Official Title: A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax

NCT Number: NCT04016805

Document Date: Protocol Version 2.0: 30-July-2020

Protocol Version: Version 2.0

Protocol Identifier: UTX-TGR-208

TITLE:
A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax

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

IND Number: 114,779

Study Chair: [redacted], MD
[redacted]
Tel: [redacted]

Medical Monitor: [redacted], MD
TG Therapeutics Inc.
Tel: [redacted]

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

Version: 1.0 **Date:** April 01, 2019
Version: 2.0 **Date: 30 July 2020**

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol UTX-TGR-208 for issuance.

Protocol Title:	A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax
Protocol Identifier:	UTX-TGR-208
Study Drugs:	Cohort A: Ublituximab and Umbralisib and Ibrutinib Cohort B: Ublituximab and Umbralisib and Venetoclax Cohort C: Ublituximab and Umbralisib and Acalabrutinib
IND Number:	114,779
Date Final:	30 July 2020

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted], MD — Print Name

DocuSigned by: [redacted] — Signature

Signer Name: [redacted] MD
Signing Reason: I approve this document
Signing Time: 13-Aug-2020 | 7:49:18 AM PDT

13-Aug-2020 — Date

STUDY CHAIR, [redacted]

[redacted], MD — Print Name

Signature — Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted] — Print Name

DocuSigned by: [redacted] — Signature

Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-Aug-2020 | 12:01:04 PM EDT

10-Aug-2020 — Date

[redacted], MS, MSF — Print Name

DocuSigned by: [redacted] — Signature

Signer Name: [redacted], MS,MSF
Signing Reason: I approve this document
Signing Time: 16-Aug-2020 | 10:42:23 PM EDT

16-Aug-2020 — Date

[redacted], PhD, RN — Print Name

DocuSigned by: [redacted] — Signature

Signer Name: [redacted] PhD,RN
Signing Reason: I approve this document
Signing Time: 24-Aug-2020 | 8:51:28 AM EDT

[redacted]e — Date

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol UTX-TGR-208 for issuance.

Protocol Title:	A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax
Protocol Identifier:	UTX-TGR-208
Study Drugs:	Cohort A: Ublituximab and Umbralisib and Ibrutinib Cohort B: Ublituximab and Umbralisib and Venetoclax Cohort C: Ublituximab and Umbralisib and Acalabrutinib
IND Number:	114,779
Date Final:	30 July 2020

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted], MD

Print Name | Signature | Date

STUDY CHAIR, [redacted]

[redacted], MD — 8/11/2020

Print Name | Signature | Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted]

Print Name | Signature | Date

[redacted], MS, MSF

Print Name | Signature | Date

[redacted], PhD, RN

Print Name | Signature | Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax
Protocol Number:	UTX-TGR-208
IND Number:	114,779
Date Final:	30 July 2020

I have read the attached protocol and agree that it contains all the necessary details for performing the trial. 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 ublituximab, and umbralisib, as well as ibrutinib, acalabrutinib, and venetoclax, and the conduct of the study.

Once the protocol has been approved by the 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) including all amendments up to and including the Washington Clarification (2002).

Print Name	Signature	Date

TABLE OF CONTENTS

1 SUMMARY OF AMENDMENTS

Version 2.0 (Dated 30 July 2020) of this protocol contains the following modifications:

- [redacted]
- Addition of Arm C: Ublituximab, umbralisib and acalabrutinib, updated protocol throughout to reflect the addition of this cohort.
- Exclusion #2 updated for clarity
- Re-treatment study schema added
- Protocol updated to correct grammatical errors throughout
- Protocol updates throughout to clarify study procedures for treatment, treatment-free observation and re-treatment
- Re-Treatment Study Schema added
- Cycle 21 ublituximab dose added during initial treatment.
- Study Assessment tables updated with the following
    - EOT removed and Treatment-Free Observation table added
    - [redacted]
    - Long-term follow up added for patients that come off re-treatment for reasons other than progression of disease
    - Re-treatment CMV surveillance updated to correct a typo and to be done every 3 cycles
- Section 11 Safety Analyses added
- Section 12 Adverse Event Reporting and Criteria updated for added clarity and to be in alignment with TG Therapeutics processes and procedures

STUDY SYNOPSIS

Protocol no.	UTX-TGR-208
Study Title	A Phase 2 Study to Assess the Efficacy and Safety of Ublituximab and Umbralisib in Subjects with Chronic Lymphocytic Leukemia (CLL) Currently Treated with Ibrutinib, Acalabrutinib or Venetoclax
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Chair	[redacted], MD
IND #	114,779
Study Sites & Enrollment	• This multi-center study may be carried out in up to approximately 8 centers • Enrollment is expected to take approximately 24 months
Study Rationale	This study is a Phase 2 open label, two treatment cohort trial evaluating addition of ublituximab and umbralisib on the rate of U-MRD in subjects with CLL who fail to achieve undetectable minimal residual disease (U-MRD) after a minimum 6-month treatment with ibrutinib, acalabrutinib or venetoclax in the front-line or relapsed or refractory setting. Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib and acalabrutinib, as well as venetoclax, a B-cell lymphoma-2 (BCL-2) inhibitor, have improved survival over previous standard of care in patients with CLL. However, depth of response to these agents is variable. Undetectable MRD, a marker of deep response, has been recognized as a meaningful endpoint as it predicts progression-free and overall survival. U-MRD is an accepted primary study endpoint in pivotal trials. In this study, investigational agents targeting anti-CD20 and dual inhibitor, phosphoinositide-3-kinase delta (PI3Kδ) and CK-1 epsilon, ublituximab and umbralisib, respectively, will be used in combination with existing therapy ibrutinib or venetoclax with the goal of achieving deeper responses and higher rates of U-MRD. Subjects will have the opportunity to discontinue study treatment and enter a period of treatment-free observation with retreatment upon disease progression.

	Ublituximab is a glycoengineered monoclonal antibody 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 is a highly-specific and orally available dual inhibitor of PI3Kδ and CK-1 epsilon with nanomolar inhibitory potency and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin and strongly upregulated in various hematologic malignancies. Given the non-overlapping mechanisms of action of these agents, the combination of ublituximab and umbralisib was explored in a Phase I/Ib study in subjects with previously treated hematologic malignancies (Lunning ASH 2015). The combination regimen was well tolerated with ublituximab administered at doses up to 900 mg per infusion, and umbralisib administered at doses up to 1200 mg daily. Clinical activity was noted in a variety of hematologic malignancies with responses reported in subjects with CLL and non-Hodgkin lymphomas. To date, over 1000 subjects have been treated with ublituximab and/or umbralisib in various clinical trials. The combination of ibrutinib and ublituximab has been shown to be safe and highly active in a Phase II study (Sharman, BJH 2016). Further, triplet therapy with ibrutinib, ublituximab, and umbralisib has been studied in subjects with CLL and NHL. This combination was well tolerated with an overall response rate of 100% in 19 subjects with CLL (Nastoupil, Lancet Haematology 2019). Ublituximab and umbralisib are being studied in combination with venetoclax in an actively enrolling study (NCT03379051). In this trial, study eligible subjects who have received at least 6 months of treatment with ibrutinib, acalabrutinib or venetoclax and remain MRD positive, will add ublituximab and umbralisib to their current treatment regimen (ibrutinib, acalabrutinib or venetoclax). Assessment of MRD will occur to determine the ability of these regimens to induce deep remission. Following achievement of U-MRD or completion of 24 Cycles without PD, subjects will enter a period of treatment-free observation. Should subjects progress during the treatment free observation period and require treatment per iwCLL criteria, retreatment will occur with the same triple therapy that induced the initial U-MRD response. Subjects who progress within 6 months of treatment free observation will be considered refractory and discontinue from the study.

	Unlike other studies of three or four novel agent combinations in CLL, subjects in this study will be selected based on failure to achieve U-MRD. This approach will prevent overtreatment of subjects who can achieve deep remission with fewer agents. Additionally, this design is unique in that subjects will be treated until achieving U-MRD with a strategy of treatment discontinuation based on depth of response. Durability of remission following discontinue of treatment will then be monitored with sequential MRD assessments.
Study Objectives	**PRIMARY OBJECTIVES** ○ To assess the rate of undetectable minimal residual disease (U-MRD) in subjects with CLL treated with the combination of ublituximab and umbralisib with either venetoclax, ibrutinib or acalabrutinib **SECONDARY OBJECTIVES** ○ To assess safety and tolerability of ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib ○ To determine the time to U-MRD at planned sequential response assessments ○ To determine progression-free survival and time to second objective disease progression from time of initiation of ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib ○ To determine the durability of clinical benefit after treatment discontinuation as measured by duration of peripheral blood U-MRD response and treatment-free survival ○ To determine the overall response rate, complete response rate, U-MRD rate, and PFS to re-treatment with ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib in subjects who progress following achievement of U-MRD followed by treatment-free observation. 

Inclusion Criteria	Subjects must meet all the following inclusion criteria to be eligible for participation in this study. Eligibility criteria must be met at screening and at Cycle 1 Day 1 prior to dosing. 1. Subjects with CLL who are currently receiving treatment with ibrutinib, acalabrutinib or venetoclax for greater than or equal to 6 months. 2. Minimal residual disease (MRD) positive (D-MRD) as determined by central lab performed during the screening period. a. For subjects receiving venetoclax: response assessment demonstrating stable disease, partial response, or complete response following initiation of current venetoclax therapy AND detectable MRD in the peripheral blood (central lab). b. For subjects receiving ibrutinib or acalabrutinib: response assessment demonstrating stable disease, partial response or partial response with lymphocytosis, or complete response AND detectable MRD in the peripheral blood (central lab). 3. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 (µL) / platelet count $\geq$ 50,000/mm^3 (µL). Growth factor to maintain these counts is permitted during screening period and throughout the conduct of the trial. b. Total bilirubin ≤1.5 times the upper limit of normal (ULN), unless a diagnosis of Gilbert's syndrome or an autoimmune hemolytic anemia. 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 modified Cockcroft-Gault formula, MDRD formula, or 24-hour urine CrCl). 4. ECOG performance status ≤ 2. 5. Male or female ≥ 18 years of age. 6. Ability to swallow and retain oral medication. 7. Female subjects who are not of child-bearing potential (see Appendix B- Contraceptive Guidelines and Pregnancy), and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female subject 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 or umbralisib, and for at least 30 days after the last dose of ibrutinib, acalabrutinib or venetoclax.

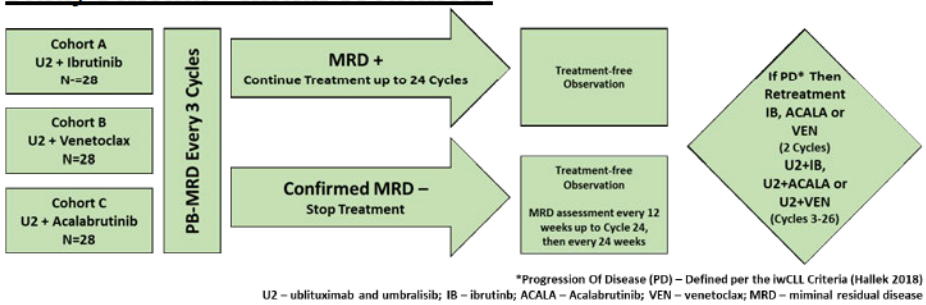
	8. Willingness and ability to comply with trial and follow-up procedures and give written informed consent.
Exclusion Criteria	1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation therapy [excluding palliative radiation to areas not including target/non-target lesion(s)], immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1/Day 1. This does not include ibrutinib, acalabrutinib or venetoclax but does include anti-CD20 therapy. a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted. 2. Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive surface Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. Subjects with positive HBc antibody or HCV antibody are eligible only if PCR is negative for HBV DNA or HCV RNA. 3. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation). 4. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required for subjects on umbralisib. 5. Live virus vaccines within 4 weeks prior to ublituximab therapy. 6. History of anaphylaxis in association with previous anti-CD20 administration. 7. For subjects receiving ibrutinib or acalabrutinib: a. Subjects requiring warfarin therapy. b. Subjects requiring strong CYP3A inhibitors and/or inducers 8. For subjects receiving venetoclax: a. Requirement for use of strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates. 9. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) b. Myocardial infarction within 6 months of enrollment

	c. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion. d. Angina not well-controlled by medication. e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of study enrollment. 10. Malignancy, including myelodysplastic syndromes, myeloproliferative syndromes or melanoma in-situ within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, 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. 11. Women who are pregnant or lactating.
Efficacy Endpoints	**<u>Undetectable Minimal Residual Disease (U-MRD) Rate</u>** U-MRD rate is defined as the proportion of subjects who have undetectable MRD in the peripheral blood as confirmed by central lab. **<u>Time to U-MRD</u>** Time to undetectable minimal residual disease is defined as the interval from enrollment to the first assessment of U-MRD. **<u>Overall response rate (ORR)</u>** ORR is defined as sum of CR and PR rates. **<u>Complete Response (CR) Rate</u>** CR rate is defined as the proportion of subjects who achieve a CR. **<u>Progression-free survival (PFS)</u>** PFS is defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression based on standard criteria (Hallek, et al., 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms). Note that lymphocytosis in

	the absence of other evidence of disease progression does not constitute disease progression. **Time to second objective disease progression (PFS2)** PFS2 is defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression on next-line treatment or death from any cause. Definitive disease progression based on standard criteria (Hallek, et al., 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms). Note that lymphocytosis in the absence of other evidence of disease progression does not constitute disease progression. [redacted] **Duration of U-MRD response** Duration of U-MRD response is defined as the interval from the first documentation of undetectable MRD to the earlier of the first documentation of presence of MRD or death from any cause. **Treatment-free survival (TFS)** TFS is defined as the interval from drug discontinuation to the earlier of initiation of retreatment for disease progression or death from any cause. Disease progression requiring treatment is based on standard criteria (Hallek, et al., 2018)
Safety Endpoints	All Adverse Events (AE's) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v5.0.
Study Design	This study is a Phase 2 open label, two treatment cohort trial evaluating addition of ublituximab and umbralisib on the rate of U-MRD in subjects with CLL who fail to achieve undetectable minimal residual disease (U-

MRD) after a minimum 6-month treatment with ibrutinib, acalabrutinib or venetoclax.

Study Schema – Initial Treatment



*Progression Of Disease (PD) – Defined per the iwCLL Criteria (Hallek 2018)
U2 – ublituximab and umbralisib; IB – ibrutinb; ACALA – Acalabrutinib; VEN – venetoclax; MRD – miminal residual disease

Enrollment

Following screening, qualified subjects will add ublituximab and umbralisib to their existing ibrutinib, acalabrutinib or venetoclax treatment. Any therapy previously given concurrently with ibrutinib, acalabrutinib or venetoclax, including anti-CD20 therapy, must have been discontinued 21 days prior to Day 1 of Cycle 1 (See Exclusion Criterion #1). Determination of enrollment in Cohort A versus Cohort B or Cohort C will depend on which agent the subject was receiving prior to screening (ibrutinib, acalabrutinib or venetoclax).

Three cohorts will be studied:

- **Cohort A:** ublituximab and umbralisib with ibrutinib
- **Cohort B:** ublituximab and umbralisib with venetoclax
- **Cohort C:** ublituximab and umbralisib with acalabrutinib

Up to approximately 28 subjects may be enrolled into each cohort.

Study Duration

MRD status of all subjects will be evaluated during cycles 3, 6, 9, 12, 15, 18, 21, and 24. If subjects achieve U-MRD status in the peripheral blood, MRD will again be assessed by peripheral blood 4 weeks later to confirm U-MRD. Subjects will remain on study treatment through 24 cycles or the occurrence of confirmed U-MRD response in the peripheral blood, after which they will enter a period of treatment-free observation.

Following achievement of U-MRD, subjects will enter a period of treatment-free observation (TFO) with serial MRD assessments every 12 weeks up to Cycle 24 then every 24 weeks thereafter, unless clinically indicated sooner.

Subjects who do not achieve confirmed U-MRD will continue treatment until the completion of 24 cycles of treatment, definitive disease

progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who complete 24 cycles of treatment and remain D-MRD (MRD positive), or those who discontinue study treatment and have not progressed will enter a period of treatment-free observation. Subjects entering treatment-free observation with D-MRD, no PB MRD assessment is required during TFO.

