABLE 6. HEMATOLOGIC INDICES AND SERUM CHEMISTRY TO BE PERFORMED LOCALLY

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	
Erythrocyte count	Monocytes	
Leukocyte count	Eosinophils	
Absolute neutrophil count	Basophils	
Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate/CO_2	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total protein
Chloride	Potassium	Uric acid

2. Quantitative Immunoglobulins (IgG, IgA, IgM)
3. Serum β-HCG test for women of child-bearing potential
4. Urine pregnancy test for women of child-bearing potential (Phase 3 patients only)
5. Coagulation lab tests to include PT and INR
6. β2-microglobulin
7. Serum virology to include HBsAg, HBcAb, HCV AB, CMV IgG and CMV IgM (site may perform CMV by PCR if that is their SOC). If HBcAb, HCV AB or CMV IgM or IgG is positive, subjects must be evaluated for the presence of active HBV, HCV, or CMV by PCR
8. Coombs test (Coombs test not required in subjects enrolled to V3.0 or later)
9. BM aspirate/biopsy. (BM for morphology by local laboratory to confirm CR, BM aspirate for MRD assessment to be analyzed at the central laboratory)
10. TLS Risk-Assessment as per venetoclax package insert. C4 pre dose labs include CMP, Mg, Phosphorus, uric acid and LDH. Venetoclax post dose ramp up labs include potassium, uric acid, phosphorus, calcium and creatinine.
11. IGHV mutation status
12. CMV by PCR

7.2 CENTRAL LABORATORY ASSESSMENTS

The following assessments will be shipped to and analyzed at a central laboratory. Please see the Study Laboratory Manual for processing, handling, and shipping instructions.

Subjects Enrolled to Phase 2:

- **MRD assessment**
  - Cycle 6: Peripheral blood at Cycle 6 for all subjects without clinical signs of progression; **repeat every 6 cycles**
  - Cycle 12 & 24: Peripheral blood; subjects in a PR or better and are MRD negative by PB, should have MRD by BM
  - CR before Cycle 12 that are MRD negative by PB: MRD in BM. If MRD BM positive, repeat MRD by BM at next response assessment and continue to draw MRD by PB
- **T/B/NK Cell Subsets:** only subjects enrolled to Protocol V1.0-2.0/Phase 2 Portion, No longer required in subjects enrolled to Phase 3
  - To be drawn pre-dose C1D1, during Cycle 4, Cycle 12, and approximately every 6 cycles thereafter until Cycle 24
- [redacted]

Protocol Version 3.0+, Subjects Enrolled to Phase 3:

- **MRD assessment**
  - MRD in peripheral blood at baseline and Cycle 6, Cycle 12, Cycle 15 and Cycle 24 (MRD drawn only if subject is in PR or better). One MRD by bone marrow aspirate should be completed for all patients who are MRD negative by peripheral blood. Thereafter, all subjects without signs of clinical progression, repeat MRD every 6 cycles (peripheral blood). See laboratory manual for collection, processing, and shipment instructions.
- **CLL mutation panel (FISH and NGS)–** Peripheral blood to be drawn at screening for FISH and NGS. Central lab FISH results required at the time of randomization for stratification.
- **Sparse PK Sampling**
- **Immunogenicity Sampling**

7.2.1 SPARSE SAMPLING PHARMACOKINETICS (SUBJECTS ENROLLED TO PHASE 3 ONLY)

All subjects enrolled to Arm A (U2 + Venetoclax) must participate in the sparse sampling population pharmacokinetic (PK) assessment. The sampling time-points below will be utilized for the population pharmacokinetic assessment. A Cycle 4, Day 1, pre-dose (baseline) sample will be obtained from all subjects, however, subjects will be randomized (when randomized into the study by the IWRS) to only 1 post-baseline sample among the timepoints listed below. On days PK samples are being obtained, umbralisib and venetoclax must be administered orally immediately at the start of the ublituximab infusion. The PK sample must be drawn prior to drug administration.

Sparse PK blood samples for all subjects will be taken as follows (Pre-dose on Cycle 4, Day 1, then one randomly assigned post-baseline sample. The possible post-baseline PK randomly assigned by the IRT system is one of the following: Day 1 of Cycles 5, 6, 9, 12 or 15.

A total of 2 serum samples should be collected from each subject for sparse population PK analyses (Pre-dose on Cycle 4, Day 1, and one randomly assigned post-baseline sample) with the possibility of one additional sample timepoint assigned later during treatment to ensure all sample timepoints for the study have been collected.

Nonlinear mixed effects modeling will be used for the population pharmacokinetic analysis. Covariates to be evaluated to assess the effect on pharmacokinetic parameters include age, weight, gender, ethnicity, hemoglobin (Hb) concentration, platelet count, white blood cell (WBC) count, liver function (ALT and AST), creatinine concentration and the co-administration of ublituximab.

7.2.3 IMMUNOGENICITY ASSESSMENT (SUBJECTS ENROLLED TO PHASE 3 ONLY)

One hundred subjects enrolled to Arm A and 100 subjects enrolled to Arm B in both treatment naïve and previously treated cohorts (total 400 patients) must participate in the ublituximab immunogenicity assessment. The sampling schedule for these subjects is detailed in Table 8 below:

TABLE 8: IMMUNOGENICITY ASSESSMENT

Visit	Scheduled time point
Cycle 1, Day 1	Pre-dose of ublituximab
Cycle 1, Day 15	Pre-dose of ublituximab
Cycle 3, Day 1	Pre-dose of ublituximab
Cycle 6, Day 1	Pre-dose of ublituximab
Cycle 12, Day 1	Pre-dose of ublituximab

See the Lab Manual for a detailed description of the procedures for central lab sample collection, processing and shipping.

8 TREATMENT PLAN

8.1 TREATMENT SUMMARY

Treatment will be administered in 28-day cycles. Patients must continue to meet eligibility in respect to adequate organ system function as per Inclusion Criteria #2 on Cycle 1 Day 1. Hematology and chemistry results must be reviewed prior to dosing on Cycle 1 Day 1 to ensure subjects meet Inclusion Criteria #2 as per the protocol.

Please see Section 8.5.3: Guidelines for Administration of Venetoclax for specific information on TLS risk, prophylaxis and assessments.

8.2 V1.0-2.0 – SUBJECTS ENROLLED TO PHASE 2 U2-V REGIMEN

TABLE 9. PHASE 2 U2-V DOSING SCHEMA

<table>
<tr><th colspan="6">Cycle 1</th></tr>
<tr><th colspan="3">Ublituximab</th><th colspan="3">Umbralisib</th></tr>
<tr><th>Day 1</th><th>Day 2</th><th>Day 8 & 15</th><th colspan="3">Day 1 – 28</th></tr>
<tr><td>150 mg</td><td>750 mg</td><td>900 mg</td><td colspan="3">800 mg daily</td></tr>
<tr><th colspan="6">Cycles 2 – 3</th></tr>
<tr><th colspan="3">Ublituximab</th><th colspan="3">Umbralisib</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Days 1 – 28</th></tr>
<tr><td colspan="3">900 mg</td><td colspan="3">800 mg daily</td></tr>
<tr><th colspan="6">Cycle 4</th></tr>
<tr><th>Ublituximab</th><th>Umbralisib</th><th colspan="4">Venetoclax</th></tr>
<tr><th>Day 1</th><th>Days 1-28</th><th>Days 1-7 (wk 1)</th><th>Days 8-14 (wk 2)</th><th>Days 15-21 (wk 3)</th><th>Days 22-28 (wk 4)</th></tr>
<tr><td>900 mg</td><td>800 mg daily</td><td>20 mg daily</td><td>50 mg daily</td><td>100 mg daily</td><td>200 mg daily</td></tr>
<tr><th colspan="6">Cycles 5 – 6</th></tr>
<tr><th>Ublituximab</th><th colspan="2">Umbralisib</th><th colspan="3">Venetoclax</th></tr>
<tr><th>Day 1</th><th colspan="2">Days 1 – 28</th><th colspan="3">Days 1 – 28</th></tr>
<tr><td>900 mg</td><td colspan="2">800 mg daily</td><td colspan="3">400 mg daily</td></tr>
<tr><th colspan="6">Cycles 7 – 24</th></tr>
<tr><th>Ublituximab</th><th colspan="2">Umbralisib</th><th colspan="3">Venetoclax</th></tr>
<tr><td rowspan="2"></td><th colspan="2">Days 1 – 28</th><th colspan="3">Days 1 – 28</th></tr>
<tr><td colspan="2">800 mg daily</td><td colspan="3">400 mg daily</td></tr>
<tr><th colspan="6">Cycle 25+ for MRD positive subjects ONLY</th></tr>
<tr><th>Ublituximab</th><th colspan="2">Umbralisib</th><th colspan="3">Venetoclax</th></tr>
<tr><td rowspan="2"></td><th colspan="2">Days 1 – 28</th><td rowspan="2" colspan="3"></td></tr>
<tr><td colspan="2">800 mg daily</td></tr>
</table>