All subjects (whether U-MRD or D-MRD following treatment) who subsequently develop clinical progression requiring treatment per iwCLL criteria (Hallek, et al., 2018) will be retreated with the same triple combination regimen previously received, provided that clinical progression occurs after 6 months of treatment-free observation. Retreatment will not be initiated upon achieving MRD positivity, but only upon clinical progression requiring treatment per iwCLL criteria. Subjects who progress within 6 months of treatment-free observation will be considered refractory and discontinue from the study.

Dosing Regimen & Treatment Study Visits

Cohort A: Ublituximab and Umbralisib with Ibrutinib

Cycle 1:

Ublituximab			Umbralisib	Ibrutinib
Day 1	**Day 2**	**Day 8 & 15**	**Daily**	**Daily**
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Ibrutinib
Day 1	**Daily**	**Daily**
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Ibrutinib
Day 1 of Cycles 9, 12, 15, 18, 21 and 24	**Daily**	**Daily**
900 mg	800 mg	previously tolerated dose

Cohort B: Ublituximab and Umbralisib with Venetoclax

Cycle 1:

Ublituximab			Umbralisib	Venetoclax
Day 1	**Day 2**	**Day 8 & 15**	**Daily**	**Daily**
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Venetoclax
Day 1	**Daily**	**Daily**
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Venetoclax

Day 1 of Cycle 9, 12, 15, 18, 21 and 24	Daily	Daily
900 mg	800 mg	previously tolerated dose

Cohort C: Ublituximab and Umbralisib with Acalabrutinib

Cycle 1:

Ublituximab			Umbralisib	Acalabrutinib
Day 1	Day 2	Day 8 & 15	Daily	Every 12 hours
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

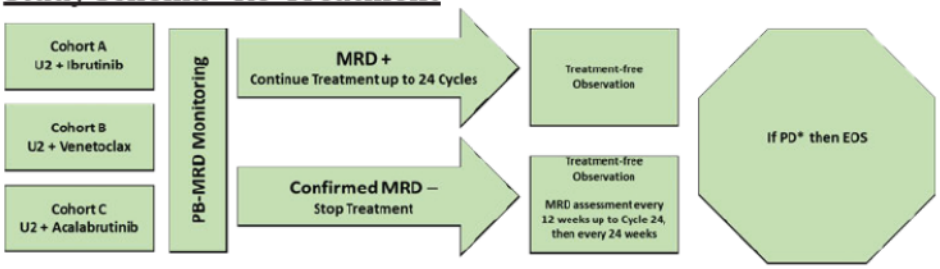
Cycles 2 through 6:

Ublituximab	Umbralisib	Acalabrutinib
Day 1	Daily	Every 12 hours
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Acalabrutinib
Day 1 of Cycles 9, 12, 15, 18, 21 and 24	Daily	Every 12 hours
900 mg	800 mg	previously tolerated dose

Study Schema - Re-Treatment



*Progression Of Disease (PD) – Defined per the iwCLL Criteria (Hallek 2018)
U2 – ublituximab and umbralisib; IB – ibrutinb; ACALA – Acalabrutinib; VEN – venetoclax; MRD – miminal residual disease; EOS – end of study

Retreatment will start with 2 cycles of single agent treatment with ibrutinib, acalabrutinib or venetoclax per the subject's history on study. Umbralisib and ublituximab will be started in Cycle 3 of re-treatment. Subjects will again be evaluated with serial peripheral blood MRD analysis. If subjects achieve U-MRD status in the peripheral blood, MRD will again be assessed by peripheral blood 4 weeks later to confirm U-MRD. Retreatment will continue until the occurrence of confirmed U-MRD response in the peripheral blood, completion of 26 cycles (24 cycles of triplet therapy), definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue study treatment and have not progressed will continue to be followed for disease progression.

Re-treatment schedule as follows:

Cohort A: Ublituximab and Umbralisib with Ibrutinib

Cycles 1 and 2:

Ibrutinib
Daily
Daily at previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 420mg daily).

Cycle 3:

Ublituximab			Ibrutinib	Umbralisib
Day 1	Day 2	Day 8 & 15	Daily	Daily
150 mg	750 mg	900 mg	At appropriate dose based on initial protocol treatment	Previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 800mg daily).

Cycles 4 through 8:

Ublituximab	Ibrutinib	Umbralisib
Day 1	Daily	Daily
900mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cycle 9 through Cycle 26:

Ublituximab	Ibrutinib	Umbralisib
Day 1 of Cycle 11, 14, 17, 20, 23 & 26	Daily	Daily
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cohort B: Ublituximab and Umbralisib with Venetoclax

Cycle 1:

Venetoclax
Day 1-28
Dose escalation per package insert to previously tolerated dose. Investigator discretion may be used to escalate subjects to a target dose that is higher than the dose last tolerated (maximum dose 400mg daily).

Cycle 2:

Venetoclax	
Day 1-7	Day 8-28
Dose escalation per package insert to previously tolerated dose, if applicable. Investigator discretion may be used to escalate subjects to a target dose that is higher than the dose last tolerated (maximum dose 400mg daily).	Tolerated dose per dose escalation

Cycle 3:

Ublituximab			Venetoclax	Umbralisib

Day 1	Day 2	Day 8 & 15	Daily	Daily
150mg	750 mg	900 mg	At appropriate dose based on previous Cycle	Previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 800mg daily).

Cycles 4 through 8:

Ublituximab	Venetoclax	Umbralisib
Day 1	**Daily**	**Daily**
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cycle 9 through Cycle 26:

Ublituximab	Venetoclax	Umbralisib
Day 1 of Cycle 11, 14, 17, 20, 23 & 26	**Daily**	**Daily**
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cohort C: Ublituximab and Umbralisib with Acalabrutinib

Cycle 1:

Ublituximab			Umbralisib	Acalabrutinib
Day 1	**Day 2**	**Day 8 & 15**	**Daily**	**Every 12 hours**
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Acalabrutinib
Day 1	**Daily**	**Every 12 hours**
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Acalabrutinib
Day 1 of Cycles 9, 12, 15, 18, 21 and 24	**Daily**	**Every 12 hours**
900 mg	800 mg	previously tolerated dose

Study Drugs	**Ublituximab** is a 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 highly specific and orally available dual inhibitor PI3K delta (δ) and CK-1 epsilon available in 200 mg tablets, supplied by TG Therapeutics, Inc. **Ibrutinib** is a Bruton's tyrosine kinase inhibitor available [redacted] in 140 mg or 420 mg tablets. **Acalabrutinib** is a kinase inhibitor available [redacted] in 100 mg capsules. **Venetoclax** is a B-cell lymphoma-2 (BCL2) inhibitor available [redacted] in 10 mg, 50 mg, and 100 mg tablets. [redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Definitions of Terms	
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCL-2	B-cell lymphoma-2
BM	Bone Marrow
BTK	Bruton's Tyrosine Kinase
Ca	Calcium
CBC	Complete Blood Cell Count
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CK-1 Epsilon	Casein Kinase-1 Epsilon
Cl	Clearance
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
Cmax	Maximum Concentration
CR	Complete Response
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebro-Vascular Accident
D, d	Day
D-MRD	Detectable Minimal Residual Disease
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicity
[redacted]	
DRG	Data Review Group
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Fc	Fragment crystallizable (region)
FCR	Fludarabine, Cyclophosphamide, Rituximab
FISH	Fluorescence in-situ hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
ITT	Intent-To-Treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia

Abbreviations and Definitions of Terms	
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LPD	Longest Perpendicular Diameter
LTFU	Long-Term Follow Up
MCL	Mantle Cell Lymphoma
MRI	Magnetic Resonance Imaging
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MZL	Marginal Zone Lymphoma
NCI-WG	National Cancer Institute – Working Group
NK	Natural Killer
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate
PCR	Polymerase Chain Reaction
PE	Physical Examination
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PK	Pharmacokinetic
PPD	Perpendicular Diameters
PPS	Per Protocol Set
PR	Partial Response
PI3Kδ	phosphoinositide-3-kinase delta
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
SPD	Sum of the Products
SUV	Standardized Uptake Value
t1/2	Half-Life of Elimination
TFO	Treatment-Free Observation
TTR	Time to response
U-MRD	Undetectable Minimal Residual Disease
ULN	Upper limit of normal
UTX	Ublituximab
V	Visit
Vd	Volume of distribution
WHO	World Health Organization

2 INTRODUCTION

2.1 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic Lymphocytic Leukemia (CLL) accounts for approximately 191,000 cases and 61,000 deaths worldwide each year (Global Burden of Disease Cancer Collaboration, 2017). CLL affects mainly older adults, accounts for one third of all diagnosed cases of leukemia, and is characterized by the accumulation of clonal mature B lymphocytes in the blood, bone marrow, and secondary lymphoid tissues (Lin K, 2002). CLL 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 (Hallek, et al., 2008) (Lin K, 2002). Subjects with 17p deletion show higher resistance to conventional chemotherapy, as well as shorter duration of survival than non 17p deletion subjects. Subjects with 11q deletion have been associated with marked lymphadenopathy (Hallek, et al., 2008). Subjects with *TP53* mutations are associated with adverse clinical outcomes (Lin K, 2002).

Historically, chemotherapy regimens in combination with monoclonal antibody therapy had been standard of care for subjects with CLL. However, novel targeted agents have entered the marketplace and improved clinical outcomes for subjects with CLL. Frontline chemotherapeutic options for subjects with CLL include an anti-CD20 monoclonal antibody in combination with either fludarabine and cyclophosphamide or bendamustine. Depending on the age and comorbidities of the patient, chlorambucil is also considered, though its use within the US has been limited. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, is approved in the front-line setting based on a randomized phase III trial demonstrating superior overall response rate (ORR), progression free survival (PFS), and overall survival (OS) as compared to chlorambucil (Barr, 2016). Acalabrutinib, another Bruton's tyrosine kinase (BTK) inhibitor, was approved by the FDA in the front-line setting for the treatment of subjects with CLL based on safety and efficacy data from two phase III trials (https://www.calquence.com/cll.html). Venetoclax, a BCL-2 inhibitor, either as monotherapy or in combination with rituximab, was approved by the FDA for the treatment of subjects with CLL in the relapsed or refractory setting (https://www.rxabbvie.com/pdf/venclexta.pdf).

Despite these advancements in available therapies, CLL remains an incurable disease, and many subjects will progress and eventually die from their disease. While novel agents including ibrutinib, acalabrutinib, and venetoclax have shifted the paradigm of CLL management, these agents are generally administered with a treat-to-progression approach under the current dosing guidelines, and depth of response is variable. Furthermore, subjects with higher risk cytogenetic abnormalities still present with a less than optimal response to approved therapies with shorter duration of response and shorter progression free survival. As such, there is a pressing need for new, innovative, targeted therapies for the treatment of subjects with relapsed or refractory CLL, especially those with cytogenetic abnormalities.

To address these needs, many studies evaluating combinations of three or four agents are underway. While combination treatment approaches are certainly appropriate in some cases, utilizing these approaches broadly may lead to overtreatment in some subjects who would have achieved deep response with a single agent. This study is designed to address these unmet needs in the treatment landscape of CLL.

2.2 UBLITUXIMAB

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for potent activity, exhibiting a unique glycosylation profile with a low fucose content, designed to induce superior antibody-dependent cytotoxicity (ADCC). Ublituximab exhibits competitive complement-dependent cytotoxicity (CDC), on par with rituximab, and has also been demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies (Esteves IT, 2011).

2.2.1 PRE-CLINICAL EVALUATIONS OF UBLITUXIMAB

2.2.1.1 IN VITRO ACTIVITY

In an in-vitro assay using B-CLL cells from patient donors, ublituximab demonstrated an enhanced ability to kill CLL cells compared to rituximab. Ublituximab demonstrated improved Fcγ receptor IIIA (FcγRIIIA)/CD16 binding and FcγRIIIA dependent effector functions compared to rituximab. Additionally, ublituximab induced higher in vitro ADCC against CLL cells, and a higher FcγRIIIA mediated interleukin-2 (IL2) production by FcγRIIIA and Jurkat cells (de Romeuf C, 2008). Ublituximab demonstrated high ADCC against both patient-derived CLL cells and NHL cell lines. Ublituximab's engagement to FcγRIIIA triggers a stronger NK cell cytotoxicity against CLL as compared to rituximab (in vitro) despite CD20 density, likely related to the glycosylation pattern (de Romeuf C, 2008).

2.2.1.2 IN VIVO ACTIVITY

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

2.2.1.3 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 Ublituximab Investigator Brochure).

2.2.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB – CLL

Ublituximab has been studied in a variety of patient populations, both as a single agent, and in combination with other agents, with over 1,000 subjects having received ublituximab therapy to date across all studies. Two Single-Agent Phase I/Ib trials have been conducted with ublituximab treating both NHL and CLL subjects, with a total of 41 subjects with relapsed or refractory CLL having been treated with single-agent ublituximab (TG-1101). Further, following demonstration of safety and tolerability in these early single agent studies, Phase I and II combination studies were undertaken with a variety of agents. Given the number of subjects who have received ublituximab in early-phase trials, the safety and side effect profile of the agent is well characterized. Summaries of the single-agent experience are provided below, as well as data with use of ublituximab in combination with ibrutinib.

In a two part, first-in human dose escalation study (protocol CD20-0703), subjects with relapsed or refractory CLL received one weekly infusion of single agent ublituximab for 4 doses in a 3+3 dose escalation design through 5 sequential dose levels. Part II of the study was a dose-confirmation component which used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg) – the clinical summary will focus on the Part II part of the study as the dose is more relevant to the clinical application used in current clinical studies. In Part II, 12 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 [1–8]. Seven subjects (58%) received at least one prior rituximab-containing regimen. The median lymphocyte bone marrow infiltration was 85% [40–94].

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

Clinical response was based on the criteria established by the National Cancer Institute (NCI)-Working Group (Hallek, et al., 2008). All subjects but one received the planned 8 infusions without any dose reduction--one patient was prematurely withdrawn due to a

concomitant secondary leukemia unrelated to ublituximab therapy. Response was evaluated at month 4 for the 11 evaluable 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. At the 1-year follow-up, no responders had progressed, demonstrating all confirmed responses were durable despite no ublituximab maintenance therapy. The median progression-free survival (PFS) was not reached at the 12-month follow-up (Cazin B, 2013).

A Phase I trial of ublituximab (Study TG-1101-101; NCT01647971) was subsequently undertaken in subjects with B-cell lymphoma or CLL who were relapsed or refractory to a prior rituximab containing regimen. This trial utilized a 3+3 design, assessing dose levels of 450, 600, 900, and 1200 mg (Sawas A, 2017). Subjects with CLL/SLL received treatment on days 1, 8 and 15 during cycles 1 and 2 (28-day cycles) followed by maintenance ublituximab on day 1 of cycles 3–6, then every 3 months for a maximum of 2 years. Subjects with NHL were treated with the same schedule except for the omission of the Cycle 2 doses. For CLL subjects, Cycle 1 Day 1 infusions were split with up to 150 mg administered on Day 1 and up to 750 mg administered on Day 2. No DLTs were observed, hence no MTD was identified. There was no significant difference in the overall number of AEs among the four dose cohorts. There appeared to be no difference in ORR between 900 and 1200 mg, with a slightly higher incidence of hematological AEs observed (grade 3 neutropenia, anemia, and thrombocytopenia) at the 1200-mg dose level. Hence, 900 mg was selected as the recommended phase 2 dose.

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

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

2.2.2.1 PHARMACOKINETICS

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

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

FIGURE 1: LINEAR MEAN SERUM CONCENTRATION-TIMES PROFILE AFTER THE FIRST, THE FOURTH AND THE EIGHTH INFUSION OF UBLITUXIMAB

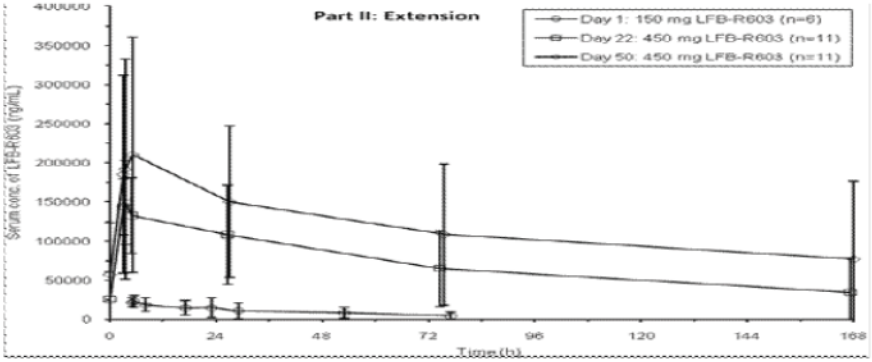


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150 MG), THE 4TH (450 MG) AND THE 8TH (450 MG) INFUSION OF UBLITUXIMAB

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

[a] mean ± SD, t_{max}: median (range) , with respect to the start of infusion *Accurate determination not possible

Concentration was still measurable in at least one patient of the cohort up to day 169. Values for C_{max} and AUC_{∞} increased from the first to the eighth infusion whereas $t_{1/2}$ term decreased.