8.3 (PROTOCOL V3.0) ARM A UBLITUXIMAB + UMBRALISIB + VENETOCLAX (U2-V) REGIMEN

TABLE 10. PHASE 3 U2-V DOSING SCHEMA

Phase 3 Arm A (U2-V) Randomized Subjects						
Cycle 1						
Ublituximab			**Umbralisib**			
Day 1	**Day 2**	**Day 8 & 15**	**Days 1 – 28**			
150 mg	750 mg	900 mg	800 mg daily			
Cycles 2 – 3						
Ublituximab			**Umbralisib**			
Day 1			**Days 1 – 28**			
900 mg			800 mg daily			
Cycle 4						
Ublituximab	**Umbralisib**		**Venetoclax**			
Day 1	**Days 1 – 28**		**Days 1-7 (wk 1)**	**Days 8-14 (wk 2)**	**Days 15-21 (wk 3)**	**Days 22-28 (wk 4)**
900 mg	800 mg daily		20 mg daily	50 mg daily	100 mg daily	200 mg daily
Cycles 5 – 6						
Ublituximab	**Umbralisib**		**Venetoclax**			
Day 1	**Days 1 – 28**		**Days 1 – 28**			
900 mg	800 mg daily		400 mg daily			
Cycles 7 –15						
Ublituximab	**Umbralisib**		**Venetoclax**			
Day 1 of Cycle 9, Cycle 12 and Cycle 15	**Days 1 – 28**		**Days 1 – 28**			
900 mg	800 mg daily		400 mg daily			

8.4 (PROTOCOL V3.0) ARM B UBLITUXIMAB + UMBRALISIB (U2) TREATMENT REGIMEN

TABLE 11. PHASE 3 U2 DOSING SCHEMA

Phase 3 Arm B Ublituximab + Umbralisib (U2) Randomized Subjects			
Cycle 1			
Ublituximab			**Umbralisib**
Day 1	**Day 2**	**Day 8 & 15**	**Days 1 – 28**
150 mg	**750 mg**	**900 mg**	**800 mg daily**
Cycles 2 – 6			
Ublituximab			**Umbralisib**
Day 1			**Days 1 – 28**
900 mg			**800 mg daily**
Cycle 7+			
Ublituximab			**Umbralisib**
Day 1, every 3 Cycles (9, 12, 15, 18 etc.)			**Days 1 – 28**
900 mg			**800 mg daily**

8.5 AGENT ADMINISTRATION

8.5.1 GUIDELINES FOR ADMINISTRATION OF UBLITUXIMAB

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line.
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:*
    - Pre-medications should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10 – 20mg or equivalent)
        - The guidance above for pre-medication represents a minimum. Additional pre-medications such as montelukast, rupatadine, famotidine, etc. may be added per institutional guidelines and treating investigator, and should be considered for initial ublituximab doses.
        - If pre-medications are administered IV: start ublituximab 30 minutes after conclusion of last pre-med infusion
        - If pre-medications are administered orally: start ublituximab 45 – 60 minutes after ingestion of pre-meds
    - Use of oral acetaminophen 650 mg (or equivalent) **should be restricted to subjects who experience fever or pyrexia after Week 1 dose, or as clinically warranted**.
    - Prophylaxis with an antiviral agent effective against hepatitis B is required in subjects with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening. If the subject has a negative reaction to the prophylactic antiviral agent, consider using a different prophylactic medicine.

- *Hypersensitivity and IRR Precautions*: Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions.
- *Subject Care Implications*:
    - 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 does not conform to the specifications. Immediately inform the Monitor/Sponsor with any product quality concerns or questions
    - It is recommended that ublituximab be administered immediately after dilution
    - No other treatment may be co-administered with ublituximab (other than for immediate intervention for an AE)
    - Since infusion related hypotension may occur, consider holding antihypertensive medications 12 – 24 hours prior to and throughout infusion of ublituximab
    - For subjects at risk for TLS in the opinion of the treating Investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered
    - Hepatitis B reactivation may occur in subjects with a positive HBsAg, negative HBsAg with positive anti-HBc and those who appear to have resolved hepatitis B infection. Promptly consult clinicians, with expertise in managing subjects with a prior history of

hepatitis B, regarding monitoring and consideration of options for hepatitis B antiviral therapy for prophylaxis/treatment

- Monitor subjects with a prior history of hepatitis B closely as clinically indicated based on liver tests and any observed signs/symptoms such as jaundice, abdominal pain, dyspepsia, decreased appetite, 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, ublituximab may be resumed, see Table 22 Study Drug Modifications. If reactivation of hepatitis B is confirmed, institute hepatitis B antiviral treatment and promptly consult clinicians with expertise in managing subjects with a prior history of hepatitis B. Once hepatitis B infection has resolved, ublituximab may be resumed at Investigator discretion after discussion with medical monitor.

8.5.1.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE - UBLITUXIMAB

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

The following are recommended infusion rate reduction/hold guidelines for subjects who experience severe IRRs in which treatment should be interrupted. Final decision for infusion rate reduction/hold or discontinuation resides with the treating Investigator.

1st or 2nd Infusion Interruption (Same Day):

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

3rd Infusion Interruption (Same Day):

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

If the infusion discontinued is the Cycle 1, Day 1 infusion, administer the scheduled Cycle 1, Day 2 dose according to the protocol dosing schedule.

If at any time during ublituximab treatment, an IRR is observed, the treating Investigator may reduce the infusion flow rate at their discretion.

8.5.1.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

TABLE 12. CYCLE 1, DAY 1 AND DAY 2 INFUSION OVER 4 HOURS

Cycle 1	Ublituximab Dose	Total Volume To Be Infused	Infusion Rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
Day 1	150 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H
Day 2	750 mg	500 mL	10 mL/H	20 mL/H	85 mL/H	200 mL/H

TABLE 13. CYCLE 1, DAY 8 AND DAY 15 INFUSIONS OVER 3 HOURS

Ublituximab Dose	Total Volume To Be Infused	Infusion Rate		
		T0 to T1H	T1H to T2H	T2H to T3H
900 mg	500 mL	50 mL/H	150 mL/H	300 mL/H

TABLE 14. CYCLE 2 AND REMAINING INFUSIONS OVER 90 MINUTES

Ublituximab Dose	Total Volume To Be Infused	Infusion Rate	
		T0 to T30'	T30' to T90'
900 mg	500 mL	200 mL/H	400 mL/H

8.5.1.3 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or his/her representative must check that the ublituximab is in accordance with the product specifications and the validity is within the retest date.

The exact dose and the date and time of administration of ublituximab must be recorded within the eCRF, subject's medical records, and/or in the drug accountability records.

The pharmacist or his/her representative should record the date dispensed and subject ID, as well as complete the accountability record in the electronic drug accountability system with information concerning the dispensation of ublituximab. Preparation should be done by the pharmacist or his/her representative according to instructions for sterile dilution.

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).

8.5.1.3.1 DILUTIONS OF UBLITUXIMAB

Ublituximab should not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. [redacted]

TABLE 15. [redacted]

Dose of ublituximab for infusion	[redacted]
Cycle 1 Day 1: 150 mg	
Cycle 1 Day 2: 750 mg	

- Withdraw appropriate volume of ublituximab from the vial as per table above
- [redacted]
- 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 16. [redacted]

Dose of ublituximab for infusion	[redacted]
Cycle 1 Day 1: 150 mg	
Cycle 1 Day 2: 750 mg	

TABLE 17. [redacted]

Dose of ublituximab for infusion	[redacted]
900 mg	

Days 8 and 15 of Cycle 1 and Day 1 of Cycles 2 and on

- [redacted]
- If not used immediately, diluted solutions must be refrigerated. After allowing the diluted bag to come to room temperature, use immediately.
- Mix diluted solution by gentle inversion prior to use. Do not shake or freeze.

8.5.2 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB

- *Method of Administration:* Umbralisib will be administered orally once daily with food
- *Potential Drug Interactions*: No drug interactions have been reported to date
- *Pre-medications:* Subjects are required to start prophylaxis treatment for *Pneumocystis jiroveci* pneumonia (PJP) and antiviral therapy prior to Cycle 1 Day 1. Choice of PJP and

antiviral prophylaxis is per Investigator discretion and institutional SOC, with the following as recommendations:

- *Antiviral Prophylaxis*: Valacyclovir (Valtrex®) 500 mg daily or Acyclovir 400 mg BID or equivalent
- *PJP Prophylaxis:* Dapsone 100 mg daily or equivalent

If antiviral or antifungal prophylaxis is not tolerated, we recommend alternating to a different prophylactic agentor modifying the schedule for the prophylactic agent, or discontinuing prophylaxis at Investigator discretion. Final choice of PJP and antiviral prophylaxis therapy is per Investigator discretion. Umbralisib will be dispensed at the sites by the research coordinator or designee under the direction of the PI or by a pharmacist at the site. Subjects must be provided drug in its original container. Subjects should be instructed to return any unused tablets when they return the bottle to the site. Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the subjects' medical record.

Umbralisib will be self-administered (by the subject). On Cycle 1 Days 1 and 2, when ublituximab will be administered, umbralisib should be administered prior to ublituximab pre-medication. Tablets should be taken at approximately the same time each day with food. Subjects should be instructed to swallow the tablets whole. Do not chew or crush umbralisib.

If a dose of umbralisib is missed, it should be taken as soon as possible on the same day. If it is missed for a period greater than 12 hours, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

8.5.2.1 DISPENSING OF UMBRALISIB

Before dispensing, the site pharmacist or his/her representative must check that the umbralisib is in accordance with the product specifications and the validity is within the retest date.

The exact dose and the date of administration of umbralisib must be recorded within the eCRF, subject's medical records, and/or in the drug accountability records. For the purpose of drug accountability and compliance, an umbralisib subject diary will be provided. Any error in drug administration should be recorded (e.g., missed dose) in the eCRF.

The pharmacist or his/her representative should record the date dispensed and subject's number, as well as complete the accountability record in the electronic drug accountability system with information concerning the dispensation of umbralisib.

8.5.2.2 DOSE HOLD/MODIFICATION: UMBRALISIB

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experiences a treatment-related AE requiring dose modification during the course of therapy, then study drug administration should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. In addition, the subject should be notified of the change in dose and the appropriate clinic staff should instruct the subject about the revised number of study medication tablets to be used per dose according to the new dose level. Any questions regarding dose modification should be referred to TG Therapeutics.