2.3 UMBRALISIB

Umbralisib is a highly specific and orally available dual inhibitor of phosphoinositide-3-kinase (PI3K) delta (δ) and CK-1 epsilon with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma 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 isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies. Umbralisib has demonstrated safety and efficacy in an ongoing Phase I clinical trial in subjects with a wide variety of relapsed or refractory hematologic malignancies.

2.3.1 PRE-CLINICAL DEVELOPMENT OF UMBRALISIB

The potency of umbralisib against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at its Km value (100 µM) (11). Selectivity over the other three isoforms, namely, α, β, and γ was also determined ([redacted] 2011) ([redacted] AKT phosphorylation in THP-1 cells. Study Report IVT-5264-ATP-08, 2011) ([redacted] AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10, 2011).
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.

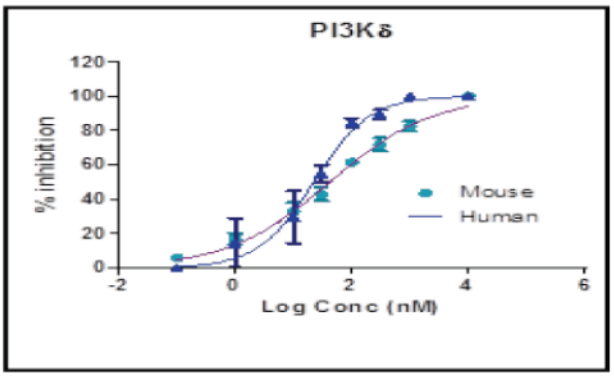


FIGURE 2: UMBRALISIB POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

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

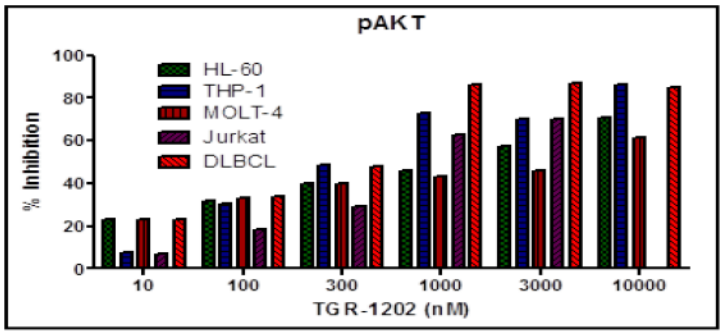
Proliferation of immortalized leukemic cells representative of various indications was determined by a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (17). Cells were incubated with umbralisib for different time-periods (72 -96 h) based on their doubling time. Data demonstrated the ability of umbralisib to inhibit leukemic cell proliferation albeit with different potencies based on the cell type.

Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of umbralisib.

Subsequent to cell viability, the effect of umbralisib on AKT phosphorylation (12, 13, 14, 15, 16) 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.

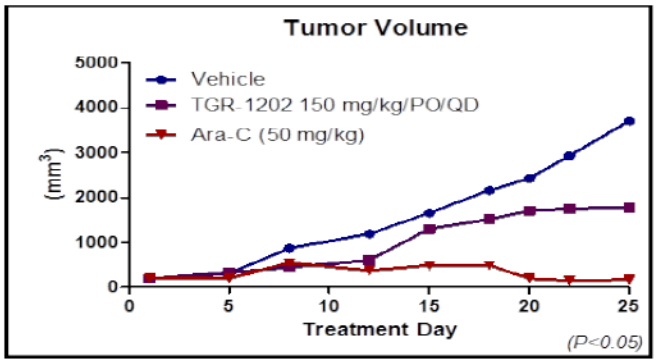
FIGURE 3: REDUCTION OF PAKT BY UMBRALISIB IN CELL LINES BY WESTERN BLOTTING



2.3.1.1 IN-VIVO ACTIVITY

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

FIGURE 4: UMBRALISIB IN VIVO EFFICACY



2.3.1.2 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 oral administration of umbralisib was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at 750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.

Once daily oral administration by capsule of umbralisib was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and

diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species.
Refer to the umbralisib Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

2.3.2 CLINICAL DEVELOPMENT OF UMBRALISIB

2.3.2.1 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 HA, 2018). There were 90 subjects enrolled and eligible for safety evaluation, and 73 subjects evaluable for efficacy in the modified intention to treat population. The median age was 64 years (range 51-72), 63% male, median number of prior therapies was 3, and 49% of subjects were refractory to their most recent prior therapy. Histological diagnoses included; CLL (n=24), FL (n=22), DLBCL (n=16), HL (n=11), MCL (n=6), MZL (n=5), WM (n=2), HCL and TCL (n=1 each). Most subjects (58%) had received 3 or more prior therapies.

Subjects 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 (see Section 2.3.2.2 Healthy Subject Pharmacokinetic Studies). This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1800 mg QD. The maximum tolerated dose (MTD) was 1200 mg QD of the micronized formulation, with 800 mg of this formulation selected as the recommended phase 2 dose based on changes in tumor burden correlated with dose-proportional plasma exposure. Intra-subject dose escalation rules allowed subjects enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts cleared safety evaluation. The most common treatment-emergent adverse events irrespective of causality were diarrhea (in 39 [43%] of 90 subjects), nausea (38 [42%]), and fatigue (28 [31%]). The most common grade 3 or 4 adverse events were neutropenia (in 12 [13%] subjects), anemia (eight [9%]) and thrombocytopenia (six [7%]). Serious adverse events considered at least possibly related to umbralisib occurred in seven subjects: pneumonia in three (3%) subjects, lung infection in one (1%), febrile neutropenia in one (1%), and colitis in two (2%), one of whom also had febrile neutropenia. Both cases of colitis occurred above the recommended phase 2 dose. No time-related trends in toxicity were noted. See the umbralisib investigator's brochure for a complete overview of the umbralisib side effect profile.

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

Among 73 subjects in the modified intention-to-treat population, which included subjects who received at least 800 mg per day of the original formulation or any dose of the micronized formulation and had at least one response assessment, 53 (73%) had reductions in disease burden, including 33 (45%) subjects with reductions of 50% or more, of which three (4%) were a complete response and 30 (41%) were a partial response. In subjects with relapsed or refractory CLL, 17 (85%) of 20 achieved an objective response, with ten (50%) achieving an objective response per 2008 iwCLL criteria, seven (35%) achieving a partial response with lymphocytosis, and the remaining three (15%) achieving stable disease. Of eight assessable subjects with CLL who had high-risk cytogenetic features, six (75%) had a response, of whom two (25%) had a partial response with lymphocytosis, and the remainder had stable disease. In subjects with follicular lymphoma, nine (53%) of 17 subjects achieved an objective response, including two (12%) who achieved a complete response; the remainder had a partial response. In subjects with diffuse large B-cell lymphoma, four (31%) of 13 achieved an objective response and two (15%) further subjects achieved stable disease. Responses for the other histologies were Hodgkin lymphoma: one complete response, four stable disease, four progressive disease; marginal zone lymphoma: one partial response, four stable disease; Waldenström's macroglobulinemia: two stable disease; and mantle cell lymphoma: one partial response, four stable disease, and one progressive disease. [redacted] Umbralisib monotherapy is being studied in a registration directed trial in various NHL subtypes (Study UTX-TGR-205 [UNITY-NHL]; NCT02793583).

2.3.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

In parallel with the Phase 1 single-arm, dose-escalation study in subjects with relapsed or refractory hematologic malignancies; two healthy subject, crossover, bioequivalence pharmacokinetics studies have been completed. The first pharmacokinetic study (TGR-1202-PK101) was a Phase 1 drug-food interaction study with a single 200 mg oral dose of umbralisib in healthy volunteers followed by a second single dose Phase 1 pharmacokinetic study evaluating the exposure profiles of two different oral formulations of 200 mg umbralisib (original formulation vs. micronized formulation) in healthy volunteers.

2.3.2.2.1 TGR-1202-PK101: FOOD EFFECT

Study TGR-1202-PK101 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 (drug product containing unmicronized drug substance). In general, administration of umbralisib under fed conditions results in a higher rate of exposure relative to when the product was given under fasting conditions. The statistical comparisons of umbralisib pharmacokinetic parameters under fasted and fed condition are shown below.

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 increased by over 173% when umbralisib was administered with food.

2.3.2.2.2 TGR-1202-PK102: FORMULATION EFFECT

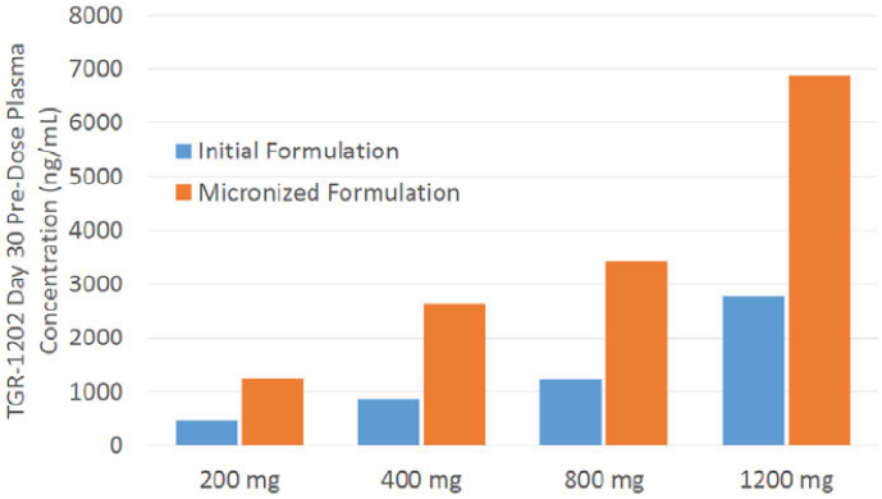
Study TGR-1202-PK102 was a two-period, randomized, two-way cross over, relative bioavailability and pharmacokinetic bioequivalence study with two different drug product formulations of umbralisib. In this study, umbralisib was administered under fasted conditions in 24 healthy subjects (12 males and 12 females) to assess the mean plasma umbralisib concentration over time following a 200 mg single dose of drug product containing unmicronized and micronized drug substance. 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 200 mg drug product containing micronized drug substance versus 200 mg drug product containing unmicronized drug substance are shown below:

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Unmicronized	Micronized		
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 micronized drug product relative to unmicronizeddrug product. The Peak plasma (C_{max}) levels of umbralisib increased by over 124% following administration of the micronized drug product relative to unmicronized drug product under fasted conditions.

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



Initial formulation = drug product containing unmicronized drug substance.

2.4 UBLITUXIMAB IN COMBINATION WITH UMBRALISIB

The combination of ublituximab and umbralisib is currently under evaluation in an ongoing Phase I/Ib study in subjects with relapsed or refractory NHL and CLL (Lunning et al., ASH 2014). In this study, ublituximab is being dosed on Days 1, 8, and 15 of Cycle 1 & 2, and on Day 1 of Cycles 4, 6, 9 and 12. After Cycle 12, no further ublituximab is administered and umbralisib is continued until removal from study.

A 3+3 dose-escalation design is being utilized to evaluate sequentially higher doses of the combination agents as illustrated below:

Cohort	Ublituximab NHL Dose	Ublituximab CLL Dose	TGR -1202 Dose (QD)
1	900 mg	600 mg	800 mg
2	900 mg	600 mg	1200 mg
3	900 mg	900 mg	400 mg (micronized)
4	900 mg	900 mg	600 mg (micronized)
5	900 mg	900 mg	800 mg (micronized)
6	900 mg	900 mg	1200 mg (micronized)

As of December 1, 2014, 27 subjects have been enrolled and are evaluable for safety, with 26 subjects evaluable for efficacy. The median age was 65 years (range 35 – 82), 17 Male/10 Female, with histologies as follows: 10 CLL/SLL, 9 FL, 7 DLBCL, and 1 patient with Richter's Transformation. Subjects had a median of 3 prior therapies, and 41% were refractory to prior therapy.

Among the 27 subjects evaluable for safety, Infusion Related Reaction (IRR) was the most prevalent adverse event (52%), followed by neutropenia (41%), nausea (37%), diarrhea (33%), fatigue (30%), and insomnia (30%). Adverse events were observed to be similar across dosing cohorts, and only one patient had their dose of umbralisib reduced (Gr. 1 diarrhea). IRR and neutropenia were managed through dose delays, with 1 CLL patient having a neutropenia related dose delay which met the criteria for a DLT, necessitating enrollment of additional CLL subjects into Cohort 1. One patient was removed from study without progressive disease due to an event of itching which was deemed possibly related to umbralisib.

Subjects were heavily pretreated, and amongst subjects with DLBCL and CLL, contained numerous high-risk subjects (67% of CLL subjects had 17p del and/or 11q del, and 5/7 evaluable DLBCL subjects were of Germinal Center-B-Cell subtype).

Responses are as follows:

- All 9 CLL/SLL subjects showed significant nodal reductions with 6 (67%) achieving a PR per iwCLL criteria (Hallek, et al., 2008). Additionally, all CLL subjects achieved a greater than 50% reduction in ALC by the end of Cycle 3.
- All 9 evaluable FL subjects displayed a nodal reduction on the combination, with 2 subjects achieving a response per Cheson 2007 criteria, including one patient with a PET negative complete response.
- Of the 7 evaluable DLBCL subjects, 3 (43%) achieved a response, including 2 complete responses which were confirmed by independent radiologic review.
- The 1 patient with Richter's Transformation exhibited a 49% nodal reduction and remains on study (duration as of data cutoff of 7+ months)

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

2.5 MRD AS A CLINICAL ENDPOINT

Given the long natural history of CLL with lengthy PFS and OS durations, finding a surrogate endpoint that is achieved more quickly and meaningfully predicts long term outcomes allows for more rapid resulting of new clinical trials and advancement of the field. Undetectable MRD, a marker of deep response, is a meaningfully endpoint as it predicts progression free and overall survival. This has been demonstrated in individual clinical trials demonstrating the relationship between U-MRD and PFS (Bottcher, et al., 2012) (Fischer, et al., 2012) (Abrisqueta, et al., 2013) (Goede, et al., 2014). Further, meta-analysis of subjects treated in 3 clinical trials (CLL8, CLL10, and CLL11) with meta-regression modeling has shown a significant relationship between treatment effect on progression free survival and MRD, supporting the use of MRD as an endpoint for CLL trials (Dimier, et al., 2018). Based on these

results, MRD undetectable disease is an accepted primary endpoint in pivotal clinical studies. Beyond using U-MRD as a trial endpoint, the utility of this marker in guiding decision regarding treatment duration is also being explored with chemotherapeutic approaches (Thompson, et al., 2018).

3 OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To assess the rate of undetectable minimal residual disease (U-MRD) in subjects with CLL treated with the combination of ublituximab and umbralisib with either venetoclax, ibrutinib or acalabrutinib

SECONDARY OBJECTIVES

- To assess safety and tolerability of ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib
- To determine the time to U-MRD at planned sequential response assessments
- To determine progression free survival and time to second objective disease progression, from time of initiation of ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib
- To determine the durability of clinical benefit after treatment discontinuation as measured by duration of peripheral blood U-MRD response and treatment-free survival
- To determine the overall response rate, complete response rate, U-MRD rate, and PFS to re-treatment with ublituximab and umbralisib with venetoclax, ibrutinib or acalabrutinib in subjects who progress following achievement of U-MRD followed by treatment-free observation.

[redacted]

3.2 EFFICACY ENDPOINTS

Undetectable Minimal Residual Disease (U-MRD) Rate

U-MRD rate is defined as the proportion of subjects who have undetectable MRD in the peripheral blood as confirmed by central lab.

Time to U-MRD

Time to undetectable minimal residual disease is defined as the interval from enrollment to the first assessment of U-MRD.