The adjunctive supportive care recommendations listed in the dosing hold and modification tables are meant to serve as guidelines and are not meant to replace Investigator discretion. Final toxicity

management decisions are the responsibility of the clinical Investigator. However, adherence to study drug dose hold, dose reduction, and dose discontinuation criteria are strongly advised for patient safety reasons. Please contact the Sponsor with any questions related to managing side effects, holding treatment or other dose modifications. If a subject discontinues only one study drug, the subject may continue treatment with the other study drug(s) per the protocol. Please see Table 22 for further guidance.

TABLE 18. STUDY DRUG DOSE REDUCTION RECOMMENDATIONS

Study Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Umbralisib	800 mg	600 mg	400 mg

A maximum of 2 dose level reductions are allowed for umbralisib.

If a subject requires a dose reduction of umbralisib due to study drug-related AE, the dose may not be re-escalated. If further evaluation of the toxicity reveals the AE was not related to umbralisib, this must be recorded in the medical record and dose re-escalation to the next higher dose level may be considered at the discretion of the Investigator.

8.5.3 GUIDELINES FOR ADMINISTRATION OF VENETOCLAX

- *Method of Administration:* Venetoclax will be administered orally once daily with a meal and water
- *Potential Drug Interactions*: Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during ramp-up phase. Please see the full FDA-approved prescribing information for the most up to date guidance regarding dosage modifications for concomitant use with strong or moderate CYP3A inhibitors or P-gp inhibitors.
- *Pre-medications:* See Table 19 for recommended TLS prophylaxis based on tumor burden from clinical trial data

U.S.: Venetoclax will be sourced by the clinical site using locally marketed product.

The vendor and lot information for each subject if available, may be requested by the Sponsor. Compliance should be reviewed with the subject at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the subjects' medical record. A subject diary will also be provided for the purpose of drug accountability and compliance.

Venetoclax will be self-administered (by the subject). If the subject misses a dose of venetoclax within 8 hours of the time it is usually taken, they should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the next day. If the subject vomits, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

8.5.3.1 TUMOR LYSIS SYNDROME

Venetoclax can cause rapid reduction in tumor and thus poses a risk for tumor lysis syndrome (TLS) in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all subjects and correct pre-existing abnormalities prior to initiation of treatment with venetoclax. Reduced renal function (creatinine clearance <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf). See venetoclax full prescribing information.

TABLE 19: REQUIRED TLS PROPHYLAXIS BASED ON TUMOR BURDEN FROM VENETOCLAX PACKAGE INSERT

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments[c, d]
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CrCl <80 mL/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x 10^9/L AND Any LN ≥5 cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.
[a] Administer intravenous hydration for any subject who cannot tolerate oral hydration.
[b] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

[c] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d] For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

8.5.3.2 PROHIBITED MEDICATIONS AND FOODS

Please see the venetoclax package insert for the most up to date information regarding drug interactions and contraindications, which can be found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf.

Strong CYP3A Inhibitors

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

For subjects who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Moderate CYP3A Inhibitors and P-gp Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors or P-gp inhibitors with venetoclax. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax by at least 50%. Monitor subjects more closely for signs of venetoclax toxicities (Venetoclax prescribing information, 2017).

Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

Avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax, as they contain inhibitors of CYP3A.

CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers or moderate CYP3A inducers. Consider alternative treatments with less CYP3A induction.

8.5.3.3 DOSE HOLD/MODIFICATION: VENETOCLAX

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experiences a treatment-related AE requiring dose modification during the course of therapy, then study drug administration should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. In addition, the subject should be notified of the change in dose and the appropriate clinic staff should instruct the subject about the revised number of study medication tablets to be used per dose according to the new dose level. Any questions regarding dose modification should be referred to TG Therapeutics. Please see Table 22 for further guidance.

If a subject discontinues only one study drug, the subject may continue treatment with the other study drug(s) per the protocol.

TABLE 20. DOSE MODIFICATIONS OF VENETOCLAX BASED ON LABORATORY PARAMETERS

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at reduced dose.
		For any events of clinical TLS[a], resume at a reduced dose following resolution.
[a] Clinical TLS is laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.		

Please refer to the US prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf) and www.venetoclax.com for the most up to date information including warnings and precautions, adverse reactions, and boxed warnings.

TABLE 21: DOSE MODIFICATION FOR TOXICITY DURING VENETOCLAX

Dose at Interruption, mg	Restart Dose Reduction, mg
400	300
300	200
200	100
100	50
50	20
20	10
During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.	

8.5.4 DOSE HOLD/MODIFICATION: UBLITUXIMAB, UMBRALISIB AND VENETOCLAX

Table 22 illustrates the dose hold and modifications for all investigational products in the present study.

Subjects should be assessed clinically for toxicity at each visit using the NCI CTCAE v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf) grading scale.

Dose hold and/or modification guidance is for adverse events considered *related* to the study drug(s). If the adverse event is *not considered related* to a study drug (ublituximab, umbralisib and/or venetoclax), then that drug does not need to be modified or held as per Investigator assessment.

If cytopenias are deemed related to the underlying disease rather than study drug, dose modifications are not required, or are per investigator discretion. If a subject discontinues one or more study drugs, the subject may continue treatment with the other study drug(s) per the protocol.

Dose reduction and/or holds are permitted as per Investigator discretion to manage adverse events related to one or more of the study drugs. The guidelines below are recommendations and are not meant to replace Investigator discretion.

TABLE 22. STUDY DRUG MODIFICATIONS

	Ublituximab	Umbralisib	Venetoclax
NCI CTCAE Grade			
Neutropenia			
Grade 1-2 neutropenia	Maintain full dose. Consider growth-factor support as warranted.	Maintain current dose. Consider growth-factor support as warranted.	Maintain current dose. Consider growth-factor support as warranted.
Grade 3 neutropenia	Maintain full dose. For recurrent or persistent Grade 3 neutropenia hold ublituximab until Grade ≤2, then resume. Consider growth-factor support as warranted.	Maintain current dose. If recurrence or persistent Grade 3, hold umbralisib until Grade ≤ 2 and resume at same dose. Consider growth-factor support as warranted.	Maintain current dose, if Grade 3 recurs or is persistent then hold venetoclax until ≤ Grade 2, after resume at the same dose. Consider growth-factor support as warranted.
Grade 4 neutropenia or occurrence of Neutropenic fever or infection	Hold ublituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; consider growth factor support as warranted; thereafter, resume at full dose	Hold umbralisib until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose. Consider growth-factor support as warranted. If recurrence after rechallenge despite maximum supportive care, hold umbralisib until ≤ Grade 3; thereafter resume umbralisib at next lower dose level.	Hold venetoclax until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume venetoclax at current dose. Consider growth-factor support as warranted. If recurrence after rechallenge despite maximum supportive care, hold venetoclax until ≤ Grade 3; thereafter resume venetoclax at next lower dose level.
Thrombocytopenia			

	Ublituximab	Umbralisib	Venetoclax
	Ublituximab	**Umbralisib**	**Venetoclax**
Grade 3 thrombocytopenia	Maintain full dose.	Maintain current dose.	Maintain current dose.
Grade 4 thrombocytopenia	Hold ublituximab until Grade ≤ 3; thereafter resume at full dose.	Hold umbralisib until Grade ≤3; thereafter, resume umbralisib at current dose. If recurrence after rechallenge despite maximum supportive care, hold umbralisib until ≤ Grade 3; thereafter resume umbralisib at next lower dose level.	Hold venetoclax until Grade ≤3; thereafter, resume venetoclax at current dose. If recurrence after rechallenge despite maximum supportive care, hold venetoclax until ≤ Grade 3; thereafter resume venetoclax at next lower dose level.
Infection (including opportunistic infection)			
	Ublituximab	**Umbralisib**	**Venetoclax**
Grade 2 infection	Consider dose hold and/or supportive care as per investigator discretion.	Consider dose hold and/or supportive care as per investigator discretion.	Consider dose hold and/or supportive care as per investigator discretion.
Grade 3 or 4 infection	Withhold ublituximab until resolved, then resume at full dose.	Withhold umbralisib until resolved, then resume at same or reduced dose.	Withhold venetoclax until resolved, then resume at same or reduced dose.
PJP	For suspected, PJP, withhold ublituximab until evaluated. Provide supportive care, once resolved resume at full dose.	For suspected, PJP, withhold umbralisib until evaluated. Provide supportive care, once resolved resume at same dose.	For suspected, PJP, withhold venetoclax until evaluated. Provide supportive care, once resolved resume at same dose.
CMV infection or viremia	Withhold ublituximab, until infection or viremia resolves, provide supportive anti-viral therapy as warranted, then resume at full dose.	Withhold umbralisib, until infection or viremia resolves, provide supportive anti-viral therapy as warranted, then resume at same or reduced dose.	Withhold venetoclax, until infection or viremia resolves, provide supportive anti-viral therapy as warranted, then resume at same or reduced dose.