Overall response rate (ORR)

ORR is defined as sum of CR and PR rates.

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

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.

Definitive disease progression based on standard criteria (Hallek, et al., 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms). Note that lymphocytosis in the absence of other evidence of disease progression does not constitute disease progression.

Time to second objective disease progression (PFS2)
PFS2 is defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression on next-line treatment or death from any cause.

Definitive disease progression based on standard criteria (Hallek, et al., 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms). Note that lymphocytosis in the absence of other evidence of disease progression does not constitute disease progression.

[redacted]

Duration of U-MRD response
Duration of U-MRD response is defined as the interval from the first documentation of undetectable MRD to the earlier of the first documentation of presence of MRD or death from any cause.

Treatment-free survival (TFS)
TFS is defined as the interval from drug discontinuation to the earlier of initiation of retreatment for disease progression requiring treatment or death from any cause.

Disease progression requiring treatment is based on standard criteria (Hallek, et al., 2018)

4 ELIGIBILITY CRITERIA

Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for participation in this study. Eligibility criteria must be met at screening and at Cycle 1 Day 1 prior to dosing.

4.1 INCLUSION CRITERIA

1. Subjects with CLL who are currently receiving treatment with ibrutinib, acalabrutinib or venetoclax for greater than or equal to 6 months.
2. Minimal residual disease (MRD) positive (D-MRD) as determined by central lab performed during screening period.
    a. For subjects receiving venetoclax: response assessment demonstrating stable disease, partial response, or complete response AND detectable MRD in the peripheral blood (central lab).
    b. For subjects receiving ibrutinib or acalabrutinib: response assessment demonstrating stable disease, partial response or partial response with lymphocytosis, or complete response AND detectable MRD in the peripheral blood (central lab).
3. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 (µL) / platelet count $\geq$ 50,000/mm^3 (µL). Growth factor to maintain these counts is permitted during screening period and throughout the conduct of the trial.
    b. Total bilirubin ≤1.5 times the upper limit of normal (ULN), unless a diagnosis of Gilbert's syndrome or an autoimmune hemolytic anemia.
    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 modified Cockcroft-Gault formula, MDRD formula, or 24-hour urine CrCl).
4. ECOG performance status ≤ 2.
5. Male or female ≥ 18 years of age.
6. Ability to swallow and retain oral medication.
7. Female subjects who are not of child-bearing potential (see Appendix B-Contraceptive Guidelines and Pregnancy), 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 or umbralisib, and for at least 30 days after the last dose of ibrutinib, acalabrutinib or venetoclax.
8. Willingness and ability to comply with trial and follow-up procedures and give written informed consent.

4.2 EXCLUSION CRITERIA

1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation therapy [excluding palliative radiation to areas not including target/non-target lesion(s)], immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1/Day. This does not include ibrutinib, acalabrutinib or venetoclax but does include anti-CD20 therapy.
    a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
2. Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive surface Hepatitis B antibody) or chronic active Hepatitis C infection (HCV) cytomegalovirus (CMV), or known history of HIV. Subjects with positive HBc antibody or HCV antibody are eligible only if PCR is negative for HBV DNA or HCV RNA. Antiviral prophylaxis for HBV reactivation should be considered for HBc antibody positive subjects at investigator discretion.

3. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation).
4. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required for subjects on umbralisib.
5. Live virus vaccines within 4 weeks prior to ublituximab therapy.
6. History of anaphylaxis in association with previous anti-CD20 administration.
7. For subjects receiving ibrutinib or acalabrutinib:
    a. Subjects requiring warfarin therapy.
    b. Subjects requiring strong CYP3A inhibitors and/or inducers.
8. For subjects receiving venetoclax:
    a. Requirement for use of strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates.
9. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV).
    b. Myocardial infarction within 6 months of enrollment.
    c. Concomitant use of medication known to cause QT prolongation or torsades de pointes should be used with caution and at investigator discretion.
    d. Angina not well-controlled by medication.
    e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of study enrollment.
10. Malignancy, including myelodysplastic, myeloproliferative syndromes or melanoma in-situ, within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, 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.

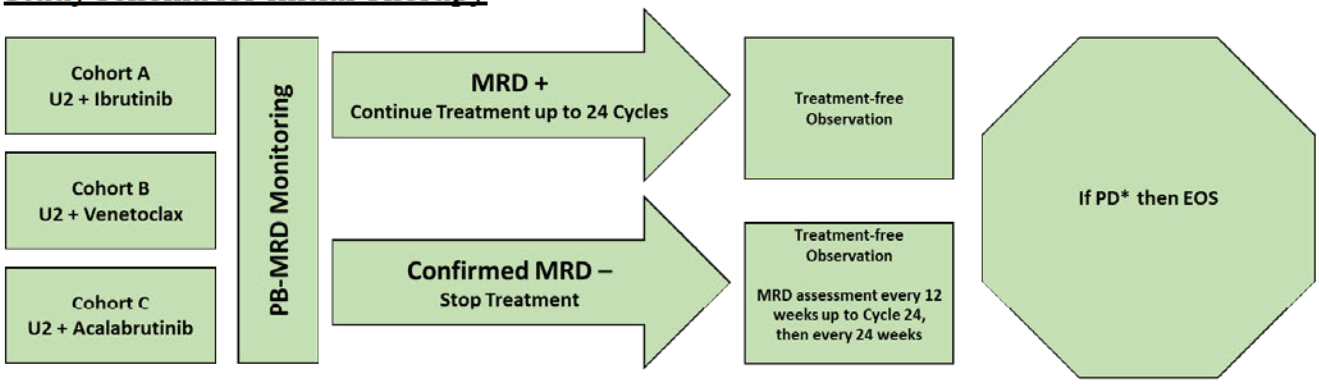
11. Women who are pregnant or lactating.

5 STUDY DESIGN

5.1 OVERVIEW OF STUDY DESIGN

This study is a Phase 2 open label, two treatment cohort trial evaluating addition of ublituximab and umbralisib on rate of U-MRD in subjects with CLL who fail to achieve U-MRD after a minimum 6-month treatment with ibrutinib, acalabrutinib or venetoclax.

Study Schema for Initial Therapy



*Progression Of Disease (PD) – Defined per the iwCLL Criteria (Hallek 2018)
U2 – ublituximab and umbralisib; IB – ibrutinb; ACALA – Acalabrutinib; VEN – venetoclax; MRD – miminal residual disease; EOS – end of study

5.2 STUDY DURATION

Subjects will remain on study treatment until the occurrence of confirmed U-MRD response in the peripheral blood, completion of 24 cycles of treatment, definitive disease progression, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue study treatment and have not progressed will continue to be followed for disease progression.

Subjects with D-MRD (MRD positive) status who receive treatment for 24 cycles and remain D-MRD, will discontinue all treatment and enter a period of treatment-free observation. For subjects entering treatment-free observation with D-MRD, no PB MRD is required.

Subjects with U-MRD (MRD negative) status who discontinue triple therapy and enter a period of treatment-free observation will have serial MRD assessments every 12 weeks up to Cycle 24 and every 24 weeks thereafter, unless clinically indicated sooner.

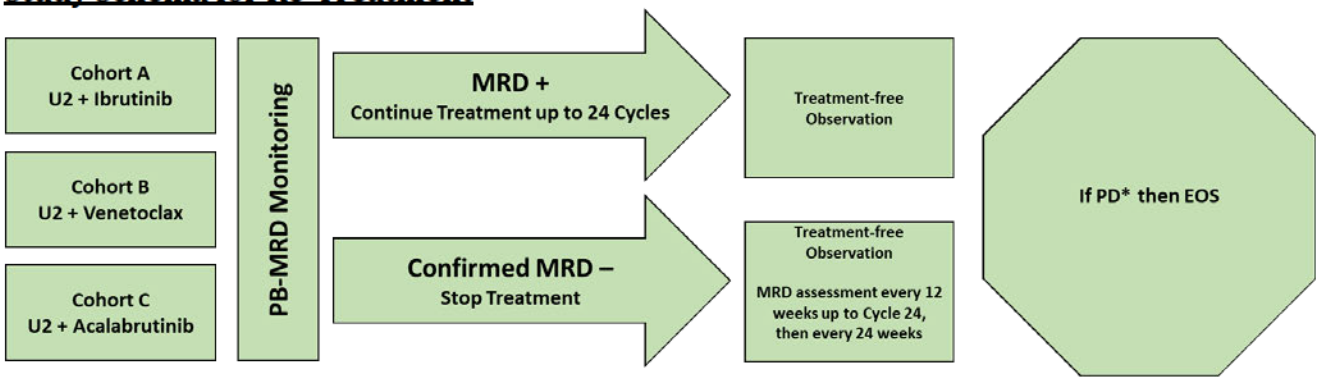
Subjects who subsequently develop clinical progression after 6 months of treatment-free observation and require treatment per iwCLL criteria (Hallek, et al., 2018) will be retreated with the triple combination regimen that induced the initial U-MRD response. Retreatment will not be initiated upon achieving MRD positivity, but only upon clinical progression requiring treatment per iwCLL criteria.

5.3 RESPONSE ASSESSMENT INITIAL TREATMENT

Response assessment will be performed cycles 3, 6, 12, 18 and 24. Best clinical response and disease progression will be assessed by investigator as per Hallek 2018.

5.4 RETREATMENT PHASE

Study Schema for Re-Treatment



*Progression Of Disease (PD) – Defined per the iwCLL Criteria (Hallek 2018)
U2 – ublituximab and umbralisib; IB – ibrutinb; ACALA – Acalabrutinib; VEN – venetoclax; MRD – miminal residual disease; EOS – end of study

Subject on treatment-free observation who subsequently develop clinical progression requiring treatment per iwCLL criteria (Hallek, et al., 2018) after 6 months of treatment-free observation will be retreated with the triple combination regimen that was previously received. Subjects who progress within 6 months of treatment-free observation discontinue from the study.

For subjects enrolled in Cohort A, retreatment will consist of 2 cycles of ibrutinib followed by treatment with ublituximab and umbralisib with ibrutinib cycles 3 through 26 of retreatment. The previously tolerated ibrutinib dose should be considered but is at investigator discretion (maximum dose 420mg daily).

For subjects enrolled in Cohort B, venetoclax should be initiated per the package insert. The target ramp-up dose should be considered based on the previously tolerated dose but is at investigator discretion (maximum dose 400mg daily). Retreatment will consist of 2 cycles of venetoclax followed by treatment with ublituximab and umbralisib with venetoclax cycles 3 through 26.

For subjects enrolled in Cohort C, retreatment will consist of 2 cycles of acalabrutiib followed by treatment with ublituximab and umbralisib and acalabrutinib cycles 3 through 26 of retreatmnt. The previously tolerated acalabrutinib dose should be considered but is at the investigator discretion.

Clinical response and U-MRD rate will be studied upon retreatment. If subjects achieve U-MRD status in the peripheral blood, MRD will be assessed by peripheral blood 4 weeks later to confirm U-MRD. Retreatment will continue until the occurrence of confirmed U-MRD response in the peripheral blood, completion of 26 cycles (24 cycles of triplet therapy),

definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue study treatment and have not progressed will continue to be followed for disease progression.

5.5 RESPONSE ASSESSMENT RE-TREATMENT

Tumor assessment will be performed cycles 7, 14, 20 and 26 then every 12 months. Best clinical response and disease progression will be investigator assessed.

5.6 DISCONTINUATION FROM STUDY

Subjects will be discontinued from the study for any of the following reasons:

- Disease progression while on study treatment
- Disease progression within 6 months during treatment-free observation
- Subject requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the subject to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Non-compliance/lost to follow-up
- Investigator discretion
- Discontinuation of the study by the Sponsor

Subjects who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression and survival for 24 months.

After withdrawal from study, subjects should be followed for AEs for 30 calendar days after their last dose of either study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigators must record his or her reasoning for this decision in the subject's medical records and as a comment on the electronic Case Report Form (eCRF).

5.7 STUDY SITES

Up to eight centers in the United States may be asked to participate in this study. Enrollment is expected to be completed approximately 24 months after the first subject is enrolled.

6 REGISTRATION AND ENROLLMENT

Subjects who are eligible and have signed an informed consent will add ublituximab and umbralisib to their existing ibrutinib, acalabrutinib or venetoclax treatment. Determination of which cohort each subject will be enrolled in will depend on which agent was received prior to screening.

Three Cohorts will be studied:

- Cohort A: Ublituximab and Umbralisib with Ibrutinib
- Cohort B: Ublituximab and Umbralisib with Venetoclax
- Cohort C: Ublituximab and Umbralisib with Acalabrutinib

After the subject signs the informed consent form and to register the subject, the completed Subject registration form will be emailed to 208registration@tgtxinc.com.

After eligibility has been confirmed, subject enrollment forms with the signed inclusion/exclusion form will be emailed to 208registration@tgtxinc.com.

If the subject is a screen failure, the site must notify TG Therapeutics by email at 208registration@tgtxinc.com.

If subject is eligible to enter the Re-Treatment phase, the completed Subject Re-Treatment Registration form will be emailed to 208registration@tgtxinc.com.

7 STUDY ASSESSMENTS AND TREATMENT SCHEDULES

7.1 STUDY ASSESSMENT AND TREATMENT SCHEDULE - INITIAL TREATMENT

Cycle=28 days	Screen	Cycle 1[1]				Cycle 2-6[2]	C9 and every 3 cycles through C24[3]	EOS*
Procedure/Days	-28-1	D1	D2	D8	D15	Day 1	Day 1	
Medical History	X							
Rai Staging	X							
ECOG	X	X				X	X	X
Physical Examination	X	X				X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X
12-Lead EKG	X							
Hematology	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	
Coagulation Studies	X	X				X	X	
HCV, HBV, CMV[5]	X							
CMV surveillance[6]						C3&6	C9, 12, 15, etc.	
PB MRD[7]	X					X	X	
[redacted]								
β_2-microglobulin	X							
Pregnancy Test[9]	X					X	X	
Response assessments[10]	X					C3 & C6	C 12, 18 & C24	
AE Evaluation	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X
Ublituximab		X	X	X	X	X	X	
Umbralisib		Daily until confirmed U-MRD[11]						
Cohort A: Ibrutinib		Daily until confirmed U-MRD[11]						
Cohort B: Venetoclax		Daily until confirmed U-MRD[11]						
Cohort C: Acalabrutinib		Every 12 hours until confirmed U-MRD[11]						

[1] Treatment Administration +/- 1 day window after cycle 1 day 1. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have - 1 day window. All assessments must be completed prior to dosing.
[2] Treatment Administration +/- 3 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 3 day window during Cycles 2 through 6.
[3] Treatment Administration +/- 7 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 7 day window for all cycles after cycle 6
[4] Vital signs to include temp, BP, HR, respirations and weight (weight only at baseline).
[5] Serum Virology to include HBsAg, HBc antibody, HCV antibody, CMV IgG and IgM. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR - See Appendix D. If the subject is CMV IgG or IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. If subject is HCV positive, evaluate HCV RNA.
[6] CMV surveillance by PCR every 3 cycles while receiving study treatment. In addition, a final CMV test by PCR should be done upon treatment discontinuation if not already done within previous 3 months.
[7] For initial treatment, MRD analysis (central lab) in peripheral blood (PB) performed within 30 days prior to Cycle 1/Day 1. MRD analysis in PB during cycles 3, 6, 9, 12, 15, 18, 21, and 24. U-MRD in PB during initial treatment must be confirmed in PB 4 approximately weeks later.
[redacted]
[9] For women of childbearing potential: Serum pregnancy test within 3 days prior to Cycle 1/Day 1; Urine pregnancy tests on Day 1 of each treatment cycle +/- 7 days.
[10] Radiology assessment should include a contrasted CT or MRI imaging of neck, chest, abdomen, and pelvis. For initial treatment, scans to be completed within 30 days prior to Cycle 1 / Day 1. All tumor evaluations post baseline assessment should be performed within 14 days of cycles 3, 6, 12, 18 and 24.. Follow up CTs to be done at investigator discretion/ per standard of care. At the time of response assessment, bone marrow to be performed as per standard of care if other criteria for complete remission are met. CR should only be confirmed once by bone marrow assessment at planned tumor assessments.
[11] If U-MRD is confirmed, subjects will complete treatment through the end of that 28-day cycle then return for their first TFO at the subsequent Cycle.