Diarrhea / Colitis			
	Ublituximab	**Umbralisib**	**Venetoclax**
Grade 2 diarrhea	Maintain full dose.	Maintain current dose of umbralisib, if tolerable, or hold and then resume at current dose level once has resolved. Consider supportive care. NOTE: If persistent Grade 2 diarrhea, despite supportive care, hold umbralisib until ≤ Grade 1. If recurrence after rechallenge, hold umbralisib until ≤ Grade 1; thereafter resume at current dose or next lower dose level at discretion of the Investigator.	Refer to venetoclax prescribing information.
Grade ≥ 3 diarrhea	Maintain full dose.	Administer supportive care. Hold umbralisib until Grade ≤2; thereafter, resume umbralisib at reduced dose. If severe diarrhea recurrence after rechallenge discontinue umbralisib.	Refer to venetoclax prescribing information.
Grade ≤ 2 colitis	Maintain full dose.	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at same or next lower dose level.	Refer to venetoclax prescribing information.
Grade 3 or 4 colitis	Maintain full dose.	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level. If recurrence after dose	Refer to venetoclax prescribing information.

		reduced and rechallenge discontinue umbralisib.	
AST (SGOT), ALT (SGPT), Bilirubin elevation			
	Ublituximab	**Umbralisib**	**Venetoclax**
Grade 1	Maintain full dose.	Maintain current dose. Assess Concomitant Medications and Risk Factors*. Monitor Labs every 1-2 weeks.	Refer to venetoclax prescribing information.
Grade 2	Maintain full dose	Maintain current dose. Assess Concomitant Medications and Risk Factors*. Begin supportive care (prednisone orally 0.5-1.0 mg/kg/day or equivalent, per Investigator discretion)*. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone. If liver toxicity recurs to Grade 2 once off steroids, re-initiate steroids and consider withholding umbralisib.	Refer to venetoclax prescribing information.
Grade ≥ 3	Withhold ublituximab until Grade ≤ 2; thereafter, resume at full dose.	Hold umbralisib. Assess Concomitant Medications and Risk Factors*. Begin/continue supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent, per	Refer to venetoclax prescribing information.

		Investigator discretion)**. Monitor labs at least weekly until Grade 1. Once resolved to Grade ≤1, taper prednisone. Resume umbralisib at next lower dose level when Grade ≤1.	

*Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc.
**Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc.
Important: Before initiating steroids, check for viral hepatitis or CMV infection.

If Grade 4 anaphylaxis is observed at any point during ublituximab treatment, permanently discontinue ublituximab treatment and intervene as per Investigator discretion.

If a subject requires a dose reduction of umbralisib due to study drug-related toxicity, the dose may not be re-escalated. If further evaluation of the toxicity reveals the event was not related to umbralisib, this must be recorded in the medical record and dose re-escalation to the next higher dose level may be considered at the discretion of the Investigator.

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experiences a treatment-related AE requiring dose modification during the course of therapy, then study drug administration should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree.

9 STUDY MEDICATION OVERVIEW AND SAFETY

9.1 UBLITUXIMAB

Chemical Name: ublituximab

Other Names: TG-1101

Classification: Recombinant chimeric anti-CD20 monoclonal antibody (mAb)

Mode of Action: Targets CD20 antigen on B cells

Description: Ublituximab is a genetically engineered chimeric mAb directed against the CD20 antigen found on the surface of B lymphocytes. It is composed of a murine variable region fused onto human constant regions.

How Supplied: Concentration of 25 mg/mL in 6 mL (150 mg) single use vials or 36mL (900mg) single use vials

Storage: Ublituximab vials must be stored in a secured limited-access refrigerated area at a temperature ranging from +2°C to + 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 polyvinyl 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 must not be frozen. Temperature should be monitored, documenting minimum and maximum daily.

Retest dates are provided via the electronic drug accountability system.

Route of Administration: Intravenous

Packaging: Ublituximab is packed in kits. Each kit contains:

- 6 vials containing 150 mg solution
  or
- One vial containing 900 mg solution

Availability: Ublituximab is available from TG Therapeutics.

The Investigator's Brochure (IB) is the primary source for safety information. The ublituximab IB includes a summary of AE data and discussion on potential risks and AEs of special interest that have been observed or may be predicted to occur with these study drugs. Refer to the most recent IB, which is updated periodically, for current information available on ublituximab.

Refer to the IB and pharmacy manual for the most up to date information.

9.2 UMBRALISIB

Chemical Name:	umbralisib
Other Names:	TGR-1202
Classification:	Phosphatidylinositol-3-Kinase (PI3K) delta inhibitor
Formulation:	See Investigator Brochure
Mode of Action:	Inhibits activity of the Class I Delta isoform of PI3K and Casein Kinase 1 Epsilon
How Supplied:	200 mg tablets
Storage:	Store at 20°C – 25°C. Excursions permitted from 15°C to 30°C.
Stability:	Retest dates will be provided periodically via the electronic drug accountability system.
Route of Administration:	Oral
Packaging:	Umbralisib is provided in bottles each containing 30 tablets
Availability:	Umbralisib is available from TG Therapeutics

The IB is the primary source for safety information. The umbralisib IB includes a summary of AE data and discussion on potential risks and AEs of special interest that have been observed or may be predicted to occur with these study drugs. Refer to the most recent IB, which is updated periodically, for current information available on umbralisib. Refer to the IB and pharmacy manual for the most up to date information.

9.3 UBLITUXIMAB + UMBRALISIB SAFETY INFORMATION

The IB is the primary source for safety information. The ublituximab and umbralisib IBs include a summary of AE data and discussion on potential risks that have been observed or may be predicted to occur with these study drugs. Refer to the most recent IBs, which are updated periodically, for current information on ublituximab and umbralisib.

9.4 VENETOCLAX

Chemical Name:	venetoclax
Classification:	BCL-2 inhibitor
Formulation:	See Prescribing Information
How Supplied:	10, 50, and 100 mg tablets

Storage: Store at or below 86°F (30°C)

Route of Administration: Oral

Packaging: Venetoclax is stored either in a wallet containing blister packs or a bottle

Availability: Venetoclax is commercially available from Abbvie Inc. and Genentech USA, Inc.

9.4.1 ADVERSE REACTIONS REPORTED IN > 10% (ANY GRADE) OF SUBJECTS WITH CLL/SLL

Please refer to the US prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf) and www.venetoclax.com for the most up to date information including warnings and precautions, adverse reactions, and boxed warnings.

- **Blood and lymphatic systems disorders:** Neutropenia, anemia, thrombocytopenia, lymphopenia, febrile neutropenia
- **Gastrointestinal disorders:** Diarrhea, nausea, abdominal pain, vomiting, constipation
- **General disorders and administration site conditions:** Fatigue, pyrexia, edema
- **Infections and infestations:** Upper respiratory tract infection, pneumonia, lower respiratory tract infection
- **Musculoskeletal and connective tissue disorders:** Musculoskeletal pain, arthralgia
- **Nervous system disorders:** Headache, dizziness
- **Respiratory, thoracic, and mediastinal disorders:** Cough, dyspnea
- **Skin and subcutaneous tissue disorders:** Rash

9.4.2 ADVERSE REACTIONS OF TLS AND RELEVANT LABORATORY ABNORMALITIES REPORTED IN SUBJECTS WITH CLL/SLL

TABLE 23. ADVERSE EVENTS OBSERVED IN SUBJECTS WITH CLL/SLL

Parameter	All Grades (%) N=66	Grade ≥3 (%) N=66
Laboratory TLS[a]	6	6
Hyperkalemia[b]	20	2
Hyperphosphatemia[b]	15	3
Hypocalcemia[d]	9	3
Hyperuricemia[e]	6	2

[a]Laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L; or were reported as TLS events.
[b]Hyperkalemia/blood potassium increased.
[c]Hyperphosphatemia/blood phosphorus increased.
[d]Hypocalcemia/blood calcium decreased.
[e]Hyperuricemia/blood uric acid increased.

Please refer to the US prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf) and www.venetoclax.com for the most up to date information including warnings and precautions, adverse reactions, and boxed warnings.

10 MEASUREMENT OF EFFECT

10.1 MEASUREMENT OF EFFECT AND METHOD OF ASSESSMENT

The determination of response and progression will be based on iwCLL criteria (Hallek et al., 2018). Radiographic and clinical tumor assessments will be subject to independent confirmation by the IRC in subjects enrolled to the Phase 3 stage of the study.

Subjects will be assessed for response/progression by physical examination and laboratory tests. In addition, at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from SD to PR, or from PR to CR, imaging should be performed to confirm the response. Conversely, imaging is required to document suspected PD by physical examination or suspected based on symptoms.

CT scan with contrast is the preferred method for radiographic tumor assessment. MRI scanning may be used at the Investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, PET, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless medically contraindicated.

Subjects will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. For Phase 3 subjects, if PD is suspected, scans and relevant clinical data should be sent to central radiology for expedited PD review. This PD confirmation should be obtained prior to subject being removed for PD (except in rare cases where it is in the patients best interest to be discontinued immediately). Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression as per the protocol.

10.2 RESPONSE REVIEW

An IRC will provide a review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumor status.

Please see imaging manual for detailed instructions for tumor assessment and submission of scans for independent review.

10.3 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

10.3.1 TARGET LESIONS

At baseline, up to 6 lymph nodes should be selected as target lesions that will be used to quantify the status of the disease during study treatment. Ideally, the target lesions should be located in disparate regions of the body.

Target lesions will be measured and recorded at baseline and as per the study assessment schedule. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each target lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each target lesion and the sum of the products (SPD) (in cm^2) for all target lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL/SLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a measurable nodal target lesion if it is ≥ 1.5 cm in long axis diameter and > 1.0 cm in short axis diameter. At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be considered.

A new node that measures ≥1.5 cm in the longest diameter (LD) will be considered progressive disease.

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

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

10.3.2 SPLEEN AND LIVER

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

By imaging, the spleen will be considered enlarged if it is >13 cm in LVD, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5 cm thickness, the LVD is recorded as 7 cm).

For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen at baseline or nadir, not changes relative to the total splenic LVD.