***EOS = End of Study** – EOS visit occurs if subject is discontinuing from the study. Please see Section 5.6 Discontinuation from study , which outlines reasons subject must discontinue from study.

7.2 STUDY ASSESSMENT AND TREATMENT SCHEDULE - TREATMENT FREE OBSERVATION

Cycle = 28 days	Treatment-Free Observation (TFO) Visits[1]	
Procedures/Days[2]	TFO1 Cycle 1 Day 1	TFO Subsequent Day 1 Every 3 Cycles for 24 cycles and every 6 cycles thereafter
ECOG	X	X
Physical Examination	X	X
Vital Signs[3]	X	X
Hematology	X	X
Chemistry	X	X
PB MRD[4]		X
AE Evaluation	X	X
Con Meds	X	X

[1] At completion of 24 cycles with no progression of disease (POD), confirmed U-MRD, or discontinuation of treatment due to toxicity in absence of POD, subjects will enter a treatment-free observation period. Study assessments will be completed every 3 cycles for 24 cycles from discontinuation of any study drug.
[2] All TFO visits have a +/- 14 day window.
[3] Vital signs to include temp, BP, HR, and respirations
[4] Subjects on treatment-free observation with U-MRD should have peripheral blood MRD assessments approximately every 12 weeks +/- 2 weeks prior to Cycle 24 and every 24 weeks +/- 2 weeks, unless clinically indicated sooner, after Cycle 24. For subjects entering treatment-free observation with D-MRD, no PB MRD is required. For subjects entering TFO due to discontinuation of treatment due to toxicity in absence of POD, MRD should be done at TFO1. If U-MRD repeat MRD in PB in 4 weeks, if D-MRD, no further PB MRD is required.

7.3 STUDY ASSESSMENT AND TREATMENT SCHEDULE – RE-TREATMENT

Cycle=28 days	Screen	Cycle 1[1]				Cycle 2[2]		Cycle 3[3]				Cycles 4-8[4]	C11-C26[5]	EOS*	LTFU
Procedures/Days	D-28 to D1	D1	D8[6]	D15[7]	D22[7]	D1	D8[7]	D1	D2	D8	D15	D1	D1 every 3 Cycles		
Physical Examination	X	X				X		X				X	X	X	
ECOG PS	X	X				X		X				X	X	X	
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead EKG	X														
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Studies	X	X				X		X				X	X		
HCV, HBV, CMV[9]	X														
CMV surveillance[10]								x				C6&8	C11, 14, 17 etc		
MRD-PB[11]	X											X[26]	X[261]		
[redacted]															
β_2-microglobulin	X														
Pregnancy Test[13]	X					X		X				X	X		
Response Assessments[14]	X											C7	X[15]		X[16]
Tumor Lysis Risk Assessment[17]		X													
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ublituximab[18]								X	X	X	X	X	X		
Umbralisib[19]								Daily until confirmed U-MRD							
Cohort A: Ibrutinib[20]		Daily until confirmed U-MRD													
Cohort B: Venetoclax[21]		Dose ramp-up as per package insert and daily until confirmed U-MRD													
Cohort C: Acalabrutinib		Every 12 hours until confirmed U-MRD													

[1] Treatment Administration +/- 1 day window after cycle 1 day 1. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have - 1 day window. All assessments must be completed prior to treatment.

[2] Treatment Administration +/- 3 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 3 day window during Cycles 2 through 6.

[3] Treatment Administration +/- 7 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 7 day window.

[4] Treatment Administration +/- 3 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 3 day window during Cycles 2 through 6.

[5] Day 1 every 3 Cycles (Cycle 11, 14, 17, 20, 23, 26): Treatment Administration +/- 7 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 7 day window.

[6] Cycle 1 Days 8, 15 & 22 assessments only for subjects receiving venetoclax.

[7] Cycle 2 Day 8 assessments only for subjects receiving venetoclax.

[8] Vital signs to include temp, BP, HR, respirations and weight (weight only at baseline).

[9] Serum Virology to include HBsAg, HBc antibody, HCV antibody, CMV IgG and CMV IgM or CMV by PCR. If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR - See Appendix D. If the subject is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR.

[10] CMV surveillance by PCR every 3 cycles while receiving study treatment. In addition, a final CMV test by PCR should be done upon treatment discontinuation if not already done within previous 3 months.

[11] For retreatment, MRD analysis should be done within 30 days of restarting therapy in peripheral blood (PB) then performed Cycles 6, 8, 11, 14, 17, 20, 23, and 26. If U-MRD in PB during retreatment repeat approximately 4 weeks later. If U-MRD confirmed approximately 4 weeks later, discontinue treatment and follow for progression and survival for 24 months.

[redacted]

[13] For women of childbearing potential: Serum pregnancy test within 3 days prior to Cycle 1/Day 1; Urine pregnancy tests on Day 1 of each treatment cycle +/- 7 days.

[14] Radiology assessment should include contrasted CT or MRI imaging of neck, chest, abdomen, and pelvis. Scans to be completed within 30 days prior to Cycle 1/Day 1.

[15] Re-treatment subjects – radiology and response assessment within 14 days of Cycles 7, 14, 20, 26 then every 12 months thereafter. At the time of response assessment, bone marrow to be performed as per standard of care if other criteria for complete remission are met. CR should only be confirmed once by bone marrow assessment at planned response assessments.

[16] Response Assessment to be done as per SOC to determine progression-free survival

[17] For subjects being re-treated with venetoclax only. Refer to section 8.3.5.1

[18] Ublituximab Cycle 3 Days 1,2, 8 & 15; Cycle 4-8 Day 1 then every 3 cycles (C11, C14, C17, C20, C23, C26). No further ublituximab after cycle 26

[19] When starting retreatment, dose of umbralisib is at the investigator's discretion, previously tolerated dose should be considered.

[20] When starting retreatment, dose of ibrutinib or acalabrutinib is at the investigator's discretion, previously tolerated dose should be considered.

[21] TLS risk assessment and TLS prophylaxis should be instituted per the venetoclax package insert for subjects on Cohort B. Refer to section 7.3.4.1 for additional lab requirements during the ramp up phase. Dose escalation should be performed per the package insert and the target dose may be 400 mg or previously tolerated dose.

*__EOS = End of Study__ – EOS visit occurs if subject is discontinuing from the study. Please see Section 5.6 Discontinuation from study , which outlines reasons subject could discontinue from study.

7.4 LABORATORY ASSESSMENTS

Laboratory assessments will be collected as specified in the study assessments and treatment schedules. Please refer to the lab manual for instructions outlining collection and shipment procedures for lab samples for central review.

7.4.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include:

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	Absolute lymphocyte count
Erythrocyte count	Monocytes	
Leukocyte count	Eosinophils	
Absolute neutrophil count	Basophils	
Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate/CO2	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total protein
Chloride	Potassium	Uric acid

2. Serum pregnancy test.
3. Coagulation lab tests to include PT and INR.
4. Beta2-microglobulin
5. Serum virology to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM or CMV by PCR during screening, then CMV by PCR at subsequent timepoints. If HBc antibody is positive the subject must be evaluated for the presence of active HBV DNA by PCR (see Appendix D). If the subject is CMV IgG or IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR.
6. Bone Marrow biopsy and aspiration for subject that meet the criteria for CR as defined by iwCLL Hallek 2018.

7.5 CENTRAL LABORATORY ASSESSMENTS

The following assessments will be shipped to and analyzed at a central laboratory. Please see Lab Manual for details of processing, handling, and shipping instructions.

- Peripheral Blood Minimal Residual Disease (MRD) Analysis (use CLL MRD specimen shipping kits, see lab manual)
- [redacted]

8 TREATMENT PLAN

8.1 TREATMENT SUMMARY

Initial Treatment Overview
Cycle = 28 days

Cohort A: Ublituximab and Umbralisib with Ibrutinib

Cycle 1:

Ublituximab			Umbralisib	Ibrutinib
Day 1	Day 2	Day 8 & 15	Daily	Daily
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Ibrutinib
Day 1	Daily	Daily
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Ibrutinib
Day 1 of Cycles 9, 12, 15, 18, 21 & 24	Daily	Daily
900 mg	800 mg	previously tolerated dose

Cohort B: Ublituximab and Umbralisib with Venetoclax

Cycle 1:

Ublituximab			Umbralisib	Venetoclax
Day 1	Day 2	Day 8 & 15	Daily	Daily
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Venetoclax
Day 1	Daily	Daily
900 mg	800 mg	previously tolerated dose

Cycle 7-24:

Ublituximab	Umbralisib	Venetoclax
Day 1 of Cycle 9, 12, 15, 18, 21 & 24	Daily	Daily
900 mg	800 mg	previously tolerated dose

Cohort C: Ublituximab and Umbralisib with Acalabrutinib

Cycle 1:

Ublituximab			Umbralisib	Acalabrutinib
Day 1	Day 2	Day 8 & 15	Daily	Every 12 hours
150 mg	750 mg	900 mg	800 mg	previously tolerated dose

Cycles 2 through 6:

Ublituximab	Umbralisib	Acalabrutinib
Day 1	Daily	Every 12 hours
900 mg	800 mg	previously tolerated dose

Cycles 7-24:

Ublituximab	Umbralisib	Acalabrutinib
Day 1 of Cycles 9, 12, 15, 18, 21 and 24	**Daily**	**Every 12 hours**
900 mg	800 mg	previously tolerated dose

8.2 RE-TREATMENT SUMMARY

Re-treatment Overview
Cycle = 28 Days

Cohort A: Ublituximab and Umbralisib with Ibrutinib (Re-Treatment)

Cycles 1 and 2:

Ibrutinib
Daily
Daily at previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 420mg daily).

Cycle 3:

Ublituximab			Ibrutinib	Umbralisib
Day 1	**Day 2**	**Day 8 & 15**	**Daily**	**Daily**
150 mg	750 mg	900 mg	At appropriate dose based on initial protocol treatment.	Previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 800mg daily).

Cycles 4 through 8:

Ublituximab	Ibrutinib	Umbralisib
Day 1	**Daily**	**Daily**
900mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cycles 9 through 26:

Ublituximab	Ibrutinib	Umbralisib
Day 1 of Cycle 11, 14, 17, 20, 23, 26	**Daily**	**Daily**
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cohort B: Ublituximab and Umbralisib with Venetoclax (Re-treatment)
Cycle = 28 days

Cycle 1:

Venetoclax
Day 1-28
Dose escalation per package insert to previously tolerated dose. Investigator discretion may be used to escalate subjects to a target dose that is higher than the dose last tolerated (maximum dose 400mg daily).

Cycle 2:

Venetoclax	
Day 1-7	**Day 8-28**
Dose escalation per package insert to previously tolerated dose, if applicable. Investigator discretion may be used to escalate subjects to a target dose that is higher than the dose last tolerated (maximum dose 400mg daily).	Tolerated dose per dose escalation

Cycle 3:

Ublituximab			Venetoclax	Umbralisib
Day 1	**Day 2**	**Day 8 & 15**	**Daily**	**Daily**
150mg	750 mg	900 mg	At appropriate dose based on previous Cycle	Previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 800mg daily).

Cycles 4 through 8:

Ublituximab	Venetoclax	Umbralisib
Day 1	**Daily**	**Daily**
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cycles 9 through 26:

Ublituximab	Venetoclax	Umbralisib
Day 1 of Cycle 11, 14, 17, 20, 23 & 26	**Daily**	**Daily**
900 mg	At appropriate dose based on previous Cycle	At appropriate dose based on previous Cycle

Cohort C: Ublituximab and Umbralisib with Acalabrutinib (Re-Treatment)

Cycle 1-2:

Acalabrutinib
Every 12 hours
previously tolerated dose

Cycle 3:

Ublituximab			Acalabrutinib	Umbralisib
Day 1	**Day 2**	**Day 8 & 15**	**Every 12 hours**	**Daily**

150 mg	750 mg	900 mg	At appropriate dose based on initial protocol treatment.	Previously tolerated dose. Investigator discretion may be used to start subjects at a higher dose than last tolerated (maximum dose 800mg daily).

Cycles 4 through 8:

Ublituximab	Umbralisib	Acalabrutinib
Day 1	**Daily**	**Every 12 hours**
900 mg	800 mg	previously tolerated dose

Cycles 9-26:

Ublituximab	Umbralisib	Acalabrutinib
Day 1 of Cycles 11, 14, 17, 20, 23 & 26	**Daily**	**Every 12 hours**
900 mg	800 mg	previously tolerated dose

8.3 AGENT ADMINISTRATION

Ublituximab treatment will be administered as an IV infusion. Umbralisib, ibrutinib, acalabrutinib and venetoclax will be self-administered orally. Ublituximab, umbralisib, ibrutinib and acalabrutinib will be administered on an outpatient basis. Venetoclax can be administered on an inpatient or outpatient basis as guided by the package insert.

8.3.1 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 should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20mg or equivalent).
    - If administered IV: start ublituximab 30 minutes after conclusion of last pre-med infusion.
    - If administered orally: start ublituximab 45-60 minutes after ingestion of pre-meds.
    - If subject does not tolerate pre-medications, or pre-medications have an adverse impact on coexisting medical conditions consider changing the pre-medication dosage, change to a different drug or discontinue at the investigator's discretion
        - Corticosteroids premeds can be stopped after Cycle 6 if subject is tolerating infusion without infusion related reactions.

- 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.
- *Hypersensitivity and Infusion Reaction 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 adverse event).
    - Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted
    - Since infusion-related hypotension may occur, investigator should consider holding antihypertensive medications approximately 12-24 hours prior to and throughout infusion of ublituximab. Decision to withhold antihypertensive medication is at investigator discretion.
    - For subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

8.3.1.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE – UBLITUXIMAB

Infusion related reactions including severe reactions have been reported with ublituximab administration in subjects with CLL. 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/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) in which treatment should be interrupted. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitor subject, institute symptomatic medical management until resolution of IRR symptoms.

- Following the judgment 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 (see Section 8.3.1.2).

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. During retreatment, if the infusion discontinued is the Cycle 3 Day 1 infusion, administer the scheduled Cycle 3 Day 2 dose according to the protocol dosing schedule.

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

8.3.1.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

Cycle 1 Day 1 & 2 infusion over 4 hours (Retreatment Cycle 3 Day 1 & Day 2)

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

Cycle 1 Day 8 & 15 infusions over 3 hours (Retreatment Cycle 3 Days 8 & Day 15)

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

Cycle 2 and remaining infusions over 90 minutes (Retreatment Cycle 4 and beyond)

Ublituximab Dose	Total volume to be infused	Infusion rate	
		T0 to T30min	T30min to T90min
900 mg	500 mL	200 mL/H	400 mL/H

8.3.1.3 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or authorized study site representative must check that the ublituximab is in accordance with the product specifications and the validity is within the re-test 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 authorized study site representative should record the date dispensed and subject's number and initials, 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 authorized study site representative according to instructions for sterile dilution.

8.3.1.3.1 DILUTIONS OF UBLITUXIMAB

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

Ublituximab vials containing 6 mL (25 mg/mL)

Dilutions for Cycle 1 Day 1 & Day 2 (Retreatment Cycle 3 Day 1 & Day 2)

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

Dilutions for ≥Cycle 1 Day 8 Infusions (Retreatment ≥ Cycle 3 Day 8)

Dose of ublituximab for infusion	[redacted]
900 mg	

8.3.2 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB

- *Method of Administration:* Umbralisib will be administered orally once daily at approximately the same time with food
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* Subjects are required to start prophylaxis for pneumocystis jiroveci pneumonia (PJP) and antiviral therapy prior to Cycle 1 Day 1 of initial treatment and prior to Cycle 3 Day 1 during retreatment. The following prophylaxis approaches are recommended:
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
    - *PJP Prophylaxis:* Dapsone 100 mg daily or Atovaquone 1,500 mg once daily or equivalent

Final choice of PJP and anti-viral prophylaxis therapy and schedule is per investigator discretion.

If anti-viral or anti-bacterial prophylaxis is not tolerated, we recommend alternating to a different prophylactic agent, reducing the dose or modifying the schedule for the prophylactic agent, or discontinuing prophylaxis at 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 all empty and partially filled bottles with any unused tablets when they return to the site. For the purpose of drug accountability and dosing, subjects should record any missed doses of umbralisib on a drug diary. 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. Tablets should be taken at approximately the same time each day with food. Subjects should be instructed to swallow the tablets whole and should not chew or crush them.

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.

8.3.2.1 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 re-test 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. Any error in drug administration (e.g., missed dose) should be recorded in the eCRF. The pharmacist or his/her representative should record the date dispensed and subject's number and initials, as well as complete the accountability record in the electronic drug accountability system with information concerning the dispensation of umbralisib.

8.3.3 GUIDELINES FOR ADMINISTRATION OF IBRUTINIB

- *Method of Administration:* Ibrutinib will be administered orally once daily with water.
- *Potential Drug Interactions*: Avoid co-administration with moderate or strong CYP3A inhibitors and/or inducers. If a moderate or strong CYP3A inhibitor must be used, follow the prescribing information. Also avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A and can alter ibrutinib pharmacokinetics.

- *Pre-medications:* None

[redacted] Ibrutinib will be self-administered by the subject. Tablets should be taken at approximately the same time each day. Subjects should be instructed to follow all package insert instructions. This includes instruction that tablets are to be swallowed whole, not chewed or crushed. If a dose is missed for the entire day, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle. Missed doses should be documented in the subject drug diary. No routine prophylactic antiemetics or premedications should be given outside of protocol requirements. However, these medications may be administered for symptoms when they occur and may be given prophylactically afterward. Refer to the ibrutinib package insert for full details at www.imbruvica.com

8.3.4 GUIDELINES FOR ADMINISTRATION OF ACALABRUTINIB

- *Method of Administration:* Acalabrutinib will be administered orally every 12 hours; swallow whole with water and with or without food.
- *Potential Drug Interactions:* CYP3A Inhibitors – Avoid co-administration with strong CY3A inhibitors. Dose adjustments may be recommended. CY3A Inducers – Avoid co-administration with strong CYP3A inducers. Dose adjustments may be recommended. Gastric Acid Reducing Agents – Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids.
- *Pre-medications:* None

[redacted] Acalabrutinib will be self-administered by the subject. Tablets should be taken every 12 hours. Subjects should be instructed to follow all package insert instructions. This includes instruction that tablets are to be swallowed whole, not chewed or crushed. If a dose is missed for more than 3 hours, it should not be replaced.

Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle. Missed doses should be documented in the subject drug diary. No routine prophylactic antiemetics or premedications should be given outside of protocol requirements. However, these medications may be administered for symptoms when they occur and may be given prophylactically afterward. Refer to the acalabrutinib package insert for full details at https://www.azpicentral.com/calquence/calquence.pdf#page=1.

8.3.5 GUIDELINES OF ADMINISTRATION FOR VENETOCLAX

- *Method of Administration:* Venetoclax will be administered orally once daily with food or water

- *Potential Drug Interactions*: Avoid co-administration with moderate or strong CYP3A inhibitors. If a moderate or strong CYP3A inhibitor must be used, follow the prescribing information. Also avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A and can alter venetoclax pharmacokinetics.
- *Pre-medications:* None

[redacted] Venetoclax will be self-administered by the subject. Tablets should be taken at approximately the same time each day with food or water. Subjects should be instructed to swallow the tablets and should not chew or crush them. If a dose of venetoclax is missed, it should be taken as soon as possible on the same day. If it is missed greater than 8 hours from scheduled dosing, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle. Missed doses should be documented in the subject drug diary.

8.3.5.1 DOSE ESCALATION OF VENETOCLAX (RETREATMENT PHASE)

All dose escalation of venetoclax and tumor lysis syndrome prophylaxis should be executed per FDA approved label and package insert refer to https://www.venclextahcp.com . 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 and drug diary.

Venetoclax starting pack provides the first 4 weeks according to the ramp-up schedule. Once the ramp-up phase is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles.

Tumor lysis risk, Prophylaxis and Assessments

Tumor Burden		Prophylaxis		Blood Chemistry[b]
		Hydration	Anti-hyperuricemics	Assessments
Low	All LN <5cm AND ALC<25 x10^9/L	Oral (1.5-2L daily)	Allopurinol[a]	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hrs • Pre-dose at subsequent ramp-up doses

Medium	Any LN 5cm to <10cm OR ALC≥25 x10^9/L	Oral (1.5-2L daily), And consider additional Intravenous	Allopurinol[a]	Outpatient • For first dose of 20 and 50mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp up doses: Pre-dose • For first dose of 20mg and 50mg: Consider hospitalization with CrCl <80ml/min
High	Any LN ≥10cm OR ALC≥25 x10^9/L AND Any LN ≥5cm	Oral (1.5-2L daily), and intravenous (150-200 mL/IV as tolerated)	Allopurinol[a], consider rasburicase if baseline uric acid is elevated	Inpatient at first dose of 20 and 50mg • 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; hrs = hours
[a] Start allopurinol or alternate xanthine oxidase inhibitor 2-3 days prior to venetoclax if not administering rasburicase
[b] Blood Chemistries include potassium, calcium, phosphorus, uric acid and creatinine

8.3.6 CRITERIA FOR ONGOING RE-TREATMENT

Continue treatment as per protocol provided the subject has:

- No intolerable toxicities related to study drug.
- D-MRD or has not completed 26 cycles of re-treatment .
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

8.4 DOSING DELAYS AND MODIFICATIONS

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_8.5x11.pdf) grading scale. Dose delay and/or modification guidance is for adverse events considered at least possibly related to the study drug. If cytopenias are deemed related to the underlying disease rather than study drug, dose modifications are not required but may be carried out per investigator discretion.

Delay of treatment is allowed for recovery of toxicities. Please contact TG Therapeutics with any questions prior to re-initiating treatment after extended drug holds. If there is a dose modification for the oral agents, the subject should be notified of the change in dose and the

appropriate staff should instruct the subject about the revised number of study medication tablets to be used per dose according to the new dose level.

In the case of drug discontinuation, subjects will be followed for disease progression.

8.4.1 DOSE DELAY: UBLITUXIMAB

No reduction in the dose of ublituximab is permitted. Please refer to 'Guidelines for Administration of Ublituximab' for detailed information on infusion rate guidance for infusion related reactions related to ublituximab.

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias or Grade ≥ 1 non-hematologic toxicities.

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

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

TABLE 2: DOSE DELAY GUIDELINES: UBLITUXIMAB

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 3 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay ublituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; consider growth-factor support as warranted; thereafter, resume at full dose.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay ublituximab until Grade ≤ 3; consider intervention with supportive care as warranted; thereafter resume at full dose.
Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level
Grade ≥3	Withhold ublituximab until Grade ≤ 2 at the discretion of the investigator; consider supportive care intervention as warranted. Resume at full dose.

8.4.2 DOSE DELAY/MODIFICATIONS: UMBRALISIB

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities.

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

TABLE 3: UMBRALISIB DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 3 neutropenia	Maintain current dose, consider supportive care. If recurrence or persistent Grade 3, consider reducing umbralisib to next lower dose level or maintain current umbralisib dose at discretion of the investigator.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay umbralisib until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider supportive care. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3 and/or neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose or at next lower dose level at discretion of the investigator.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay umbralisib until Grade ≤3; thereafter, resume at full dose. Consider supportive care intervention as warranted. If recurrence after re-challenge, delay umbralisib until Grade ≤ 3; thereafter resume umbralisib at current dose or at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 1 & 2	Stop all therapy and hold until complete resolution. Restart umbralisib at one lower dose level. Restart ublituximab (if applicable) at full dose. If recurrence after re-challenge, discontinue all treatment therapy.
Grade ≥ 3	Discontinue all therapy
For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required for subjects receiving umbralisib.	
Diarrhea and/or Colitis	
Diarrhea Grade ≤2	Maintain current dose level if tolerable or hold and then resume at current dose level once has resolved. **NOTE**: If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
Diarrhea Grade ≥3	Withhold umbralisib until Grade ≤2. Resume at full dose or next lower dose level as per discretion of investigator If recurrence after re-challenge, resume at next lower dose level at discretion of the investigator.
Colitis (all Grades)	Hold umbralisib. Treat with supportive care and after resolution of colitis, resume umbralisib at next lower dose level
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks.
Grade 2	Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Begin supportive care (prednisone 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 by 10 mg per week until off. If liver toxicity recurs to Grade 2: ○ Re-initiate steroids. ○ Monitor labs at least weekly until Grade 1. ○ Consider delaying umbralisib. ○ Once resolved to Grade ≤1 ○ If umbralisib was delayed, restart umbralisib at current dose. ○ Taper prednisone by 10 mg per week until off.
Grade ≥3	Delay umbralisib. Assess concomitant medications and risk factors*. Begin/continue supportive care (prednisone 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: ○ Restart umbralisib at one lower dose level. ○ Taper prednisone by 10 mg per week until off.
* 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.	
All Other Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level
Grade ≥3	Withhold umbralisib until Grade ≤2. If recurrence after re-challenge, delay umbralisib until Grade ≤ 2; thereafter resume umbralisib at current dose or at next lower dose level at discretion of the investigator.

TABLE 4: STUDY DRUG DOSE LEVELS

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

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

8.4.3 DOSE MODIFICATIONS OF IBRUTINIB, ACALABRUTINIB OR VENETOCLAX

If toxicity is attributable to ibrutinib, acalabrutinib or venetoclax in the opinion of the investigator, the investigator and research team should follow recommendations per ibrutinib, acalabrutinib or venetoclax FDA approved prescribing information and/or per investigator discretion.

Subjects who experience an adverse event attributed to ibrutinib, acalabrutinib or venetoclax will be allowed to delay drug dosing in order to recover from the toxicity. Subjects may resume ibrutinib, acalabrutinib or venetoclax, provided the toxicity has

resolved to Grade ≤2 or baseline. Please refer to www.imbruvica.com or https://www.venclextahcp.com or https://www.calquence.com/ for full prescribing information including dose modifications for adverse reactions.

8.5 ORDERING UBLITUXIMAB AND UMBRALISIB

Once the clinical study site receives regulatory approval (IRB/IEB), the Sponsor and/or Sponsor designee performs the Site Initiation Visit and inspection of pharmacy, the site is officially open for enrollment, and a subject is identified, a shipment of pre-determined quantity of ublituximab and umbralisib will be shipped to the clinical study site.

Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms for both ublituximab and umbralisib. If any abnormality on the supplied boxes (ublituximab) or bottles (umbralisib) is observed, the pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee at productquality@tgtxinc.com.

To place an order to maintain stock or replace damaged drug, email TGDrugOrder@tgtxinc.com. Indicate the protocol ID, drug and quantity needed and date necessary to receive drug.

9 STUDY MEDICATION OVERVIEW AND SAFETY

9.1 UBLITUXIMAB

Chemical Name:	ublituximab
Other Names:	TG-1101
Classification:	Recombinant chimeric anti-CD20 monoclonal antibody
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.
How Supplied:	Concentration of 25 mg/mL in 6 mL (150 mg) single-use glass vials.
Storage:	Ublituximab must be stored in a secured limited-access refrigerated area at a temperature ranging from +2°C to +8°C. Ublituximab must not be frozen.
Stability:	Once a vial of ublituximab has been opened and/or diluted it must be used immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions it is stable for 8 hours at 25°C. Retest dates will be provided periodically by the sponsor.
Route of Administration:	Intravenous
Packaging:	Ublituximab is packed in kits. Each kit contains: • Six vials containing 150 mg solution of ublituximab each The container closure system for the vials containing 6 mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with an aqua plastic and aluminum cap.

Availability:	Ublituximab is available from TG Therapeutics.

9.2 UMBRALISIB

Classification:	Phosphatidylinositol-3-Kinase (PI3K) Delta Inhibitor
Formulation:	See Investigator Brochure
Mode of Action:	Irreversibly inhibits activity of the Class I Delta isoform of PI3K
How Supplied:	200 mg tablets
Storage:	Store at 20°C - 25°C. Excursions permitted 15°C to 30°C.
Stability:	Retest dates will be provided periodically by Sponsor.
Route of Administration:	Oral
Packaging:	Umbralisib is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.
Availability:	Umbralisib is available from TG Therapeutics.

9.3 UBLITUXIMAB AND UMBRALISIB COMBINATION - COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS) – UBLITUXIMAB + UMBRALISIB

The following adverse events were observed in subjects treated with the combination of ublituximab and umbralisib and were considered at least possibly related to one or more of the study medications. For updated safety information and the list of adverse events of special interest, see the current Investigator's Brochures for ublituximab and umbralisib.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** anemia, neutropenia
- **Gastrointestinal Disorders:** diarrhea, nausea, vomiting
- **General Disorders and Administration Site Conditions:** fatigue
- **Injury, Poisoning and Procedural Complications:** infusion related reaction
- **Metabolism and Nutrition Disorders:** decreased appetite

Common (≥ 1% - < 10%)

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Cardiac Disorders:** cardiac failure congestive
- **Ear and Labyrinth Disorders:** ear congestion, ear discomfort
- **Eye Disorders:** conjunctival pallor, conjunctivitis, corneal oedema, vision blurred
- **Gastrointestinal Disorders:** abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastroesophageal reflux disease, haematochezia, salivary hypersecretion, stomatitis
- **General Disorders and Administration Site Conditions:** asthenia, chills, face oedema, infusion site pain, local swelling, oedema peripheral, pyrexia, systemic inflammatory response syndrome
- **Hepatobiliary Disorders:** hyperbilirubinaemia
- **Immune System Disorders:** hypogammaglobulinaemia
- **Infections and Infestations:** bronchitis, cellulitis, clostridium difficile colitis, enterocolitis infectious, oral candidiasis, oral herpes, otitis media, pneumonia, pneumonia streptococcal, rhinovirus infection, sepsis, sepsis syndrome, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection
- **Injury, Poisoning and Procedural Complications:** wound
- **Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, computerised tomogram thorax abnormal, immunoglobulins decreased, weight decreased
- **Metabolism and Nutrition Disorders:** dehydration, failure to thrive, hyperglycaemia, hyperuricaemia, hypokalaemia, hypophosphataemia
- **Musculoskeletal and Connective Tissue Disorders:** joint swelling, muscle spasms, muscular weakness, myalgia, pain in extremity
- **Nervous System Disorders:** dizziness, dysgeusia, headache, lethargy, sinus headache, somnolence
- **Psychiatric Disorders:** agitation, anxiety
- **Renal and Urinary Disorders:** micturition urgency, renal failure, renal failure acute
- **Reproductive System and Breast Disorders:** scrotal cyst, semen discolouration
- **Respiratory, Thoracic and Mediastinal Disorders:** choking, cough, dysphonia, dyspnea, epistaxis, hypoxia, oropharyngeal pain, pneumonitis, productive cough, sinus congestion
- **Skin and Subcutaneous Tissue Disorders:** alopecia, cold sweat, dermatitis acneiform, dermatitis bullous, dry skin, ecchymosis, pruritus, rash, maculo-papular, rosacea, urticaria
- **Vascular Disorders:** hypertension

9.4 IBRUTINIB

Classification: Covalent inhibitor of the enzyme Bruton's tyrosine kinase (Btk)

Formulation: See Prescribing Information

How Supplied: 140 mg strength capsules

Storage:	See ibrutinib prescribing information
Route of Administration:	Oral
Potential Drug Interactions:	Avoid co-administration with strong and moderate CYP3A inhibitors. Subjects taking strong CYP3A inhibitors are excluded from this trial. If a moderate CYP3A inhibitor must be used, see ibrutinib prescribing information for dose reduction guidelines and further information. Also avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A and can alter ibrutinib pharmacokinetics. The coadministration of ibrutinib with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers.
Availability:	[redacted]

9.4.1 UBLITUXIMAB AND UMBRALISIB AND IBRUTINIB COMBINATION - COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in subjects treated with the combination of ublituximab and umbralisib and ibrutinib and were considered at least possibly related to one or more of the study medications in a TG Therapeutics, Inc. sponsored combination trial. For updated safety information on ublituximab and umbralisib and the list of adverse events of special interest, see the current Investigator's Brochures for ublituximab and umbralisib. See the current ibrutinib US full prescribing information for the list of warnings and precautions and updated safety information (https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf).