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the spleen in its LVD or decrease to ≤ 13 cm by imaging is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% from nadir (minimum increase of 2 cm) is required for declaration of splenic progression. By imaging, the liver will be considered enlarged if it is >18 cm in LVD.

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the liver in its LVD or decrease to ≤ 18 cm is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥ 50% from nadir (minimum increase of 2 cm) is required for declaration of hepatic progression.

Splenic and/or hepatic progression, if the only criteria for PD, must be documented by CT/MRI scan.

10.3.3 NON-TARGET LESIONS

Any other measurable and abnormal nodal lesions not selected for quantitation as target lesions may be considered non-target lesions. In addition, non-measurable evidence of CLL/SLL such as nodal lesions with both diameters <1.0 cm, extra-nodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-target disease.

The presence or absence of non-target disease should be recorded at baseline and as per the study assessment schedule. If present at baseline, up to 6 non-target lesions should be recorded. The non-target disease at baseline will be used as a general reference to further characterize regression or progression of CLL/SLL during assessments of the objective tumor response during treatment. Measurements are not required, and these lesions should be followed as “present” or “absent”.

10.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized as CR, CRi, nPR, PR, SD, or PD. In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status, and partial response with lymphocytosis (PR-L) for subjects who have an elevated absolute lymphocyte count but otherwise meet all criteria for a PR.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started).

10.4.1 COMPLETE RESPONSE

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

- No evidence of new disease
- ALC in peripheral blood of <4 x 10^9/L
- Regression of all nodal masses to normal size <1.5 cm in the LD
- Normal spleen and liver size
- No constitutional symptoms

- Cytological or pathological evaluation of the BM smear or biopsy must be at least normocellular for age, without evidence for typical CLL/SLL lymphocytes by morphological criteria. This evaluation is not based on a flow cytometry–based MRD assessment
- Peripheral blood counts meeting all the following criteria:
  - ANC ≥1.5 x 10^9/L without need for exogenous growth factors (e.g., G-CSF);
  - Platelet count ≥100 x 10^9/L without need for exogenous growth factors;
  - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin);

10.4.2 COMPLETE RESPONSE WITH INCOMPLETE MARROW RECOVERY (CRi)

Subjects who fulfill all the criteria for a CR (including BM criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular BM that is related to prior or ongoing drug toxicity (and not to CLL/SLL) will be considered as a CR with incomplete marrow recovery (CRi).

10.4.3 PARTIAL RESPONSE

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

- No evidence of new disease;
- A change in disease status meeting ≥2 of the following criteria, with the exception that if only 1 parameter was abnormal before therapy, only 1 needs to improve:
  - In a subject with baseline lymphocytosis (ALC ≥4 x 10^9/L), a decrease in peripheral blood ALC by ≥50% from baseline; or a decrease to <4 x 10^9/L;
  - A decrease by ≥50% from the baseline in the SPD of the target nodal lesions and no new enlarged lymph nodes (diameter ≥ 1.5cm);
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 10.3.2;
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 10.3.2;
  - A decrease by ≥50% from baseline in the CLL/SLL marrow infiltrate or in B-lymphoid nodules.
- No target, splenic, liver, or non-target disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting 1 of the following criteria:
  - Platelet count >100 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors;
  - Hemoglobin >110 g/L (11.0 g/dL) or ≥50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin).

10.4.4 PARTIAL RESPONSE WITH PERISTENT LYMPHOCYTOSIS (PR-L)

Subjects who fulfill all the criteria for a PR but have not had a decrease in peripheral blood ALC by ≥50% from baseline or a decrease to <4 x 10^9/L will be considered as a PR with persistent lymphocytosis (PR-L).

10.4.5 STABLE DISEASE

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

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

10.4.6 DEFINITIVE DISEASE PROGRESSION

The occurrence of any of the following events indicates definitive PD when compared with nadir values:

- Evidence of any new disease:
  - A new node that measures ≥1.5 cm in the LD;
  - An increase by ≥50% in greatest determined diameter of any previous site (≥1.5 cm);
  - New or recurrent splenomegaly, with LVD > 13 cm;
  - New or recurrent hepatomegaly, with LVD > 18 cm; Unequivocal reappearance of an extra-nodal lesion that had resolved;
  - A new unequivocal extra-nodal lesion of any size;
  - *New non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL).

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

- Evidence of worsening of target lesions, spleen or liver, or non-target disease:
  - Increase from the nadir by ≥50% from the nadir in the SPD of target lesions;
  - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of ≥1.5 cm;
  - Splenic progression, defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and LVD >13 cm);
  - Hepatic progression, defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and LVD >18 cm);
  - Unequivocal increase in the size of non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL/SLL);
  - Transformation to a more aggressive histology (e.g., Richter's syndrome) as established by lymph node or other tissue biopsy (with the date of the biopsy being considered the date of CLL/SLL progression if the subject has no earlier objective documentation of CLL/SLL progression).

- Occurrence of cytopenias (decrease in platelet count or hemoglobin) directly attributable to CLL/SLL and unrelated to autoimmune cytopenias confirmed by BM biopsy showing an infiltrate of clonal CLL/SLL cells
  - The current platelet count is <100 x 10^9/L and there has been a decrease by ≥50% from the highest on study platelet count at least 3 months after treatment;
  - The current hemoglobin is <110 g/L (11.0 g/dL) and there has been a decrease by ≥20 g/L (2 g/dL) from the highest on study hemoglobin at least 3 months after treatment.

If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation pending confirmation of progression. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL/SLL

will not be considered definitive disease progression; in such subjects, both CLL/SLL-related and non-CLL/SLL-related causes for the constitutional symptoms should be considered.

Worsening of disease during temporary interruption of study treatment (e.g., for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. Subjects who meet the criteria for PD at any assessment may, in consultation with the Study Chair, remain on study for confirmation of PD at the following disease assessment. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL/SLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

10.4.7 NON-EVALUABLE

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

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

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

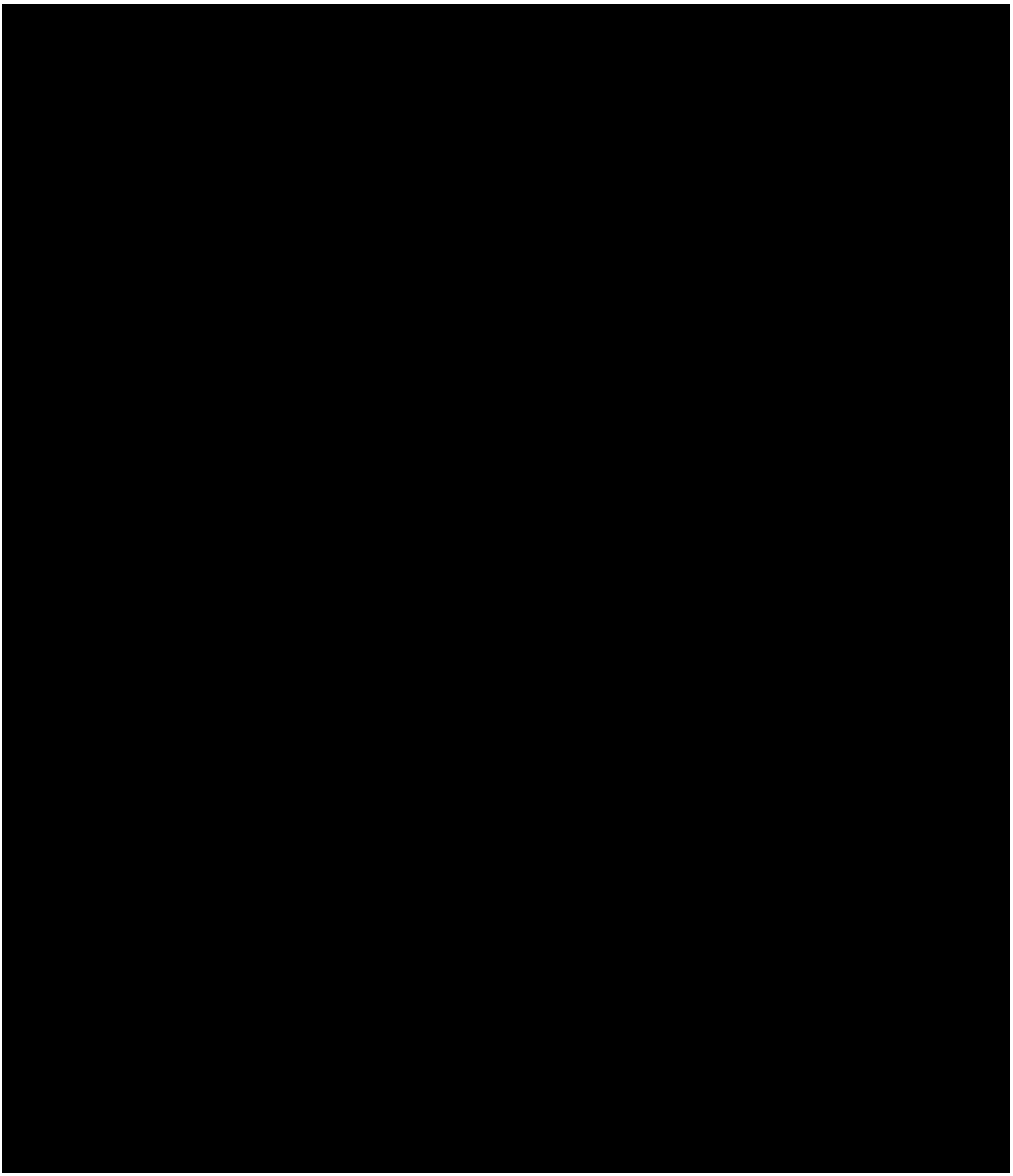
10.4.8 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of umbralisib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above ALC of 5,000/mcL) may occur. The onset of isolated lymphocytosis usually occurs during the first few weeks of umbralisib therapy and usually resolves within 3 to 4 months. Subjects with lymphocytosis in the absence of other signs of progression should be continued on study drug until the occurrence of definitive disease progression (i.e., disease progression that is manifest by worsening CLL/SLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy.