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** neutropenia, thrombocytopenia
- **Gastrointestinal Disorders:** diarrhoea, nausea, stomatitis, vomiting
- **General Disorders and Administration Site Conditions:** fatigue, pyrexia
- **Injury, Poisoning, and Procedural Complications:** infusion related reaction
- **Nervous System Disorders:** dizziness
- **Skin and Subcutaneous Tissue Disorders:** rash

Common (≥ 1% - < 10%)

- **Blood and Lymphatic System Disorders:** anaemia, increased tendency to bruise, leukocytosis, leukopenia, pancytopenia
- **Cardiac Disorders:** atrial fibrillation, atrial thrombosis, cardiac tamponade, palpitations, pericardial effusion
- **Ear and Labyrinth Disorders:** tinnitus, vertigo

- **Eye Disorders:** vision blurred
- **Gastrointestinal Disorders:** abdominal distension, abdominal pain, constipation, dyspepsia, gastroesophageal reflux disease, mouth ulceration, odynophagia, upper gastrointestinal haemorrhage
- **General Disorders and Administration Site Conditions:** asthenia, chills, feeling jittery, influenza like illness, oedema peripheral, pain
- **Immune System Disorders:** pemphigus
- **Infections and Infestations:** bronchitis, cellulitis, lung infection, oral candidiasis, oral herpes, paronychia, pneumonia, respiratory tract infection, sepsis, septic shock, sinusitis, skin candida, streptococcal bacteraemia, upper respiratory tract infection, urinary tract infection, varicella
- **Injury, Poisoning and Procedural Complications:** contusion
- **Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, coagulation time prolonged, lipase increased, weight decreased
- **Metabolism and Nutrition Disorders:** decreased appetite, hyperglycaemia, hypertriglyceridaemia, hypoalbuminaemia, hypocalcaemia, hypokalaemia, hypophosphataemia
- **Musculoskeletal and Connective Tissue Disorders:** arthritis, bone pain, muscle spasms, muscle tightness, musculoskeletal pain, myalgia, neck pain, pain in extremity
- **Neoplasms Benign, Malignant, and Unspecified:** basal cell carcinoma
- **Nervous System Disorders:** amnesia, headache, lethargy, mental impairment, neuropathy peripheral, subdural hygroma, syncope, tremor
- **Psychiatric Disorders:** anxiety, confusional state, insomnia
- **Renal and Urinary Disorders:** dysuria, haematuria, pollakiuria, polyuria
- **Reproductive System and Breast Disorders:** penile blister
- **Respiratory, Thoracic and Mediastinal Disorders:** cough, dysphonia, dyspnoea, haemoptysis, lung infiltration, oropharyngeal pain, pleural effusion, pneumonitis, pulmonary oedema
- **Skin and Subcutaneous Tissue Disorders:** alopecia, blister, butterfly rash, dermatitis bullous, dry skin, ecchymosis, eczema, epistaxis, onychoclasis, petechiae, pruritus, pruritus generalized, rash generalized, rash macular, rash maculo-papular
- **Vascular Disorders:** flushing, hypertension

9.5 VENETOCLAX

Classification:	B cell lymphoma 2 (BCL-2) Inhibitor
Formulation:	See package insert/prescribing information
Mode of Action:	High affinity binding and inhibition of BCL-2
How Supplied:	10, 50 and 100 mg tablets

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

Administration: Oral

Potential Drug Interactions: *Concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated per the USPI dated June, 2018.*

Packaging:

Packaging Presentation	Number of Tablets	National Drug Code
Starting Pack	Each pack contains four weekly wallet blister packs: •Week 1 (14 x 10 mg tablets) •Week 2 (7 x 50 mg tablets) •Week 3 (7 x 100 mg tablets) •Week 4 (14 x 100 mg tablets)	0074-0579-28
Starting Pack	Each pack contains four weekly wallet blister packs: •Week 1 (14 x 10 mg tablets) •Week 2 (7 x 50 mg tablets) •Week 3 (7 x 100 mg tablets) •Week 4 (14 x 100 mg tablets)	0074-0579-28
10 mg Wallet	14 x 10 mg tablets	0074-0561-14
50 mg Wallet	7 x 50 mg tablets	0074-0566-07
10 mg Unit Dose	2 x 10 mg tablets	0074-0561-11
50 mg Unit Dose	1 x 50 mg tablet	0074-0566-11
100 mg Unit Dose	1 x 100 mg tablet	0074-0576-11
100 mg Bottle	120 x 100 mg tablets	0074-0576-22

Availability: [redacted]

9.5.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS

See the current venetoclax US Prescribing Information (USPI) for the latest safety information including, but not limited to adverse drug reactions, contraindications, warnings and precautions (https://www.rxabbvie.com/pdf/venclexta.pdf).

System Organ Class MedDRA 17.1 Preferred Term	M12-175 Arm A N = 116 n (%)	M13-982 N = 158 n (%)	M14-032 N = 62 n (%)	Total N = 336 n (%)
Any adverse event	115 (99.1)	155 (98.1)	61 (98.4)	331 (98.5)
Blood and lymphatic system disorders	79 (68.1)	90 (57.0)	32 (51.6)	201 (59.8)
Anaemia	29 (25.0)	38 (24.1)	18 (29.0)	85 (25.3)
Neutropenia	52 (44.8)	63 (39.9)	15 (24.2)	130 (38.7)
Thrombocytopenia	24 (20.7)	29 (18.4)	12 (19.4)	65 (19.3)
Gastrointestinal disorders	95 (81.9)	103 (65.2)	41 (66.1)	239 (71.1)
Constipation	24 (20.7)	19 (12.0)	9 (14.5)	52 (15.5)
Diarrhoea	60 (51.7)	54 (34.2)	21 (33.9)	135 (40.2)
Nausea	55 (47.4)	53 (33.5)	19 (30.6)	127 (37.8)
Vomiting	22 (19.0)	17 (10.8)	9 (14.5)	48 (14.3)
General disorders and administration site conditions	76 (65.5)	83 (52.5)	29 (46.8)	188 (56.0)
Fatigue	46 (39.7)	33 (20.9)	13 (21.0)	92 (27.4)
Oedema peripheral	18 (15.5)	12 (7.6)	6 (9.7)	36 (10.7)
Pyrexia	30 (25.9)	25 (15.8)	2 (3.2)	57 (17.0)
Infections and infestations	92 (79.3)	111 (70.3)	27 (43.5)	230 (68.5)
Upper respiratory tract infection	60 (51.7)	25 (15.8)	4 (6.5)	89 (26.5)
Metabolism and nutrition disorders	71 (61.2)	68 (43.0)	38 (61.3)	177 (52.7)
Hyperphosphataemia	12 (10.3)	20 (12.7)	12 (19.4)	44 (13.1)
Hypokalaemia	16 (13.8)	13 (8.2)	8 (12.9)	37 (11.0)
Nervous system disorders	56 (48.3)	58 (36.7)	18 (29.0)	132 (39.3)
Headache	28 (24.1)	21 (13.3)	5 (8.1)	54 (16.1)
Respiratory, thoracic, and mediastinal disorders	70 (60.3)	49 (31.0)	19 (30.6)	138 (41.1)
Cough	35 (30.2)	16 (10.1)	8 (12.9)	59 (17.6)

9.5.2 WARNING PRECAUTIONS

The information summarized for venetoclax is based on the USPI dated June, 2018.

9.5.2.1 CONCERNS RELATED TO ADVERSE EFFECTS

Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL subjects with high tumor burden. Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5week 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. Reduced renal function (CrCl <80 mL/min) further increases the risk. Subjects should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemic agents. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and are contraindicated.

Grade 3 or 4 neutropenia occurred in 41% (98/240) of subjects treated. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF)

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

Based on its mechanism of action and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in subjects at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman. Advise females of reproductive potential to avoid pregnancy during treatment.

9.5.3 PHARMACODYNAMICS AND PHARMACOKINETICS

Absorption

Following multiple oral administrations under fed conditions, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state C max was 2.1 ± 1.1 µg/mL and AUC0-24 was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1-to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal.

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 µM (0.87-26 µg/mL). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution (Vdss/F) of venetoclax ranged from 256-321 L in subjects.

Elimination

The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. The pharmacokinetics of venetoclax does not change over time.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4/5. M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro*.

Excretion

After single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax dose to healthy subjects, >99.9% of the dose was recovered in feces and <0.1% of the dose was excreted in urine within 9 days, indicating that hepatic elimination is responsible for the clearance of venetoclax from the systemic circulation. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces.

10 MEASUREMENT OF EFFECT

During the study period, all subjects will be evaluated for response as per Section 7: Study Assessments and Treatment Schedules. The determination of response and progression will be based on iwCLL criteria (Hallek, et al., 2018). Radiographic and clinical tumor assessments will be performed by the study team/investigator.

All baseline assessments to characterize disease will be performed within 30 days of Cycle 1 Day 1.

10.1 METHOD OF ASSESSMENT

In addition to clinical examination, radiographic evaluation will be used in all subjects enrolled. 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 also 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 should not be used 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.

10.2 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

10.2.1 TARGET LESIONS

Measurable disease is not a requirement for study enrollment. For subjects with measurable disease 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 in disparate regions of the body. Only peripheral nodes need be selected as target lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

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 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 LD and >1.0 cm in the LPD will be considered progressive disease.

In cases in which a large lymph node mass has split into multiple components, all subcomponents 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.

10.2.2 SPLEEN AND LIVER

Both the spleen and liver will be assessed by CT/MRI scan and/or 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 further characterize the objective tumor response of the measurable dimensions of the CLL during treatment. All spleen and liver LVD measurements should be recorded in centimeters.

By imaging, the spleen will be considered enlarged if it is >12 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 ≤ 12 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.

10.2.3 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 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 during assessments of the objective tumor response during treatment. Measurements are not required, and these lesions should be followed as "present" or "absent".

10.3 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized by the treating investigator as CR, 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.

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). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

10.4 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 target nodal masses to normal size ≤1.5 cm in the LD
- Normal spleen and liver size

- Regression to normal of all nodal non-target disease and disappearance of all detectable non-nodal, non-target disease
- Peripheral blood counts meeting all of 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)

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

10.5 PARTIAL RESPONSE

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

- No evidence of new disease
- A change in disease status meeting ≥2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: 1) only lymphadenopathy is present at baseline; 2) only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:
  - 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
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 10.2.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 10.2.2
  - A decrease by ≥50% from baseline in the CLL 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:
  - ANC >1.5 x 10^9/L or >50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)
  - 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)

10.6 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

10.7 DEFINITIVE DISEASE PROGRESSION

The occurrence of any of the following events indicates definitive PD:

- Evidence of any new disease:
  - A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD
  - New or recurrent splenomegaly, with a minimum LVD of 14 cm
  - New or recurrent hepatomegaly, with a minimum LVD of 20 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).
- 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 and an LPD of > 1.0 cm
  - Splenic progression, defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
  - Hepatic progression, defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)
  - Unequivocal increase in the size of non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)
  - Transformation to a more aggressive histology (e.g., Richter's syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).
- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL 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
  - 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

*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.

If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be

considered definitive disease progression; in such subjects, both CLL-related and non-CLL-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. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

10.8 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.

10.9 LYMPHOCYTOSIS DURING THERAPY

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

11 STATISTICAL CONSIDERATIONS

11.1 SAMPLE SIZE AND POWER

The study includes two treatment cohorts. Cohort A is comprised of subjects who will receive ibrutinib in combination with ublituximab and umbralisib. Cohort B is comprised of subjects who will receive venetoclax in combination with ublituximab and umbralisib. Cohort C is comprised of subjects who will receive acalabrutinib in combination with ublituximab and umbralisib. The efficacy of the combination therapy will be evaluated separately for the three cohorts.

[redacted]

11.2 ANALYSIS POPULATIONS

Safety population:
The Safety Population will consist of all subjects who receive at least one dose of any study drug. It will be used to evaluate safety.

Intent-to-Treat (ITT) population:
The ITT population will consist of all subjects who receive any study drug. It will be used to evaluate efficacy endpoints. Subjects with detectable MRD at baseline who do not have disease assessment at any post-baseline visits will be considered non-responders.

11.3 PATIENT 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.

11.4 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.

11.5 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. The proportion of subjects completing each cycle of treatment will be summarized.

11.6 EFFICACY ANALYSES

Each subject will be assigned to one of the following categories: undetectable minimal residual disease or detectable minimal residual disease.

Further, response will be categorized as 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) 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 will be determined by the treating clinician. 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 lymphocytosis.

11.6.1 STATISTICAL ANALYSES

11.6.1.1 PRIMARY EFFICACY ENDPOINT

Best overall U-MRD rate will be reported as well as a proportion during cycles 3, 6, 9, 12, 15, 18, 21 and 24. The U-MRD rate is defined as the proportion of subjects with detectable MRD at baseline who convert to U-MRD in the peripheral blood on two sequential peripheral blood studies at least 4 weeks apart post-baseline. Subjects with detectable MRD at baseline 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 U-MRD rate. The 95% confidence intervals (Clopper-Pearson) for the MRD negativity rate will be presented.

11.6.1.2 SECONDARY AND EXPLORATORY EFFICACY OUTCOMES

Other efficacy outcomes include: time to undetectable minimal residual disease, overall response rate (ORR), complete response (CR) rate, progression free survival (PFS), time to second objective disease progression (PFS-2), [redacted], duration of peripheral blood U-MRD response, and treatment free survival (TFS).

11.6.1.2.1 TIME TO UNDETECTABLE MINIMAL RESIDUAL DISEASE

Time to undetectable minimal residual disease is defined as the interval from enrollment to the first assessment of U-MRD. It will be estimated by the Kaplan Meier method. For subjects who do not achieve U-MRD, it will be censored at the last MRD assessment.

11.6.1.2.2 OVERALL RESPONSE RATE

ORR will be determined according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (Hallek et al. 2018).

Overall Response Rate (ORR) is defined as percent of subjects who achieve CR or PR. Best ORR may be reported as well as a proportion during the first 6, 12, 18 and 24 cycles. The 95% confidence intervals for the response rates will be presented. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters.

11.6.1.2.3 COMPLETE RESPONSE RATE

CR rate is defined as the percent of subjects who achieve a CR. CR may be reported as a proportion during the first 6, 12, 18 and 24 cycles and overall. The 95% confidence intervals will be presented. Additional logistic analyses model may be used to assess the impact of demographic and baseline parameters.

11.6.1.2.4 PROGRESSION FREE SURVIVAL

The median PFS and the probability of subjects alive and progression-free during the first 6, 12, 18, and 24 cycles will be estimated using the Kaplan-Meier method. PFS is defined as the interval between enrollment and the earlier of date of progression or death due to any cause. For each estimate, a 95% confidence interval will be reported. For subjects who are alive without definitive disease progression, it will be censored at the last assessment.

11.6.1.2.5 TIME TO SECOND OBJECTIVE DISEASE PROGRESSION (PFS2)

PFS2 is defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression on next-line treatment or death from any cause. The median duration of PFS2 and the probability of subjects who are alive and do not have progression on next-line treatment during the first 6, 12, 18 and 24 cycles will be estimated using the Kaplan-Meier method. For subjects alive without definitive disease progression on next-line treatment (including subjects who are alive and do not have next-line treatment), it will be censored at the last assessment.

Definitive disease progression based on standard criteria (Hallek, et al., 2018) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms). Note that lymphocytosis in the absence of other evidence of disease progression does not constitute disease progression.

[redacted]

11.6.1.2.7 DURATION OF PERIPHERAL BLOOD UNDETECTABLE MINIMAL RESIDUAL DISEASE RESPONSE

Duration of U-MRD response is defined as the interval from the first documentation of undetectable MRD to the earlier of the first documentation of presence of MRD or death from any cause. The Kaplan-Meier estimate for the duration will be based on subjects who achieve U-MRD response. For subjects alive without presence of MRD, it will be censored at the last MRD assessment.

11.6.1.2.8 TREATMENT-FREE SURVIVAL

Treatment free survival (TFS) is defined as the interval from drug discontinuation to the earlier of initiation of retreatment for disease progression requiring treatment or death from any cause. Disease progression requiring treatment is based on standard criteria (Hallek, et al., 2018). TFS will be estimated using the Kaplan-Meier method for subjects who discontinued initial study treatment. For subjects alive without initiation of retreatment, it will be censored at the last date know alive.

11.1 SAFETY ANALYSES

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented by the treatment regimens received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

12 ADVERSE EVENT REPORTING AND CRITERIA

12.1 ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a subject or 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 drug has been administered. It is the responsibility of the Investigator, based on his/her knowledge and experience, to determine which untoward medical occurrences should be considered AEs.

12.2 CRITERIA FOR SERIOUS ADVERSE EVENT

The criteria for serious adverse events (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 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 judgment 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 an SAE.

Situations Not Considered SAEs:
Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient 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.

12.3 ADVERSE EVENTS / SERIOUS ADVERSE EVENT GRADING

The Investigator should use the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for grading severity of AEs. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf#search=%22ctcae%205.0%22

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 noninvasive 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.

12.4 ADVERSE EVENTS (AE'S) AND TREATMENT EMERGENT ADVERSE EVENTS (TEAE'S)

All AEs and SAEs occurring on study will be listed by subject. The frequency and percentages of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term (PT), where treatment-emergent is defined as any AE that:

- Occurs after first dosing of study medication and through the end of the study or up through 30 days after the last dose of study treatment, or
- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related.

TEAEs that are considered at least possibly related to study treatment will be tabulated as well as deaths, SAEs, and events resulting in treatment discontinuation.

At each level of summarization, a subject will be counted only once for each AE, SOC, or PT experienced within that level. In the summation for AE severity, within each level of AE, SOC, or PT experienced, the one with the highest severity will be included. In the summation for AE's relationship to the study drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the study drug will be included.

12.5 ADVERSE EVENTS / SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the relationship of any adverse event to the use of study drugs (whether none, one, or both), 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.

12.5.1 RECORDING OF ADVERSE EVENTS

All adverse events of any subject during the course of the study will be reported on the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to study drug treatment (i.e., whether the event is related or unrelated to study drug administration – either ublituximab, umbralisib, venetoclax, ibrutinib). If the adverse event is serious, it should be reported as soon as possible and no greater than 24 hours to the sponsor or designee. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to ublituximab, umbralisib, venetoclax or ibrutinib from Cycle 1/Day 1 until 30 calendar days after discontinuation or completion of either protocol-specific treatment as defined by the protocol for that subject, are to be recorded on the eCRF.

12.5.2 ABNORMAL LABORATORY VALUES AND VITAL SIGNS

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the subject to discontinue study treatment, or the investigator insists that the abnormality should be reported as an AE. Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, 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.

Clinical Laboratory Results will be summarized. Summary statistics for actual values and for changes from baseline will be tabulated for 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 when applicable. Subject incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

12.5.3 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization. Subjects should be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment (ublituximab, umbralisib, venetoclax, ibrutinib or acalabrutinib). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the eCRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

12.6 SERIOUS ADVERSE EVENTS

12.6.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

The definitions of serious adverse events (SAEs) are given 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:

- results in death,
- is immediately life-threatening,
- requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. 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 malignancy (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 serious adverse event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is suspected to be at least possibly related to study medication(s) and is an unexpected event. SUSAR reporting is encompassed within SAE reporting guidelines as defined in this section.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- 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 a serious adverse event to the Sponsor.

12.6.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

It is important to distinguish between "serious" and "severe" adverse events, 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.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last study treatment. Sponsor or designee should be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, see the appropriate form.
All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to the sponsor as SAEs within the CRF and on the SAE form followed until resolution (with autopsy report if applicable).

CLL progression or death due to CLL progression should be reported by the investigator as a serious adverse event only if it is assessed that the study drugs caused or contributed to the CLL progression (i.e. by a means other than lack of effect). Unrelated events of CLL progression should be captured on the appropriate eCRF.

The investigator must review and sign off on the SAE data on the SAE report. The SAE should be reported to the Sponsor at safety-inbox.biotech@iqvia.com within 24 hours of the first knowledge of the event by the treating physician or research personnel on the SAE Form and followed until resolution (with autopsy report if applicable). When an SAE is reported to the sponsor or designee, the same information should be entered on the eCRF within 24 hours (1 business day). Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate SAE form.

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

12.7 SPONSOR SAE REPORTING REQUIREMENTS

Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the regulatory agencies and competent authorities by a written safety report within 15 calendar days of notification. Following the submission to the regulatory agencies and competent authorities, Investigators and trial sites will be notified of the SUSAR. Investigators must report SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

12.8 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported.

12.9 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 after the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

12.9.1 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 AE 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 AE 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 AE eCRF for each recurrence.

12.9.2 ABNORMAL LABORATORY VALUES

Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, 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.

12.9.3 DEATHS

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of the subject's CLL for up to 30 days post the last dose of study drug will not be reported as an AE. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sponsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical

concept on the Adverse Event 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 Adverse Event page.

12.9.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission of >24 hours or prolongs hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. See section 12.6.1.

12.9.5 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 AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

12.9.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

The following are events of special interest, and will need to be reported expeditiously:

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female subjects of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix B- Contraceptive Guidelines and Pregnancy) 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 as soon as possible.

If a subject becomes pregnant while enrolled in the study, an SAE form should be completed and submitted to the Sponsor. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor. Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting.

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, subjects should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary and Second Malignancy

Any secondary malignancy (occurring as a direct result of study drug administration, including but not limited to MDS) and/or second primary malignancy (unrelated, new cancer, including but not limited to MDS and MPD) event must be reported via the SAE form (in addition to the routine AE reporting mechanisms). Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in the protocol.

13 CLINICAL DATA COLLECTION AND MONITORING

13.1 SITE MONITORING PLAN

A Sponsor representative or designee will have made a site visit to each institution within 12 months prior to initiating the protocol to inspect the drug storage area, and fully inform the Investigator of his/her responsibilities for studies and the procedures for assuring adequate and correct documentation.

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 initiation, the electronic case report forms (eCRFs) and other pertinent study materials will be reviewed with the investigator's research staff. During the course of the study, the Sponsor will make visits to the sites as necessary in order to review protocol compliance, examine eCRFs, and individual subject medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that subject confidentiality is maintained.

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.

13.2 CURRICULA VITAE AND FINANCIAL DISCLOSURES

All Principal Investigators will be required to submit to the Sponsor or its designee an up-to-date signed curriculum vitae (CV), current within two years, a current copy of their medical license, and a completed FDA form 1572 and financial disclosure statement. In addition, all sub-investigators will be required to submit to the Sponsor or its designee an up-to-date signed CV, current within two years, a current copy of their medical license, and a completed financial disclosure statement.

13.3 DATA OWNERSHIP AND PUBLICATION

By conducting this study, the Investigator affirms to Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes. 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.

14 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, 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 documents (e.g., study diary), subject recruitment procedures (e.g., 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 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. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

If applicable, the PI will notify the IRB **within 90 days** of the end of the study, or if the study terminates early, the PI must notify the IRB **within 15 days** of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC). The Sponsor will either prepare or review all submission documents prior to submission to the IRB.

14.2 REGULATORY APPROVAL

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies 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. 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. HIPAA regulations require that, in order to participate in the study, a subject must sign an authorization from the study that he or she has been 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.

Measures to protect confidentiality include: only a unique study number and initials will identify subjects 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. Subject names or addresses will not be entered in the eCRF or database. 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.

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

Before the study may begin, certain documentation required by FDA regulations and/or local regulatory authorities must be provided by the Investigator. The required documentation should be submitted to the Sponsor.

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;
- 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;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB-approved consent form containing permission for audit by representatives of the Sponsor, the IRB, and the FDA;
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- GCP Certificate for study training;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

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

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 where appropriate.

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 Section 13 and 21 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, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. 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

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of the Sponsor and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted to the FDA or other regulatory authorities by the Sponsor as applicable, and specifically when an increase to dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and REC and/or FDA and Competent Authority approval include, but are not limited to, the following:

- Change to study design
- Risk to subject
- Increase to dose or subject exposure to drug
- Subject number increase of more than 20%
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, 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, initials and date of birth will identify the subject in the eCRF. If the subject's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the subject number and subject's initials. 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.
Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities and the sponsor or its representative(s).

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

In addition to the Clinical Monitoring component of this protocol, the Sponsor's Quality Assurance (QA) department shall establish an Auditing Plan document separate from the protocol to establish the criteria by which independent auditing shall 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 applicable regulations.

Each study site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for study conduct, 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) and by the maintenance of a drug–dispensing log by the investigator. 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. The Sponsor reserves the right to release literature publications based on the results of the study.

A clinical study report will be prepared upon completion of the study. The Sponsor will disclose the study results, in the form of a clinical study report synopsis, to the IEC and the applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report and its addendum will comply with ICH E3 guidelines for structure and content of a clinical study report.

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.

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 data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes.
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.

16 REFERENCES

Abrisqueta, P., Villamor, N., Terol, M., González-Barca, E., González, M., et al. (2013) Rituximab maintenance after first-line therapy with rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) for chronic lymphocytic leukemia. *Blood*, 122(24), 3951-3959.

Altekruse SF, K. C. (2010, November). *SEER Cancer Statistics Review*. Retrieved from seer.cancer.gov: http://seer.cancer.gov/csr/1975.2007

Barr P, Robak, T., Owen, C. J., Tedeschi, A., Bairey, O., Bartlett et al. (2016). Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. *Blood*, 128(22), 234.

Bottcher, S., Ritgen, M., Fischer, K., Stilgenbauer, S., Busch, R., et al. (2012). Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *Journal of Clinical Oncology*, 30(9), 980-988.

Burris HA, Flinn I., Patel MR., Fenske TS., Deng C., et al. (2018). Umbralisib, a novel PI3Kδ and casein kinase-1ε inhibitor, in relapsed or refractory chronic lymphocytic leukaemia and lymphoma: an open-label, phase 1, dose-escalation, first-in-human study. *Lancet Oncology*, 19(4), 486-496.

Cazin B, Leprêtre S., Coiffer B., Aurran T., Cartron G, et al. (2013). Final results of a multicenter phase Ib single agent study with the novel anti-CD20 monoclonal antibody ublituximab (TG-1101) in patients with relapsed chronic lymphocytic leukemia (CLL). presented at the Congress of the European Hematology Association, Stockholm, Sweden, June 13-16, 2013 (p. abstractP111).

de Romeuf C, Dutertre CA, Le-Garff-Tavernier M, Gaucher C, Glacet A. et al. (2008). Chronic lymphocytic leukaemia cells are effeciently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. *British Journal of Haematology, 6*(140), 635-643.

Dimier, N., Delmar, P., Ward, C., Morariu-Zamfir, R., Fingerle-Rowson, G., et al. (2018). A model for predicting effect of treatment on progression-free survival using MRD as a surrogate endpoint in CLL. *Blood*, 955-962.

Esteves IT, Dumontet C, Herveau, S, Reslan L, Brune F, et al. (2011). LFB-R603 (ublituximab), a third-generation monoclonal anti-CD20 antibody, displays additive antitumor activity with antileukemic chemotherpeutic agents in mouse xenograft models. *American Society of Hematology*, abstract 1660.

Fischer, K., Cramer, P., Busch, R., Böttcher, S., Bahlo, J., et al. (2012). Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *Journal of Clinical Oncology*, 3209-3216.

Genentech Inc. (2013, September). Rituxan (rituximab) Prescribing Information. South San Francisco, CA.

Global Burden of Disease Cancer Collaboration. (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.*, 524. Retrieved June 5, 2014, from www.cancer.org: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

Goede, V., Fischer, K., Busch, R., Engelke, A., Eichhorst, B., et al. (2014). Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *New England Journal of Medicine*, 370, 1101-1110.

Hallek, M., Cheson, B., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., et al. (2018). Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. *Blood*, 131(25), 2745-2760.

Hallek, M., Cheson, B., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., et al. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood, 111(12*), 5446-5456.

Hillmen P, A. P. (2018). High, durable minimal residual disease negativity (MRD–) with venetoclax + rituximab (VenR) in relapsed/refractory (R/R) CLL: MRD kinetics from phase 3 MURANO study. *J Clin Oncol, 36*, Suppl; abstr 7508.

Lin, K., Sherrington, P., Dennis, M., Matrai, Z., Cawley, J., et al. (2002). Relationship between p53 dysfunction, CD38 expression, and IgV(H) mutation in chronic lymphocytic leukemia. *Blood*, 100(4): 1404-9.

Lunning, MA, Vose JM, Schreeder MT, Fowler N, Nastoupil L, et al. (2014) Ublituximab, a Novel Glycoengineered Anti-CD20 mAb, In Combination with TGR-1202, a Next Generation Once Daily PI3Kδ Inhibitor Demonstrates Activity in Heavily Pre-Treated and High-Risk Chronic Lymphocytic Leukemia and B-Cell Lymphoma. Blood, 124(21): 801.

Lunning, M. A., Vose, J., Fowler, N., Nastoupil, L., Burger, J. A., et al. (2015). Ublituximab TGR-1202 Demonstrates Activity and a Favorable Safety Profile in Relapsed/Refractory B-Cell NHL and High-Risk CLL: Phase I Results. *Blood*, *126*(23), 1538–1538.

Nastoupil, L. J., Lunning, M. A., Vose, J. M., Schreeder, M. T., Siddiqi, T., et al. (2019). Tolerability and activity of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: a phase 1 dose escalation and expansion trial. *The Lancet Haematology*, *6*(2):e100-e109.

O'Connor OA, D. C. (2014). A phase I trial of ublituximab (TG-1101), a novel anti-CD20 monoclonal antibody (MAB) in B-cell lymphoma patients with prior exposure to rituximab. *American Society of Clinical Oncology*, (p. abstract 8524). Chicago.

[redacted] (2011). *PI3Kgamma enzyme assay.* Shameerpet, India: Incozen Therapeutics.

Sawas A, F. C. (2017). A phase 1/2 trial of ublituximab, a novel anti-CD20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia previously exposed to rituximab. *British Journal of Haematology*, 243-253.

[redacted] (2011). *AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

[redacted]((2011). *AKT phosphorylation in THP-1 cells. Study Report IVT-5264-ATP-08.* Shameerpet, India: Incozen Therapeuticis PVT Ltd.

Sharman, J. P., Farber, C. M., Mahadevan, D., Schreeder, M. T., Brooks, H. D., et al. (2016). Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *British Journal of Haematology*, *176*(3), 412–420.

Thompson, P., Peterson, C., Strati, P., Jorgensen, J., Keating, M., et al. (2018). Serial minimal residual disease (MRD) monitoring during first-line FCR treatment for CLL may direct individualized therapeutic strategies. *Leukemia*, 32(11);2388-2398.

17 APPENDIX A – CLL RESPONSE DEFINITION

Assessment of response will follow the guidelines published by Hallek et al. (2018).

Assessment of response should include a careful physical examination and evaluation of the blood and marrow.

Table 4 - Response definition after treatment for CLL patients

GROUP	PARAMETER	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1,5 cm	Decrease ≥ 50% (from baseline) [1)]	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size*	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline	Change of -49% to +49%
B	Platelet count	≥ 100.000/µl	≥ 100.000/µl or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49 to +49%
	Hemoglobin	≥ 11,0 g/dl (untransfused and without erythropoietin)	≥ 11 g/dl or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dl from baseline secondary to CLL	Increase < 11,0 g/dl or < 50% over baseline, or decrease < 2 g/dl
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules.	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

1) Sum of the products of 6 or less lymph nodes (as evaluated by CT scans and physical exam in clinical trials, or by physical exam in general practice).

CR, complete remission: all of the criteria have to be met; **PR, partial remission**: for a PR at least 1 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal. If only one parameter of both groups A and B is abnormal prior to therapy, only 1 needs to improve. **PD, progressive disease**: at least one of the above criteria of group A or group B has to be met; **SD, stable disease**: all of the above criteria have to be met. Constitutional symptoms alone do not define PD.

*Spleen size is considered normal if < 13 cm. There is not firmly established, international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

18 APPENDIX B- CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

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

Contraceptive Guidelines for Females of Child-Bearing Potential:

Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, must use effective contraception during the study and for 4 months after the last dose of ublituximab or umbralisib, and for at least 30 days after the last dose of ibrutinib, acalabrutinib or venetoclax. 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 six 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 two 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 childbearing 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 ≤ 3 days prior to initiating treatment.

Fertile Males

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 4 months after the last dose of ublituximab or umbralisib, and for at least 30 days after the last dose of ibrutinib, acalabrutinib or venetoclax. They should also not father a child during this period.

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to TG Therapeutics within 24 hours of learning of its occurrence as outlined in the Safety Reporting section of this protocol. The pregnancy, both pregnant female and infant (if applicable), should be followed up for 6 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

19 APPENDIX C – 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.

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

CDC

www.cdc.gov/hepatitis

21 APPENDIX E – CYP3A INDUCERS, CYP3A INHIBITORS, P-GP INHIBITORS AND P-GP SUBSTRATES

Examples of clinical **inhibitors** for P450-mediated metabolisms. Please note this is not a comprehensive list, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers for more information.

	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