11 STATISTICAL CONSIDERATIONS

Details of the analyses will be provided in the Statistical Analysis Plan.

11.1 SAMPLE SIZE AND POWER



[redacted]

11.2 GENERAL ANALYSIS CONVENTION

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher.

Summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries will present data by cohort and overall, if appropriate. The data listings will include all available efficacy and safety data.

11.3 ANALYSIS POPULATION

The safety population will consist of all subjects who received at least one dose of study drug (ublituximab, umbralisib, or venetoclax). For the Phase 2 component, the ITT population will consist of all subjects who received at least one dose of each study drug (ublituximab, umbralisib, and venetoclax).

For Phase 3, the ITT population will consist of all randomized subjects, regardless of administration of study treatment. Analyses of this population will assign subjects the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications. Subjects who received treatment in the group that is different from what they have been randomized to, will be noted in the clinical study report. The ITT population is the primary analysis population for efficacy analyses.

The per protocol population will include all ITT subjects without major protocol violations. Major protocol violations will be documented. Analyses based on per protocol population may be performed.

11.4 SUBJECT DISPOSITION

Subject disposition summaries will include the number and percentage of enrolled/randomized subjects in the safety, ITT, and per protocol populations. The summaries will also include the reasons for permanent discontinuation of study treatment and study.

11.5 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures. The analyses of baseline characteristics will be performed for the ITT population.

11.6 MEDICAL HISTORY

Medical history will be captured at the screening visit. Medical history will be coded using MedDRA and will be summarized by MedDRA system organ class and preferred term for the safety population.

11.7 EXTENT OF EXPOSURE

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

11.8 EFFICACY ANALYSES

Each subject will be assigned to one of the following categories: 1) CR (including CRi), 2) PR, 3) PR-L, 4) SD, 5) PD, 6) early death from malignant disease, 7) early death from toxicity, 8) early death because of other cause, or 9) unknown (not assessable, insufficient data).

Many of the efficacy measures will be based on disease assessments. The best clinical response as well as disease progression may be assessed by an IRC. Definitive disease progression will be based on standard criteria (Hallek et al., 2018) occurring for any reason (e.g., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than treatment-related lymphocytosis.

11.9 SAFETY ANALYSES

Safety analyses will be performed using the safety population. Safety analyses will be primarily based on the incidence, severity, and type of AEs, as well as on clinically meaningful laboratory results, physical examination, and vital signs as available. Safety variables will be tabulated and presented by the dose of ublituximab, umbralisib, and/or venetoclax actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

Detailed information collected for each AE will be included in a listing: AE term, start/stop dates of the AE, seriousness, severity, relationship to study drug(s), action taken, and outcome. In addition, the number and percentage of subjects experiencing at least one treatment-emergent AE will be tabulated by body system, preferred term, and CTCAE grade. Treatment-emergent AEs, drug-related AEs, AESIs, SAEs, AEs with a fatal outcome, and AEs leading to discontinuation/dose modification will be further summarized. Summary statistics for actual values and for changes from baseline will be tabulated for clinical laboratory results by scheduled visit. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized and graded per NCI CTCAE Version 5.0 as applicable. Subject incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

11.10 MISSING VALUE HANDLING PROCEDURES

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter and are presented in the Statistical Analysis Plan.

11.11 STATISTICAL ANALYSES

11.11.1 PRIMARY EFFICACY VARIABLES

11.11.1.1 PROGRESSION-FREE SURVIVAL (PHASE 3)

PFS is defined as the number of days between randomization and the date of progression (as confirmed by the IRC) or death due to any cause, whichever occurs first. Subjects who had no event (progression or death) will be censored at the day of their last adequate disease assessment. If no baseline or post-baseline assessment is available, the subject will be censored at the date of randomization. If death or PD occurs after 2 or more consecutive missing disease assessments, censoring will occur at the date of the last adequate disease assessment prior to the missed assessments. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last adequate disease assessment prior to initiation of new therapy.

Hypothesis testing for comparison between the treatment arms will be performed using a stratified (by randomization stratification factors) log-rank test via SAS Lifetest procedures. For each treatment arm, the median duration of PFS and the proportion of subjects alive and progression-free at 6, 12, 24, and 36 months will be estimated using the Kaplan-Meier method. For each estimate, a 95% confidence interval will be reported. The hazard ratio with 95% confidence interval will be estimated by stratified (by randomization stratification factors) Cox proportional hazards model.

Sensitivity analyses will be conducted, including using investigator assessment of PFS, using different censoring rules (ignoring new anti-cancer therapy, ignoring 2 or more consecutive missing assessments). In addition, the potential impact of COVID-19 on patients for the efficacy results may be included in the sensitivity analysis (censoring all subjects at the last adequate assessment if subject discontinued study or death due to COVID-19). Other sensitivity analyses may be conducted as needed.

11.11.1.2 COMPLETE RESPONSE RATE (PHASE 2)

CR rate is defined as the percent of subjects who achieve a CR or CRi. Estimated CR rate with exact 95% confidence interval based on Clopper-Pearson method will be presented for the Phase 2 component.

11.11.1.3 OVERALL RESPONSE RATE (PHASE 2)

ORR will be determined according to the criteria of the iwCLL (Hallek et al., 2018).

ORR is defined as percent of subjects who achieve CR, CRi, PR or PR-L. Estimated ORR with exact 95% confidence interval based on Clopper-Pearson method will be presented for the Phase 2 component.

11.11.2 SECONDARY EFFICACY OUTCOMES

11.11.2.1 MINIMAL RESIDUAL DISEASE NEGATIVITY

The MRD negativity rate is defined as the proportion of subjects who achieve MRD negative status post-baseline. Subjects who do not have an MRD assessment at any post-baseline visits will be considered non-responders and will be included in the denominator when calculating MRD negativity rate. Estimated MRD negativity rate with exact 95% confidence interval based on Clopper-Pearson method will be presented for the Phase 2 component, while the Phase 3 will utilize a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors.

11.11.2.2 DURATION OF RESPONSE

DOR defined as the interval from the first documentation of CR, CRi, PR or PR-L to the earlier of the first documentation of definitive disease progression or death from any cause. This variable will be analyzed using Kaplan-Meier method for responders only. The estimated median DOR with 95% confidence interval will be presented.

11.11.2.3 TIME TO RESPONSE (TTR)

TTR is defined as the interval from enrollment to first documentation of CR, CRi, PR, or PR-L. TTR will be analyzed via Kaplan-Meier method.

11.11.2.4 COMPLETE RESPONSE RATE

For the Phase 3 portion of the study, CR rate will be analyzed using a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters.

11.11.2.5 OVERALL RESPONSE RATE

For the Phase 3 portion of the study, ORR rate will be analyzed using a CMH test stratified by the randomization factors. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters.

11.11.2.6 OVERALL SURVIVAL

Overall Survival (OS) is defined as the interval from randomization to death from any cause. As subjects are expected to survive for a long time relative to the duration of the study, OS analysis may not be reliable due to heavily censored data. OS data will be censored at the last documented date that the subject is confirmed alive for subjects who withdraw consent or are lost to follow-up prior to the end of the study, and for subjects whose vital status in the study cannot be determined. The Kaplan-Meier estimator for OS will be presented for all subjects in the ITT population. An interim analysis of OS will occur at the time of the PFS analysis, and a final OS analysis will occur 1 year after the PFS analysis.

11.11.3 INTERIM ANALYSES

One interim analysis is planned for each of the Treatment Naïve and Previously Treated cohorts during the conduct of the study to assess efficacy and safety of U2-V compared with U2 and to allow for release of the results earlier than the planned final analysis in case of significant difference in treatment effect in favor of U2-V.

For the Treatment Naïve cohort, the interim analysis will be performed when approximately 115 PFS events have occurred in both treatment arms combined (67% of the 172 events required for the final primary efficacy analysis). The stopping boundary is based on a Lan-DeMets O'Brien Fleming type spending function. Based on 115 events, the duration of PFS will be tested at the interim analysis, approximately corresponding to a 1-sided p-value of 0.00618 (HR of 0.65). If the number of events is not exactly 115 by the time of the analysis, then the boundary will be updated to reflect the number of events.

For the Previously Treated cohort, the interim analyses will be performed when approximately 82 PFS events have occurred in both treatment arms combined (67% of the 122 events required for the final primary efficacy analysis). The stopping boundary is based on a Lan-DeMets O'Brien Fleming type spending function. Based on 82 events, the duration of PFS will be tested at the interim analysis, approximately corresponding to a 1-sided p-value of 0.00618 (HR of 0.60). If the number of events is not exactly 82 by the time of the analysis, then the boundary will be updated to reflect the number of events.

The DSMB will evaluate efficacy and safety data at the interim analyses and recommend if the study result for each individual cohort should be released early. The same stratification factors as specified in the primary efficacy endpoint analysis will be used. For each of the treatment naïve and previously treated cohorts individually, if the p-value of the stratified 1-sided log-rank test is ≤ 0.00618 for the IRC-assessed PFS analysis and the observed HR is favorable for the U2-V combination treatment, the cohort will have shown statistically significantly longer duration of PFS in the U2-V arm and will have met its primary efficacy endpoint. The results are expected to be presented to the health authorities for potential registrational purposes.

The final primary efficacy analyses for each cohort will be performed when approximately 172 PFS events and 122 PFS events have been observed in the treatment naive and previously treated cohorts,

respectively, where PFS will be tested at the significance level of approximately 0.0462 (two-sided), corresponding to detecting an HR of ≤ 0.74 or less for the treatment naïve cohort and an HR of ≤ 0.70 or less for the previously treated cohort. If necessary, the statistical test level will be adjusted to incorporate the alpha spent at the interim analysis so that the overall type I error rate will be maintained at the 2-sided 0.05 level.

11.11.4 MULTIPLICITY OF PHASE 3 PART

In the efficacy analyses, the following gatekeeping procedures will be implemented to preserve the overall type I error rate across the primary and secondary endpoints of the Phase 3 part of the study at a 2-sided significance level of 0.05.

The type I error control is applied separately to the two cohorts of the study (the treatment naïve cohort and the previously treated cohort) as they are intended to be conducted and analyzed independently and have independent powering.

The primary endpoint PFS analysis will serve as the gatekeeper for the secondary endpoint analyses, i.e., the primary efficacy hypothesis must be rejected before the efficacy hypotheses for the secondary efficacy endpoints can be evaluated.

The secondary endpoints will be sequentially tested at the 2-sided 0.05 significance level in the following order:

- Complete Response (CR) Rate
- Rate of Undetectable Minimal Residual Disease (uMRD)
- Overall Response Rate (ORR)
- Overall Survival (OS)

If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints. Note, CR Rate, uMRD, and ORR will only be tested once either at the interim or final analysis depending on the outcome of the PFS analysis.

11.11.5 STOPPING RULES

For the Phase 3 portion of the study the following stopping rules will be followed:

- >2 treatment-related Grade 5 events of the same preferred term;
- >5% of enrolled patients discontinuing all therapies due to a treatment-related hematologic toxicity of the same preferred term; OR
- >5% of enrolled patients discontinuing all therapies due to a treatment-related non-hematologic toxicity of the same preferred term.

12 ADVERSE EVENT REPORTING AND CRITERIA

12.1 DEFINITION OF ADVERSE EVENT

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition. An AE can occur at any time, including during screening, run-in or washout periods, even if no study treatment has been administered. It is the responsibility of the Investigator, based on their knowledge and experience, to determine which untoward medical occurrences should be considered AEs.

12.2 CRITERIA FOR SERIOUS ADVERSE EVENTS (SAE)

The definitions of SAEs are described below. The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that meets at least one of the following criteria:

- **Results in death:**
  In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome “Fatal”. The death itself will not be reported as an SAE, unless the cause of the death is unknown (e.g., in case of unexplained or sudden death);
- **Is life-threatening:**
  The term "life-threatening" refers to an event in which the subject is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization;**
- **Results in persistent or significant disability/incapacity;**
  A disability is defined as any substantial disruption of a subject’s ability to conduct normal life functions;
- **Is a congenital anomaly/birth defect; and/or**
- **Is medically important.**
  Medical and scientific judgement must be exercised in deciding whether an AE is considered “medically important”. Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of disease (including fatal outcomes), if documented by use of appropriate method (for example, as per IWCLL Hallek et al., 2018), should not be reported as a SAE.

Situations Not Considered SAEs:

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported i.e., could meet the definition of important medical event):

- Emergency Department or Emergency Room;
- Hospitalization for drug administration, diagnostic procedure, or social circumstances;
- Outpatient or same day surgery units;
- Observation or short-stay unit;
- Rehabilitation facility;
- Hospice or skilled nursing facility;
- Nursing homes, Custodial care or Respite care facility.

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the Sponsor, but if hospitalization is prolonged due to an event this would be reportable to Sponsor or designee.

Serious Versus Severe AEs:

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

12.2.1 ADVERSE EVENT/SERIOUS ADVERSE EVENT GRADING

The NCI CTCAE v5.0 is to be used for the grading of severity of AEs.

For AEs not covered by the NCI CTCAE grading system, the following definitions should be used:

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

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2.2 ADVERSE EVENTS / SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the causal relationship of any AE to the study drug(s) (whether no study drug, monotherapy or combination therapy was administered), based on available information, using the following guidelines:

- **Not Related**: Clear cut temporal and/or mechanistic relation to a cause other than the study drug(s)
- **Doubtful**: There is no reasonable possibility that the event is related to the study drug(s) but a definite cause cannot be ascertained
- **Possible**: There is still a reasonable possibility that the cause of the event was the study drug(s) but there exists a more likely cause of the event such as complications of progressive disease
- **Probable**: The most likely cause of the event is the study drug(s) but other causes cannot be completely excluded
- **Definite:** Clear cut temporal and/or mechanistic relation to the study drug(s). All other causes have been eliminated. Events classified as definite will often be confirmed by documenting resolution on discontinuation of the study drug and recurrence upon resumption

12.2.3 ADVERSE EVENT/SERIOUS ADVERSE EVENT RECORDING

All non-serious AEs regardless of relationship to the study drugs are to be recorded on the eCRF from Cycle 1/Day 1 until 30 days after discontinuation or completion of protocol-specific treatment. . Immune-related AE (irAEs) are to be recorded on the eCRF from Cycle 1/Day 1 until 90 days after study discontinuation or completion of protocol-specific treatment. All AEs must include the Investigator's assessment of the event's seriousness, severity, and causality to study drug.

All serious AEs (i.e. SAEs) regardless of relationship to the study drug(s) are to be recorded on the eCRF and the SAE Report Form from signing of informed consent until 30 days after discontinuation or completion of protocol-specific treatment. Immune-related SAEs (irSAEs) are to be recorded on the eCRF and SAE Report Form from signing of informed consent until 90 days after study discontinuation or completion of protocol-specific treatment. All SAEs must include the Investigator's assessment of the event's seriousness, severity, and causality to study drug.

If an AE is deemed by the Investigator as serious, as per the SAE criteria, it should be reported **as soon as possible and no later than 24 hours** of awareness to the Sponsor or designee using the SAE Report Form and recorded within the same timeframe on the eCRF. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported **as soon as possible but no later than 24 hours** to the Sponsor or designee using the SAE Report Form and recorded on the eCRF. SAEs should be followed until resolution (including results of an autopsy report, if applicable). The Investigator must review and sign off on the data on the SAE Report Form

and transmission of the SAE Report Form should be confirmed by the site personnel submitting the form.

Disease progression or death due to disease progression should be reported by the Investigator as a SAE **only** if it is assessed that the study drugs caused or contributed to the disease progression (i.e., by a means other than lack of effect). Unrelated events of CLL/SLL progression should be captured on the appropriate eCRF and not on the AE eCRF.

Other untoward events occurring in the framework of the study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study drug that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs (non-serious and serious) resulting in discontinuation should be followed until resolution or stabilization of the event for up to 30 days (for any AEs/SAEs) or 90 days (for irAEs/irSAEs) as part of the study follow-up period. All new AEs (non-serious and serious) occurring during the follow-up period must be reported and followed until resolution unless, in the Investigator's judgement, these are not likely to improve due to the underlying disease.

After the 30-day (for any AEs/SAEs) or 90-day (for irAEs/irSAEs) follow-up period, only AEs and SAEs, which include death, assessed by the Investigator as drug-related are to be reported in the eCRF or SAE Report Form, as applicable.

After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug.

Investigators must report SAEs and follow-up information to their responsible IRBs/Independent Ethics Committee (IEC) according to the policies of the responsible IRB/IEC.

Investigators should use correct medical terminology/concepts and avoid colloquialisms and abbreviations when recording AEs or SAEs on the eCRF and/or SAE Report Form.

12.2.3.1 ABNORMAL LABORATORY VALUES, PHYSIOLOGICAL RESULTS, AND VITAL SIGNS

Abnormal laboratory values, physiological test results (e.g., QTc prolongation in electrocardiogram [ECG]), or vital signs should not be reported as an AE unless any criterion for an SAE is fulfilled, if it results in the subject to discontinue study drug, if it is associated with an overdose, or in the Investigator's judgement the abnormality should be reported as an AE.

If an abnormal finding is associated with a clinical sign and/or symptom, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

12.3 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

12.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the eCRF. If a persistent AE becomes more severe (changes from a Grade 1 or 2 AE to a Grade 3 or 4 AE) or lessens in severity (changes from a Grade 3 or 4 AE to a Grade 1 or 2 AE), it should be recorded on a separate SAE Report Form and/or eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or eCRF for each recurrence.

12.5 DEATHS

Deaths that occur during the protocol-specified AE reporting period and are attributed by the Investigator solely to progression of the subject's disease progression for up to 30 days post the last dose of study drug will be recorded on the appropriate study eCRF and **not** reported on the AE page of the eCRF and will be exempted from SAE reporting.

All other on-study deaths (i.e. not solely attributed to CLL/SLL progression), will be reported to the Sponsor or designee on an SAE Report Form and recorded on the AE page of the eCRF.

When recording the death as an SAE, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF AE page.

12.6 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission or prolongs hospitalization should be documented and reported as an SAE. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. See Section 12.2.1 Serious Adverse Event Criteria.

12.7 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing relevant medical condition is one that is present at the start of the study. Such conditions should be recorded on the study's appropriate medical history eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the appropriate SAE Report Form and/or eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

12.8 PREGNANCY

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the study, all female subjects of child-bearing potential (the definition of females of child-bearing potential are listed in Appendix A - Contraception Guidelines) 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 subject may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the subject must not receive any study drug(s) and must be discontinued from the study.

If an Investigator suspects that a subject may be pregnant after the subject has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the subject must be discontinued from the study, and the Investigator must notify the Study Chair or Medical Monitor within 24 hours of awareness.

Pregnancy should be recorded on a Pregnancy Report Form and reported by the Investigator to the Sponsor or designee in the same timeframe (within 24 hours of awareness) as reporting an SAE.

The Pregnancy should be followed up to 6 months after the end of the pregnancy, which can include birth, spontaneous abortion, or voluntary termination, to collect the outcome with details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, as applicable. Follow-up to a pregnancy should be recorded on a Pregnancy Report Form and should include an assessment of the causal relationship to the study drug and reported by the Investigator to the Sponsor or designee. Pregnancy outcomes must be reported for the female partners of any males who took study drug on the Pregnancy Report Form. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Any SAE experienced during pregnancy must be reported on the SAE Report Form. Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be reported as an SAE using the previously described process for SAE reporting.

12.9 STUDY DRUG OVERDOSE

Symptomatic and asymptomatic overdose must be reported in the appropriate eCRF. Any accidental or intentional overdose with any of the study drug(s) that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor or designee immediately (within 24 hours of awareness) using the SAE Report Form, and following the same process described for SAEs. If a study

drug overdose occurs, subjects should stop study drug and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

13 CLINICAL DATA COLLECTION AND MONITORING

13.1 DATA AND SAFETY MONITORING BOARD

For the Phase 3 randomized stage of this study, an independent Data Safety Monitoring Board (DSMB) will be established to advise the Sponsor on safety and provide benefit/risk oversight of the study. This independent DSMB will meet approximately every 6-9 months to review the AEs, SAEs, and safety trends (if any) depending on enrollment. The DSMB will recommend changes in the protocol conduct or corrective actions as necessary. They may advise the Sponsor to terminate the study early or modify the protocol to address safety signals or benefit/risk concerns that they may identify. Relevant output from the DSMB meetings will be archived in the TGTX trial master file or designated controlled location.

13.2 SITE MONITORING PLAN

A study initiation site visit, a teleconference and/or a planned Investigator meeting will be performed to review Investigator responsibilities and protocol requirements. During the study, the Sponsor or Sponsor delegate will make visits to the sites as defined in the monitoring plan in order to review protocol compliance, examine eCRFs, laboratory data, safety data, and individual subject medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements.

Site monitoring shall be conducted to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

13.3 CURRICULA VITAE AND FINANCIAL DISCLOSURES

All Principal Investigators will be required to submit to the Sponsor or its designee a current signed curriculum vitae (CV), , and a completed FDA form 1572 (or equivalent) and financial disclosure statement. In addition, all sub-investigators will be required to submit to the Sponsor or its designee a current signed CV, and a completed financial disclosure statement.

13.4 DATA OWNERSHIP AND PUBLICATION

The results of and all data generated during the conduct of this study belong to the Sponsor, are considered Sponsor's proprietary and confidential information, and are subject to the confidentiality provisions in the Clinical Trial Agreement (CTA) governing the participation of the Investigator in the study. Sponsor retains the sole and exclusive right to the first publication of the results of this study. Such publication is intended to be a multi-center publication, collected from all investigators and institutions participating in the study rather than publication based on individual site data. Any manuscripts, abstracts, or other presentation materials generated by Investigator must be reviewed and approved by the Sponsor prior to submission as set forth in the CTA and must meet all other applicable conditions set forth in the CTA.

14 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

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

14.1 IRB APPROVAL

The study protocol, ICF, IB, available safety information, subject-facing documents (e.g., study diary), advertisements), information about payments (i.e., PI payments) and compensation available to the subjects and documentation evidencing the PI's qualifications must be submitted to the IRB per their guidelines for ethical review and approval prior to the study start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document.

Premature termination of this study may occur at the discretion of the Sponsor due to a safety concern, or a regulatory authority or ethics committee decision. If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects.

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

14.2 REGULATORY APPROVAL

As required by local regulations, the Sponsor will ensure approval of the appropriate regulatory bodies is obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

Safety updates for ublituximab and/or umbralisib will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

14.3 INSURANCE AND INDEMNITY

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

14.4 INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are

relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the Investigator to the subject. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

If an amendment to the protocol substantially alters the study design or the potential risks to the subjects, the subject's consent to continue participation in the study must be obtained.

14.5 CONFIDENTIALITY

Subject Confidentiality

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. To protect the personal data of subjects, Sponsor will assign a unique study number to each subject, which will be used on the eCRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Participant names or other information that would make the participant identifiable will not be entered in the eCRF or database or transferred in other documents submitted to Sponsor. No material bearing a subject's name will be kept on file by the Sponsor.

Subjects will be informed of their rights within the ICF. HIPAA regulations require that, in order to participate in the study, the subject should be informed of following:

What protected health information (PHI) will be collected from subjects in this study;

- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the study;

- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of study-related procedures and data. The subject must be informed about the potential for this type of monitoring and auditing access.

14.6 INVESTIGATOR AND STAFF INFORMATION

Personal data of the investigators and sub-investigators may be included in the Sponsor database and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

14.7 FINANCIAL INFORMATION

The finances for this study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

15 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

15.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

The Sponsor/Sponsor designee will ensure that documentation is required to be in place before the study may start, in accordance with FDA regulations and/or local regulatory authorities, ICH E6, and Sponsor SOPs will be available before any study sites are initiated..

Documents at a minimum required to begin the study include, but are not limited to, the following:

- A signature authorized protocol and contract;
- A copy of the official IRB approval of the study and the IRB members list or assurance verification;
- Current Curricula Vitae for the principal Investigator and any associate Investigator(s) who will be involved in the study;
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory;
- Form FDA 1572 (Statement of Investigator), or equivalent appropriately completed and signed;
- A copy of the IRB-approved consent form
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- GCP Certificate for study training;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

15.2 STUDY DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the subject's eCRF are to be supported by source documentation .

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, EKG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Site Study File/SSF or ISF) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF

must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP and 8 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, IRB approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug s.. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

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

If the Investigator relocates, retires, or for any reason withdraws from the study, either the Sponsor or its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Sponsor. The Investigator must obtain the Sponsor written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study and will be transferred to the Sponsor at the conclusion of the study.

15.3 AMENDMENTS TO THE PROTOCOL

If an amendment to the protocol is required, the amendment will be originated by the Sponsor and approved by the Sponsor and the Study Chair. The written amendment must be submitted to the IRB/Ethics at the investigator's facility for the approval per IRB/Ethics requirements.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable.

If an amendment to the protocol substantially alters the study design or the potential risks to the subjects, their consent to continue participation in the study should be obtained.

15.4 DATA COLLECTION

The study eCRF is the primary data collection instrument for the study. An electronic case report form will be utilized for the collection of all data and all data will be entered using the English language and should be kept current to enable the monitor to review the subjects' status throughout the course of the study.

In order to maintain confidentiality, only study number, subject number, and partial date of birth will identify the subject in the eCRF. The Investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

15.5 STUDY MONITORING, AUDITING, AND INSPECTING

The Investigator will permit study-related monitoring, quality audits, and inspections by government regulatory authorities, the Sponsor or its representative(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or QA reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

15.6 QUALITY ASSURANCE AND QUALITY CONTROL

Independent auditing may be conducted during the conduct of the study to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to GCP and applicable regulations.

Each study site shall be required to have processes that enable compliant study conduct, and investigator oversight of data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

Accurate and reliable data collection will be ensured by verification and cross check of the eCRFs against the investigator's records by the study monitor (source document verification) Collected data

will be entered into a computer database and subject to electronic and manual quality assurance procedures.

15.7 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. By conducting this study, the Investigator affirms to the Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including the results of and data generated from this study, except as exempted for regulatory purposes.

A clinical study report will be prepared upon completion of the study. The format of the clinical study report will comply with ICH E3 guidelines for structure and content of a clinical study report. The Sponsor will comply with any applicable local laws/regulations regarding the posting of study results.

The financial disclosure information will be provided to the Sponsor prior to study participation from all PIs and Sub-Investigators who are involved in the study and named on the FDA 1572 form.

All data generated during the conduct of this study is owned by the Sponsor and may not be used by the Investigator or affiliates without the expressed written consent of the Sponsor.

All manuscripts, abstracts, or other presentation materials generated by site investigators must be reviewed and approved by the Sponsor prior to submission as set forth in the clinical trial agreement (CTA) governing the Investigator or his/her institution's participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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17 APPENDIX A - CONTRACEPTION GUIDELINES

Female Not of Child-bearing Potential are Defined as Follows:

Women 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 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least 6 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.

Contraception Guidelines for Females of Child-Bearing Potential:

Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 4 months after the last treatment dose of ublituximab and for at least 30 days after last treatment dose of umbralisib or venetoclax. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
4. Oral contraception, injected or implanted hormonal methods.
5. Use of a combination of any 2 of the following (a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for females of child-bearing potential:

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

Females of child-bearing potential must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment.

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 treatment dose of ublituximab and for at least 30 days after last treatment dose of umbralisib or venetoclax, and should not father a child in this period.

18 APPENDIX B – NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

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.

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.

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20 APPENDIX D – CYP3A INDUCERS, CYP3A INHIBITORS, P-GP INHIBITORS AND P-GP SUBSTRATES

Examples of clinical **inhibitors** for P450-mediated metabolisms

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

Examples of clinical **inducers** for P450-mediated metabolisms

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

Examples of clinical **substrates** for transporters

Transporter	Substrate
P-gp	dabigatran, digoxin, fexofenadine

Examples of clinical **inhibitors** for transporters

Transporter	Substrate
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil