Official Title:	**A Multi-Center, Open-Label, Study to Evaluate the Safety and Efficacy of Ublituximab (TG-1101) in Combination With TGR-1202 for Patients Previously Enrolled in Protocol UTX-TGR-304**
NCT Number:	NCT02656303
Document Date:	Protocol Version 6.0: 23 February 2019

Protocol version/Date: Version 6.0/January 22, 2019

Local Protocol #: Protocol UTX-TGR-204

TITLE:

A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304

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

IND Numbers: **Ublituximab** 114,779 **Umbralisib (TGR-1202)** 116,762

Study Chair: [redacted], MD, PhD
[redacted]
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Tel: [redacted] ext. [redacted]

Study Coordination: TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
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Version: 1.0	**Date:** 14 September 2015
Version: 2.0	**Date:** 24 August 2016
Version: 3.0	**Date:** 7 March 2017
Version: 4.0	**Date:** 29 March 2017
Version: 5.0	**Date:** 20 October 2017
Version: 6.0	**Date: 22 January2019**

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol UTX-TGR-204 for issuance.

Protocol Title:	**A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304**
Protocol Number:	UTX-TGR-204
Trial Drug:	Ublituximab (TG-1101) + Umbralisib (TGR-1202)
IND Numbers:	**Ublituximab** 114,779 **TGR-1202** 116,762
Date FINAL:	22 January 2019

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted] MD
Print Name

[redacted]

[redacted]
Date

STUDY CHAIR

[redacted] MD, PhD
Print Name

[redacted]

[redacted]
Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted]
Print Name

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2/23/2019
Date

[redacted] MS, MSF
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[redacted]
Signature

2/23/2019
Date

STATISTICIAN, Consultant to TG Therapeutics, Inc.

[redacted] Ph.D.
Print Name

[redacted]
Digitally signed by [redacted]
Date: 2019.02.23 12:44:52 -05'00'
Signature

Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304	
Protocol Number:	UTX-TGR-204	
Trial Drug:	Ublituximab (TG-1101) + Umbralisib (TGR-1202)	
IND Numbers:	**Ublituximab**	**TGR-1202**
	114,779	116,762
Date FINAL:	22 January 2019	

I have read the attached protocol and agree that it contains all the necessary details for performing UTX-TGR-204.

I will provide copies of the protocol and of the ublituximab and umbralisib Investigators' Brochures, which were furnished 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 and the conduct of the study.

Once the protocol has been approved by the IRB/IEC, I will not modify this protocol without obtaining the prior approval of TG Therapeutics and of the IRB/IEC. 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

Version 2.0 (Dated 24 August 2016) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- All subjects are now required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy, whereas this was previously at investigator discretion (See Section 6.2.2);
- The phrasing of response assessment intervals has been revised for clarity from "at Weeks 12, 24, 36, 48, and every 12 weeks thereafter," to "following the completions of cycles 3, 6, 9 12, 15, 18 and every 3 cycles thereafter";
- Schedule of assessments and treatment schedule (Section 5) was updated, including
    - Revised wording for Tumor Evaluation (as listed above) and
    - Updated Urine Pregnancy Test schedule,
- The shelf life of ublituximab has been increased to 36 months from 24 months when stored between +2°C / +8°C to reflect newly available stability data on ublituximab drug product; and
- Sections 7.1.1, and 7.2.1 were updated to include the most recent adverse event information related to ublituximab and TGR-1202 corresponding to the latest Investigator Brochures.

Version 3.0 (Dated 7 March 2017) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- Inclusion criteria #1a has been updated to provide a minimum time on a study arm of 2 cycles
- Inclusion criteria #2 has been updated to include units (per microliter) in regard to absolute neutrophil count and platelet count;
- Exclusion criteria #4 has been updated to clarify prophylaxis as "anti-pneumocystis pneumonia prophylaxis";
- Exclusion criteria #6 has been added to exclude subjects with prior live virus vaccines;
- Appendix B – Contraceptive Guidelines and Pregnancy has been revised to delete the word "highly" effective as well as to include follow up recommendations for subjects entering the study from treatment arm B in study UTX-TGR-304 (obinutuzumab arm).
- CT scan evaluation has been revised to allow for every 3 or 6 cycle CT Scans after Cycle 9 at the discretion of the investigator, to limit exposure to radiation.
- The 21-day timeframe for signing informed consent has been removed.

Version 4.0 (Dated 29 March 2017) of this Protocol is the third amendment to this clinical trial and contains the following modifications:

- Definition of Serious Adverse Event has been updated.

Version 5.0 (Dated 20 October 2017) of this Protocol is the fourth amendment to this clinical trial and contains the following modifications:

- Inclusion Criteria 1a was updated to include the statement: There is no required timeframe to begin treatment on the 204 protocol, however, if other therapies to treat the disease are implemented in the interim, the subject will not be eligible to enroll in the study.
- Exclusion Criteria 4 was updated to clarify the use of anti-pneumocystis pneumonia prophylaxis

- Treatment schedule in section 5 was updated to:
  - increase the screening period from 21 to 28 days.
  - include MRD testing for subjects who have a PR
  - increase the window for scans from +/- 7 days to +/- 14 days
- Section 6.1 was updated to specify the treatment schema for subjects crossing over from each of the 4 arms in the 304 protocol
- Section 6.2.1.3.1 and Section 7.1 were both updated to include information regarding a new vial size for ublituximab;
- Sections in 6.4 were updated with the latest dose delay/modification guidance for ublituximab and TGR-1202. This section also includes guidance for diarrhea and colitis events.
- Section 6.4.3 was updated to include process of transferring drug from the 304 protocol, if applicable
- Sections 7.1.1, and 7.2.1 were updated to include the most recent adverse event information related to ublituximab and TGR-1202 corresponding to the latest Investigator Brochures;
- The following statement was removed from section 8.2.1: "At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be considered. Because nodal target lesions that have one or both diameters >0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2 (i.e., if all lymph nodes measure < 1.0 cm^2)" to allow for more accurate measurements of nodal target lesions.
- Minor administrative updates and typographical errors were corrected throughout.
- Updated throughout to include the generic name of TGR-1202: umbralisib

Version 6.0 (Dated 22 January 2019) of this Protocol is the fifth amendment to this clinical trial and contains the following modifications:

- Protocol updated throughout with minor editorial and administrative changes.
- Section 3 Eligibility Criteria updated as follows:
  - Inclusion Criteria 2a clarified to account for subjects with cytopenias due to bone marrow involvement.
  - Inclusion Criteria 2b clarified to allow subjects with Gilbert's Disease and Autoimmune Hemolytic Anemia.
  - Inclusion Criteria 2d updated to utilize the modified Cockcroft Gault utilizing ideal body mass.
  - Exclusion Criteria 4 added as follows - Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV IgM is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by PCR
- Section 5 Study Assessments and Treatment Schedule updated as follows:
  - Tumor Evaluations updated within the table with the following language - Evaluations are to be obtained during cycles 3, 6 & 12. Following cycle 12, evaluations should occur at least every 12 cycles.

  - Serum Virology added to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM at screening and CMV surveillance added while subjects are receiving umbralisib.
- Section 5 - Table 2: Follow Up Assessments Schedule added to clarify follow up assessments if a subject comes off study drug.
- Section 6 Treatment Plan: Updated to clarify PJP and anti-viral prophylaxis language and modified to provide more clear guidelines for timing of pre-medications for ublituximab.
- Section 6.4 Dosing Delays/Dose Modification: Removed requirement for subjects to discontinue study drugs if held for more than 28 days.
- Section 7.3 Comprehensive Adverse Events and Potential Risks (CAEPRS) – Ublituximab + TGR-1202 Combination updated based on Investigator Brochures Version 6.0, dated 20JUL2018.

STUDY SYNOPSIS

Protocol No.	UTX-TGR-204
Study Title	A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304
Sponsor	TG Therapeutics Inc. (New York, NY, USA)
Study Sites & Enrollment	This study will be opened only at sites that participate in the parent trial UTX-TGR-304.
Study Rationale	Ublituximab (also known as TG-1101) 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 causes lysis of B cells. Umbralisib (also known as TGR-1202) is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies. Ongoing studies are evaluating the combination of ublituximab + TGR-1202 in subjects who previously relapsed from or are refractory to anti-CD20 antibody therapy as well as PI3K delta inhibitor therapy (Lunning, et. al. ASCO 2015, Fowler, et. al. ASCO 2015). A Phase 3, randomized study (UTX-TGR-304) to assess efficacy and safety of ublituximab in combination with TGR-1202 compared to obinutuzumab in combination with chlorambucil in subjects with CLL is being conducted. UTX-TGR-304 will also compare ublituximab alone and TGR-1202 alone to the combination of ublituximab plus TGR-1202. This protocol is intended to provide the opportunity for subjects who progress on UTX-TGR-304 Treatment Arms B (obinutuzumab plus chlorambucil), C (ublituximab), or D (TGR-1202) to receive treatment with the combination. Additionally, at the time of UTX-TGR-304 study closure, this protocol is intended to allow subjects from Treatment Arm A (ublituximab plus TGR-1202) to continue combination therapy.
Study Objectives	**For subjects previously on Arms B, C, & D of Study UTX-TGR-304:** **Primary Objectives** • To observe the overall response rate (ORR) defined as the sum of complete responses (CR) and partial responses (PR) **Secondary Objective** • To observe the progression-free survival (PFS) and duration of response (DOR) • To observe the % of subjects that achieve MRD negativity

	• To observe the safety of ublituximab in combination with TGR-1202 **For subjects previously on Arm A of Study UTX-TGR-304:** **Primary Objectives** • To evaluate the progression-free survival (PFS) and duration of response (DOR) **Secondary Objective** • To evaluate the safety of ublituximab in combination with TGR-1202
Inclusion Criteria	1. Prior treatment in clinical trial UTX-TGR-304 a. Confirmed progression by IRC from Arms B, C, or D after at least two cycles of treatment in trial UTX-TGR-304. There is no required timeframe to begin treatment on the UTX-TGR-204 protocol; however, if other therapies to treat the disease are implemented in the interim, the subject will not be eligible to enroll in the study. b. Non-progressing subjects from Arm A may be eligible for enrollment when protocol UTX-TGR-304 is completed 2. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) > 750 x 10^3/mm^3 (0.75 K/µL) mL of blood / platelet count > 40 x 10^3/mm^3 (40 K/µL) mL of blood unless cytopenias are related to bone marrow involvement. b. Total bilirubin ≤1.5 times the upper limit of normal (ULN) with the exception of Gilbert's Disease and 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 (using ideal body mass [IBM]). 3. ECOG performance status ≤ 2 4. Ability to swallow and retain oral medication 5. Willingness and ability to comply with trial and follow-up procedures, give written informed consent
Exclusion Criteria	1. Prior treatment with obinutuzumab + chlorambucil (Arm B subjects) or ublituximab (Arm C subjects) within 7 days of Cycle 1/Day 1. 2. Subjects refractory to (progressing on) UTX-TGR-304 Treatment Arm A (ublituximab + TGR-1202). 3. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation). 4. Evidence of chronic active Hepatitis B defined as Hepatitis B surface antigen positive or Hepatitis B DNA positive by PCR (HBV, NOT including subjects with prior hepatitis B vaccination who are Hepatitis B surface antibody positive only;) or chronic active Hepatitis C infection (HCV) defined as Hepatitis C RNA positive by PCR, cytomegalovirus (CMV) DNA positive by PCR, or known history of HIV. If HBc antibody, HCV antibody or CMV IgG and/or IgM antibody is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by PCR - See Appendix D.

	5. 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 pneumonia prophylaxis is required prior to Cycle 1/Day 1 and for the first 2 cycles. After cycle 2, is per investigator discretion. 6. Woman who are pregnant or lactating. 7. Live virus vaccines four (4) weeks prior to or during ublituximab therapy.
Efficacy Endpoints	**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. 2008) 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) other than lymphocytosis. **Minimal Residual Disease (MRD) Negativity Rate** MRD negativity rate is defined as the proportion of subjects who are MRD negative. **Duration of response (DOR)** DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause.
Safety Endpoints	All AEs will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v4.0.
Study Design	This study is intended to serve as a compassionate use study to allow subjects who have previously progressed on Arms B, C & D in the parent trial UTX-TGR-304 to receive ublituximab plus TGR-1202. Those subjects must have had confirmed disease progression by the independent radiology committee (IRC). Additionally, at the termination of study UTX-TGR-304, non-progressed subjects from Treatment Arm A may be enrolled to this study. Subjects from Treatment Arms B, C, and D may start treatment with ublituximab + TGR-1202, while subjects entering this study from Treatment Arm A may continue their treatment until they show disease progression, are unable to continue treatment for any reason such as lack of tolerability, or until the treatment is commercially available.

<table>
<tr><td></td><td>During the study period, all subjects will be evaluated for response by CT and/or MRI. Evaluations are to be obtained at approximately cycles 3, 6, and 12. Following cycle 12, evaluations should occur at least every 12 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have scans completed per institutions standard of care and reported in the EDC until progressive disease or subject begins another anti-cancer treatment. Date of progression, beginning of new treatment, and/or death should be entered in the eCRF. Subjects should remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator discretion or other reasons. Subjects who discontinue from study treatment and have not progressed should continue to be followed for progression.</td></tr>
<tr><td>Dosing Regimen</td><td>Each Cycle = 28 days

<u>Ublituximab + TGR-1202 Regimen</u>

Subjects will receive ublituximab + TGR-1202 as described in protocol UTX-TGR-304. Subjects will receive TGR-1202 orally daily and ublituximab as an intravenous administration as per the schedule specified in the parent protocol and outlined in the table below. This schedule is specific to subjects that were in UTX-TGR-304 Arms B, C, and D. Subjects previously in Arm A of protocol UTX-TGR-304 will continue the schedule received while on study UTX-TGR-304 with TGR-1202 orally daily, and ublituximab every 3 months.

Cycle 1:
<table>
<tr><th colspan="3">Ublituximab</th><th>TGR-1202</th></tr>
<tr><th>Day 1</th><th>Day 2</th><th>Day 8 & 15</th><th>Daily</th></tr>
<tr><td>150 mg</td><td>750 mg</td><td>900 mg</td><td>800 mg</td></tr>
</table>
Cycles 2 through 6:
<table>
<tr><th>Ublituximab</th><th>TGR-1202</th></tr>
<tr><th>Day 1</th><th>Daily</th></tr>
<tr><td>900 mg</td><td>800 mg</td></tr>
</table>
After Cycle 6:
<table>
<tr><th>Ublituximab</th><th>TGR-1202</th></tr>
<tr><th>Day 1, Q3 months</th><th>Daily</th></tr>
<tr><td>900 mg</td><td>800 mg</td></tr>
</table>
Ublituximab Premedication:

Ublituximab should be started approximately 30 minutes after the conclusion of the last pre-medication infusion and should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). If pre-medication is given orally, they should be given approximately 45-60</td></tr>
</table>

	minutes prior to the beginning of the ublituximab infusion. After Cycle 1, adjustments may be made to the antihistamine and/or corticosteroid dosing if deemed medically necessary. Please contact TG Therapeutics with any questions. Ublituximab infusion in Cycle 1 only is split between Day 1 and Day 2, with the subject receiving up to 150 mg on Day 1 and remainder of the dose on Day 2 for subject crossing over from UTX-TGR-304 Arms B and D For all 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.
Study Drugs	Ublituximab is a glycoengineered, recombinant chimeric monoclonal antibody against the CD20 antigen, available as a 10 mg/mL or 25 mg/mL concentrate for solution for infusion, supplied by TG Therapeutics, Inc. Umbralisib (TGR-1202) is a highly specific and orally available PI3K delta (δ) inhibitor available in 200 mg tablets, supplied by TG Therapeutics, Inc.
Statistical Considerations	Subjects from Treatment Arms B, C and D in Study 304 may enter this study upon documented progression of disease as confirmed by the independent central radiology review group. At the end of Study 304, non-progressed subjects from Treatment Arm A may also be enrolled to this Phase 2 Companion Study. It is undetermined the number of subjects that may enter this Companion Study, however it may not exceed the total number of subjects that have enrolled in Study 304. As this study is intended as a compassionate use study for subjects progressing on Study 304, no formal hypothesis testing will be conducted. Efficacy and safety may be presented descriptively with subjects grouped by the treatment that the subjects received during the UTX-TGR-304 protocol prior to entering the Companion Study and overall.
Estimated Study Duration	This study will remain open as long as there are subjects enrolling or who have been enrolled to Study UTX-TGR-304.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations and Definition of Terms	
δ	Delta
Ab	Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
AUC	Area Under the Curve
BM	Bone Marrow
Ca	Calcium
CBC	Complete Blood cell Count
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
Cl	Clearance
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximum Concentration
CMV	Cytomegalovirus
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
D, d	Day
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRG	Data Review Group
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Fc	Fragment crystallizable (region)
FL	Follicular Lymphoma
FU	Follow-up
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation of Technical Requirementsfor Registration of Pharmaceuticals for Human Use
IRR	Infusion-related reaction
IV	Intravenous
LDH	Lactate dehydrogenase

Abbreviations and Definition of Terms	
MCL	Mantle Cell Lymphoma
MRD	Minimal Residual Disease
MRT	Mean Residence Time
MZL	Marginal Zone Lymphoma
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
NCI-WG	National Cancer Institute – Working Group
NK	Natural Killer
NHL	Non-Hodgkin's Lymphoma
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PI3K	Phosphoinositide-3-kinase
PCD	Programmed cell death
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
R-FC	Rituximab-Fludarabine, Cyclophosphamide
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SLL	Small lymphocytic leukemia
SOC	System Organ Class
t1/2	Half-Life of Elimination
ULN	Upper limit of normal
UTX, TG-1101	Ublituximab
V	Visit
Vd	Volume of distribution
WHO	World Health Organization
WM	Waldenström's Macroglobulinemia

1 INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

In the US, an estimated 15,720 new cases of Chronic Lymphocytic Leukemia (CLL) will be reported in 2014 with deaths totaling 4,600 due to the disease according to American Cancer Society estimates (American Cancer Society, 2014). 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, P53 gene mutation, and 11q deletion (Hallek M, 2008) (Lin K, 2002). Subjects with 17p deletion show higher resistance to conventional chemotherapies as well as shorter duration of survival than non 17p deletion subjects. Subjects with 11q deletion have been associated with marked lymphadenopathy (Hallek M, 2008). Subjects with P53 gene mutations are associated with an adverse clinical outcome (Lin 2002).

Chemotherapy regimens in combination with monoclonal antibody therapy comprise the current standard of care for subjects with CLL, with novel targeted agents now entering the market. Frontline therapy for subjects with CLL generally consists of the anti-CD20 monoclonal antibody rituximab, in combination with either fludarabine and cyclophosphamide, or bendamustine. Depending on the age and comorbidities of the subject, chlorambucil is also considered, though its use within the US has been limited. Other anti-CD20 antibodies have also been approved for the treatment of CLL, including ofatumumab and obinutuzumab. Recently the BTK inhibitor, ibrutinib was approved by the FDA for the treatment of subjects with CLL in the relapsed or refractory setting after demonstrating superiority to ofatumumab as measured by progression free survival (Byrd et al, 2014). Despite these advancements in available therapies, CLL remains an incurable disease, and many subjects will progress and eventually die from their disease. Furthermore, subjects with higher risk cytogenetic abnormalities still present with a less than optimal response to approved therapies and shorter duration of response and progression free survival. As such, there is a pressing need for new, innovative, targeted therapies for the treatment of subjects with relapsed/refractory CLL, especially those with cytogenetic abnormalities.

1.2 BACKGROUND

A Phase 3 randomized study (UTX-TGR-304) to assess the efficacy and safety of ublituximab in combination with TGR-1202 compared to obinutuzumab in combination with chlorambucil in subjects with chronic lymphocytic leukemia (CLL) was launched in September 2015. As part of the study design, subjects from Treatment Arms B, C, and D with disease progression confirmed by the independent review committee (IRC), may be enrolled into this companion study. In addition, at the end of the UTX-TGR-304 study, non-progressed subjects from all treatment arms may also be enrolled to this companion study.

1.3 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

introduce superior antibody-dependent cytotoxicity (ADCC). Ublituximab has maintained competitive complement-dependent cytotoxicity (CDC) and has also 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.

1.4 TGR-1202 (UMBRALISIB)

TGR-1202 is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma 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. TGR-1202 has demonstrated safety in ongoing Phase I, II, and III clinical trials in subjects with hematologic malignancies and solid tumors. TGR-1202 is manufactured by Alembic Pharmaceuticals and supplied by TG Therapeutics, Inc.

1.5 UBLITUXIMAB IN COMBINATION WITH TGR-1202

The combination of ublituximab and TGR-1202 is currently under evaluation in an ongoing Phase I/Ib study in subjects with relapsed or refractory NHL and CLL (Lunning et al., ASH 2015). 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 TGR-1202 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 subject 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 subject had their dose of TGR-1202 reduced (Gr. 1 diarrhea). IRR and neutropenia were managed through dose delays, with 1 CLL subject having a neutropenia related dose delay which met the criteria for a DLT, necessitating enrollment of additional CLL subjects into Cohort 1. One subject

was removed from study without progressive disease due to an event of itching which was deemed possibly related to TGR-1202.

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 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 subject 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 subject 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 TGR-1202 is well tolerated and active in subjects with relapsed or refractory hematologic malignancies, including those with CLL (both high and low risk).

2 OBJECTIVES

2.1 STUDY OBJECTIVES

Primary Objectives

- To observe the overall response rate (ORR) defined as the sum of complete responses (CR) and partial responses (PR)

Secondary Objective

- To observe progression-free survival (PFS) and duration of response (DOR)
- To observe the % of subjects that achieve MRD negativity
- To observe the safety of ublituximab in combination with TGR-1202

2.2 EFFICACY ENDPOINTS

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 randomization 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. 2008) 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) other than lymphocytosis.

Minimal Residual Disease (MRD) Negativity Rate
MRD negativity rate is defined as the proportion of subjects who are MRD negative.

Duration of response (DOR)
DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause

3 ELIGIBILITY CRITERIA

3.1 INCLUSION CRITERIA

1. Prior treatment in clinical trial UTX-TGR-304
   a. Confirmed progression by IRC on Arms B, C, or D after at least two cycles of treatment in trial UTX-TGR-304. There is no required timeframe to begin treatment on the UTX-TGR-204 protocol; however, if other therapies to treat the disease are implemented in the interim, the subject will not be eligible to enroll in the study.
   b. Non-progressing subjects on Arm A may be eligible for enrollment when protocol UTX-TGR-304 is completed.
2. Adequate organ system function, defined as follows:
   a. Absolute neutrophil count (ANC) > 750 x 10^3/mm^3 (0.75 K/μL) / platelet count > 40 x 10^3/mm^3 (40 K/μL) unless cytopenias are related to bone marrow involvement.
   b. Total bilirubin ≤1.5 times the upper limit of normal (ULN) with the exception of Gilbert's Disease and 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).
3. ECOG performance status ≤ 2
4. Ability to swallow and retain oral medication
5. Willingness and ability to comply with trial and follow-up procedures, give written informed consent

3.2 EXCLUSION CRITERIA

1. Prior treatment with obinutuzumab + chlorambucil (Arm B subjects) or ublituximab (Arm C subjects) within 7 days of Cycle 1/Day 1
2. Subjects refractory to (progressing on) UTX-TGR-304 Treatment Arm A (ublituximab + TGR-1202)
3. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation)
4. Evidence of chronic active Hepatitis B defined as Hepatitis B surface antigen positive or Hepatitis B DNA positive by PCR (HBV, NOT including subjects with prior hepatitis B vaccination who are Hepatitis B surface antibody positive only;) or chronic active Hepatitis C infection (HCV) defined as Hepatitis C RNA positive by PCR, cytomegalovirus (CMV) DNA positive by PCR, or known history of HIV. If HBc antibody, HCV antibody or CMV IgG and/or IgM antibody is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by PCR - See Appendix D.
5. 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 pneumonia prophylaxis is required prior to Cycle 1/Day 1 and for the first 2 cycles. After Cycle 2, is per investigator discretion.
6. Woman who are pregnant or lactating.
7. Live virus vaccines four (4) weeks prior to or during ublituximab therapy.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This Companion Study is intended for subjects who previously enrolled to the parent trial UTX-TGR-304. Subjects from Treatment Arms B, C, and D with disease progression confirmed by the independent review committee (IRC), may be enrolled into this Companion Study. At the end of the UTX-TGR-304 study, non-progressed subjects from Treatment Arm A may also be enrolled to this Companion Study. Subjects from Treatment Arms B, C, and D may start treatment with ublituximab + TGR-1202, while subjects entering the Companion Study from Treatment Arm A may continue their treatment as specified by this protocol. All subjects enrolled to the Companion Study should receive ublituximab in combination with TGR-1202 (at the same dose and schedule as the Treatment Arm A in UTX-TGR-304) until they show disease progression, are unable to continue treatment for any reason such as lack of tolerability, or until the treatment is commercially available.

During the study period, all subjects will be evaluated for response by CT and/or MRI. Evaluations are to be obtained at approximately cycles 3, 6 and 12. Following cycle 12, evaluations should occur at least every 12 cycles unless clinically indicated more frequently. Subjects should remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed should continue to be followed for progression per institutional standard of care and reported in eCRF. Date of progression, beginning of new treatment, and/or death should be entered in the eCRF.

4.2 REGISTRATION

Subjects who are eligible and who have signed an informed consent will be enrolled. Please see Study Manual for enrollment procedures.

4.3 STUDY SITES

Only sites participating in UTX-TGR-304 will be included in this study.

4.4 DISCONTINUATION FROM STUDY TREATMENT

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

- Disease progression
- Intolerable toxicity related to study drug
- 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) should continue to be followed for progression.

Subjects who discontinue all study treatment but remain on study for disease progression assessment will have an End of Treatment (EOT) visit and will continue to be followed for adverse events (treatment-related AEs and disease-related AEs), disease progression and other protocol required procedures (see Section 5, Table 2 for EOT and follow up assessment schedule). All new treatment-related AEs occurring within 30 calendar days from treatment discontinuation must be reported and followed until resolution, unless, in the opinion of the investigator, these events are not likely to improve because of the underlying disease. In this case the investigators must record the reason for not conducting the 30-day safety evaluation in the subject's medical records and as a comment on the electronic Case Report Form (eCRF).

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

Subjects who discontinue from the study will have an End of Study visit (EOS - see Section 5, Table 2)

No formal futility analysis of efficacy or safety will be conducted in this study, however if Study 304 is closed for futility for either safety or efficacy reasons, then this Study UTX-TGR-204 will also be terminated.

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

The table below lists all of the required assessments that should be performed at each study visit.

TABLE 1: STUDY ASSESSMENT AND TREATMENT SCHEDULE

Cycle (C) = 28 days	Screening[1]	Cycle 1[2]				Maintenance[3]		Cycles 15+[4]	End of study
						Cycles 2 – 6	Cycle 9 & 12		
Procedure \ Days (D)	-28-0	D 1	D 2	D 8	D 15	Day 1	Day 1	Q 3 cycles	
Medical History	X								
Rai Staging	X								
ECOG performance status	X	X			X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X
Vital signs (pulse, BP, temp)	X	X		X	X	X	X	X	X
BM aspirate/biopsy[5]	X								
Serum Pregnancy Test[6]	X								
Urine Pregnancy Test[7]						X	X	X	X
Hematology[8]	X[9]	X	X	X	X	X	X	X	X
Serum Chemistry	X[9]	X		X	X	X	X	X	X
FISH Panel[10]	X								
Tumor evaluation[11]	X	Evaluations are to be obtained during cycles 3, 6 & 12. Following cycle 12, evaluations should occur at least every 12 cycles							
Serology: HCV, HBV, CMV[12]	X								
CMV Surveillance						X[13]	X	X[13]	
MRD[14]						For subjects in PR or CR beginning at the Cycle 6 response assessment			
Ublituximab[15]		X	X[15]	X[15]	X[15]	X	X	Q3 months	
Umbralisib (TGR-1202) Dose		Days 1 – 28 (Daily)							
Adverse events (CTC v4.0)		Throughout the study							X[16]
Concomitant Medication		Throughout the study							X

[1] Tests that have already been completed as part of the requirements for UTX-TGR-304 may be used to evaluate eligibility for this companion study
[2] Treatment Administration +/- 1 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have - 1 day window
[3] Treatment Administration +/- 3 day window Cycles 2-6. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 3 day window during Cycles 2 through 6. Treatment Administration +/- 7 day window after Cycle 6. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 7 day window for all cycles after cycle 6
[4] 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
[5] Unilateral bone marrow aspirate and/or biopsy performed at investigator discretion in subjects for whom assessment of extent of CLL involvement and bone marrow cellularity is important. In addition, a post-baseline bone marrow biopsy should be completed to confirm potential CR by radiological assessment.
[6] For women of child bearing potential, completed within 3 days of Cycle 1 Day 1.
[7] For women of child bearing potential, completed within 3 days of visit
[8] Must be obtained prior to ublituximab administration if on day of infusion.
[9] Must be done within 14 days of cycle 1 day 1
[10] For del(13q), del(11q), del(17p), and (12) trisomy, t(11:14)
[11] Scans should be completed approximately 45 days prior to Day 1 of Cycle 1. Radiology assessment should include CT or MRI imaging of chest, abdomen, and pelvis.
[12] Serum virology to include HBsAg, HBc antibody, HCV antibody and CMV IgG and IgM. If HBc antibody, HCV antibody or CMV IgM is positive, subjects must be evaluated for the presence of active HBV, HCV or CMV by PCR
[13] Q3 months CMV screening by PCR for all subjects.
[14] Peripheral blood sample may be analyzed by local lab. For subjects MRD negative by peripheral blood, a bone marrow should be completed to confirm MRD negativity. If a bone marrow is not completed, another peripheral blood sample should be collected to confirm the MRD negativity at least 12 weeks later. MRD should continue to be evaluated for subjects with PR/CR at response assessment intervals until 2 consecutive peripheral blood MRD negative results, or 1 negative peripheral blood MRD and 1 negative bone marrow MRD are observed.
[15] Subjects who received ublituximab on UNITY-CLL trial (Arm C), will not receive split dosing on Day 1 and 2 of cycle 1. Subjects should receive full dose on Cycle 1, Day 1 and will not receive Day 8, and 15 during Cycle 1.
[16] If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of treatment visit, continue to monitor and record up through 30 days after study drug discontinuation.

TABLE 2: FOLLOW UP ASSESSMENTS SCHEDULE

Procedures[1]	Off Protocol Treatment for Non-PD (AE, investigator decision, etc.) NOT Receiving Non-Protocol Treatment	Off Protocol Treatment for Non-PD (AE, investigator decision, etc.) Receiving Non-Protocol Treatment	Off Protocol Treatment for PD
ECOG Performance Status	X		
Physical Exam	X		
Vital Signs	X		
Hematology	X		
Chemistry	X		
MRD	X		
Con Meds	To be followed for 30 days after last day of study drug(s)		
AE Evaluation	To be followed for 30 days after last day of study drug(s)		
Tumor Evaluations[2]	X		
EOT Page	X	X	X
Post Treatment Visits	X		
EOS Visit[3]		X	X

[1] PFS off treatment should be assessed per institutional standard of care.
[2] CT or MRI imaging of the Neck, Chest, Abdomen, and Pelvis should be completed per institutional standard of care. There is no central radiology review for this study.
[3] EOS visit should be documented in the EDC once subject has PD and/or starts non-protocol therapy.

5.1 LABORATORY EVALUATIONS - OVERVIEW

All subjects should visit the study center on the days specified within this protocol. The complete schedule of assessments is shown in Section 5. The baseline physical examination with vital signs, medical history, Rai staging, evaluation of concomitant medications, ECOG PS, bone marrow aspirate/biopsy (if applicable), complete blood count/full blood count (3-part differential accepted), serum chemistry, and CLL FISH panel, should be done within 28 days prior to initiation of treatment (14 days for CBC and Chemistry). For women of child bearing potential, a serum pregnancy test should be completed within 3 days (72 hours) prior to Day 1 of Cycle 1 and a urine pregnancy test within 3 days of assessment as per the table in Section 5. Tumor assessment scans should be performed ≤45 days prior to initiation of treatment. In the event that the subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

5.1.1 LABORATORY EVALUATIONS (LOCAL LAB)

1. Hematologic profile and serum chemistry to include:

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
Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	
Erythrocyte count	Monocytes	
Absolute neutrophil count	Eosinophils	
Absolute leukocyte count	Basophils	

2. Serum and urine pregnancy tests
3. Baseline bone marrow aspirate/biopsy (if applicable)
4. CLL FISH Panel
5. MRD for subjects in CR or PR beginning at Cycle 6 response assessment
6. Serum Virology to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM. If HBc antibody, HCV antibody or CMV IgM are positive the subject must be evaluated for the presence of active HBV, HCV or CMV by PCR - See Appendix D. For all subjects approximately every 3 months CMV screening by PCR. CMV surveillance will discontinue 30 days after last dose of umbralisib, or as otherwise clinically indicated per investigator discretion.

6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

Treatment will be administered on an outpatient basis in 4-week (28 day) cycles for subjects that roll over from 304 Arms B, C, and D.

Treatment Schema for Subjects Crossing over from Arm A:

Subjects who crossover from Treatment Arm A will continue their treatment where they left off at the termination of protocol UTX-TGR-304.

Treatment Schema for Subjects Crossing over from Arms B and D:

Cycle 1:

Ublituximab			TGR-1202
Day 1	**Day 2**	**Day 8 & 15**	**Daily**
150 mg	750 mg	900 mg	800 mg

Cycles 2 through 6:

Ublituximab	TGR-1202
Day 1	**Daily**
900 mg	800 mg

After Cycle 6:

Ublituximab	TGR-1202
Day 1, Q3 months	**Daily**
900 mg	800 mg

Treatment Schema for Subjects Crossing over from Arm C:

Cycle 1 should start 28 days after the last dose of ublituximab (given on the 304 study)

Cycles 1 through 6:

Ublituximab	TGR-1202
Day 1	**Daily**
900 mg	800 mg

After Cycle 6:

Ublituximab	TGR-1202
Day 1, Q3 months	**Daily**
900 mg	800 mg

6.2 AGENT ADMINISTRATION

Ublituximab treatment will be administered as an IV infusion while TGR-1202 will be administered orally, both on an outpatient basis.

6.2.1 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:* Ublituximab should be started approximately 30 minutes after the conclusion of the last pre-medication infusion and should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). If pre-medication is given orally, they should be given approximately 45-60 minutes prior to the beginning of the ublituximab infusion. After C1 adjustments can be made to the antihistamine and/or corticosteroid dosing should subject exhibit adverse effects from the agents or have a medical condition the pre-medications adversely impacts after discussion with TG Therapeutics contact.
    - 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).
    - Concurrent glucocorticoid therapy as long as started for at least 7 days prior to study entry (≤ 10 mg per day of prednisone or equivalent) is allowed as clinically warranted.
    - Since infusion-related hypotension may occur, consider holding antihypertensive medications 12-24 hours prior to and throughout infusion of ublituximab.
    - For subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

6.2.1.1 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 6.2.1.2.

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.

6.2.1.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

Cycle 1 Day 1 & 2 infusion over 4 hours

Cycle 1	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
Day 1	150 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H
Day 2	750 mg	500 mL	10 mL/H	20 mL/H	85 mL/H	200 mL/H

Cycle 1 Day 8 & 15 infusions over 3 hours

Ublituximab Dose	Total volume to be infused	Infusion rate		
		T0 to T1H	T1H to T2H	T2H to T3H
900 mg	500 mL	50 mL/H	150 mL/H	300 mL/H

Cycle 2 and remaining infusions over 90 minutes

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

6.2.1.3 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or his/her representative must check that the ublituximab is in accordance with the product specifications and the validity is within the 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 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 ublituximab. Preparation should be done by the Pharmacist or his/her representative according to instructions for sterile dilution.

6.2.1.3.1 DILUTIONS OF UBLITUXIMAB

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

[redacted]

Dilutions for Cycle 1 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

Dose of ublituximab for infusion	[redacted]
900 mg	

[redacted]

Dilutions for Cycle 1 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

Dose of ublituximab for infusion	[redacted]
900 mg	

6.2.2 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB (TGR-1202)

- *Method of Administration:* Umbralisib will be administered orally once daily with food
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.

- *Pre-medications:* Subjects are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PJP) and antiviral therapy prior to Cycle 1, Day 1, and must continue through Cycle 2, and per investigator discretion afterward. Choice of PJP and anti-viral prophylaxis therapy is per investigator discretion, with the below recommendations:
    - Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
    - PJP Prophylaxis: Dapsone 100 mg daily or equivalent.

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

TGR-1202 will be dispensed at the sites by the research coordinator or designee under the direction of the PI or by a pharmacist at the site. Subjects must be provided drug in its original container. Subjects should be instructed to return any unused tablets when they return the bottle to the site. Study drug compliance should be reviewed with the subject at the beginning of each new treatment cycle and as needed. Missed doses will be documented in the subjects' medical record.

Umbralisib will be self-administered (by the subject). Tablets should be taken at approximately the same time each day with food (within 30 minutes of a meal). 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.

6.2.2.1 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. For the purpose of drug accountability and dosing, subjects should record any missed doses of umbralisib on a drug diary. Any error in drug administration should be recorded (e.g., missed dose) in the eCRF

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

6.3 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that subject has:

- No intolerable toxicities related to study drug.
    - If treatment is delayed greater than 2 cycles, notify TG Therapeutics prior to re-initiation.
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

6.4 DOSING DELAYS/DOSE MODIFICATION

Subjects should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_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, or are per investigator discretion.

If greater than 2-cycle delay of treatment occurs for recovery of toxicities as outlined in Section 6.4 DOSING DELAYS/DOSE MODIFICATION, re-initiation of treatment is at the discretion of the investigator. Contact TG Therapeutics prior to re-initiating treatment with any questions. If a subject discontinues treatment due to toxicity, then the subject should continue to be followed for progression as described in Table 2: FOLLOW UP ASSESSMENTS SCHEDULE. If a subject withdraws consent or has documented progression, an end of study visit should be completed.

6.4.1 DOSE DELAY: UBLITUXIMAB

No reduction in the dose of ublituximab is permitted. Please refer to Section 6.2.1.2 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. Delay of both study drugs (individually or together) is allowed for recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If delay is greater than 2-cycles, notify TG Therapeutics prior to re-initiating with any questions. If the subject withdraws consent or has documented progression, an end of study visit should be completed.

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

TABLE 3: 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.

6.4.2 DOSE DELAY/MODIFICATIONS: UMBRALISIB (TGR-1202)

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experiences a treatment-related adverse event requiring dose modification during the course of therapy, then study drug administration should be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree. Contact TG Therapeutics prior to study drug re-initiation for dose delays exceeding 2 cycles with any questions. Time for recovery from toxicity is allowed for all study drugs (ublituximab and/or umbralisib: individually or together) to allow recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If a delay greater than 2-cycles is necessary for both study drugs, then notify TG Therapeutics prior to re-initiation. If the subject withdraws consent or has documented progression, an end of study visit should be completed.

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

TABLE 4: **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, resume at next lower dose level 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 rechallenge, resume 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 rechallenge, resume at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 1 & 2	Withhold umbralisib as warranted, provide supportive care and hold until complete resolution. Resume umbralisib at one dose lower. If recurrence after re-challenge, discontinue umbralisib.
Grade ≥ 3	Discontinue umbralisib and intervene as warranted.
***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 at start of therapy.**	
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	

Grade 1	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Monitor Labs every 1-2 weeks
Grade 2	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Begin supportive care (40-60 mg prednisone orally per day or equivalent)** • Monitor labs at least weekly until Grade 1 • Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. o If liver toxicity recurs to Grade 2 once off steroids, re-initiate steroids with 10 mg per week taper until off. o Consider withholding umbralisib. If delay is greater than 2 cycles notify TG Therapeutics prior to re-initiating.
Grade ≥3	• Hold Umbralisib. If delay is greater than 2 cycles notify TG Therapeutics prior to re-initiating. • Assess Concomitant Medications and Risk Factors* • Begin/continue supportive care (40-60 mg prednisone orally per day or equivalent)** • Monitor labs at least weekly until Grade 1 • Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off • Resume -1 dose level when Grade ≤1

* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc.

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

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 rechallenge, 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.
All Other Non-Hematological Adverse Events	
Grade ≤ 2	Maintain current dose level.
Grade ≥ 3	Withhold umbralisib until Grade ≤2. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.

TABLE 5: **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.

6.4.3 ORDERING UBLITUXIMAB AND UMBRALISIB (TGR-1202)

Once 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.

6.4.4 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment should continue through Cycle 1 and beyond unless one of the following criteria applies:

- Disease progression or inter-current illness that prevents further treatment,
- Subject decides to withdraw from the study, or changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

During the study period, all subjects will be evaluated for response by CT and/or MRI. Evaluations are to be obtained at approximately cycles 3, 6 and 12. Following cycle 12, evaluations should occur at least every 12 cycles unless clinically indicated more frequently. Subjects will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed should continue to be followed for progression per institutional standard of care.

7 STUDY MEDICATION OVERVIEW AND SAFETY

7.1 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 10 mg/mL in 15 mL (150 mg) or 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 / + 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.

Ublituximab has a shelf-life of 36 months if stored between +2°C / + 8°C, based on stability data.

Route of Administration: Intravenous

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

- Six vials containing 150 mg solution of ublituximab each
  or
- One vial containing 150 mg solution of ublituximab (used as replacement, if needed)

The container closure system for the vials containing 6mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with an aqua plastic and aluminum cap.

The container closure system for the vials containing 15 mL is a Type I plus borosilicate vial closed by a siliconized bromobutyl rubber stopper sealed with a white plastic and aluminum cap.

Availability: Ublituximab is available from TG Therapeutics.

7.2 UMBRALISIB (TGR-1202)

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:	Umbralisib: 200 mg tablets
Storage:	Store at 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.

7.3 COMPREHENSIVE ADVERSE EVENTS AND POSSIBLE RISKS - UBLITUXIMAB + UMBRALISIB COMBINATION

The following adverse events were observed in subjects treated with the combination of ublituximab + umbralisib and were considered at least possibly related to one or both of the study medications. The preliminary safety data as of May 1, 2018 is provided for a total of 75 subjects exposed to ublituximab + umbralisib with a maximum follow up of 3+ years. See the latest ublituximab and umbralisib Investigator's Brochures for updated safety information a complete list of all adverse events reported regardless of causality.

7.3.1 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

7.3.2 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, gastrooesophageal reflux disease, haematochezia, salivary hypersecretion, stomatitis

General Disorders and Administration Site Conditions: asthenia, chills, face oedema, infusion site pain, local swelling, odedema 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

8 MEASUREMENT OF EFFECT

During the study period, all subjects will be evaluated for response by CT and/or MRI. Evaluations are to be obtained at approximately cycles 3, 6 and 12. Following cycle 12, evaluations should occur at least every 12 cycles unless clinically indicated more frequently. The determination of response and progression will be based on IWCLL criteria (Hallek M, 2008) by the treating investigator.

CT scan is the preferred method of tumor assessment, but MRI may be used at the investigator's discretion. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the study. All baseline assessments to characterize disease will be performed within approximately 45 days of Cycle 1 Day 1, prior to initiation of therapy.

Subjects should remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression as per the protocol.

8.1 METHOD OF ASSESSMENT

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

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

Relevant clinical and radiographic information required to make each tumor status assessment must be requested for source verification.

8.2 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

8.2.1 TARGET LESIONS

At baseline, up to 6 lymph nodes should be selected as target lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the target lesions should be located 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 nodal target lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

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.

8.2.2 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.

8.2.3 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".

8.3 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized 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.

8.4 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

- Morphologically negative bone marrow defined as <30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- 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 (including bone marrow criteria) 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).

8.5 PARTIAL RESPONSE

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

- No evidence of new disease
- A change in disease status meeting ≥2 of the following criteria, with 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 8.2.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 8.2.2
  - 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)

8.6 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

8.7 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).

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

- Evidence of worsening of target lesions, spleen or liver, or non-target disease:
  - Increase from the nadir by ≥50% from the nadir in the SPD of target lesions
  - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of >1.5 cm 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

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.

8.8 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.

8.9 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of umbralisib, 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 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.

9 STATISTICAL CONSIDERATIONS

This section describes the statistical methods to be used to analyze the efficacy and safety endpoints.

9.1 SAMPLE SIZE

As no formal hypothesis testing is being conducted in this study, the sample size is not based on powering for any study objectives. Subjects from Treatment Arms B, C and D in Study 304 may enter this study upon documented progression of disease as confirmed by the independent central radiology review group. At the end of the study, non-progressed subjects from Treatment Arm A may also be enrolled to this Phase 2 Companion Study. It is undetermined the number of subjects that may enter this Companion Study, however it may not exceed the total number of subjects that have enrolled in Study 304, which may be up to approximately 700 subjects.

9.2 GENERAL ANALYSIS CONVENTION

The primary objective of this compassionate use study is to allow subjects progressing in Arms B, C, and D of study UTX-TGR-304 to receive, and for subjects previously in Arm A to continue to receive, combination therapy with ublituximab plus umbralisib. As the study is primarily observational, no formal hypothesis testing will be conducted. Continuous data will be described using the following descriptive statistics: n, mean, median, minimum and maximum. Data will be displayed in all listings sorted by treatment group (based on the treatment arm the subject was on in Study 304) and subject number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. Unless otherwise specified, the denominator for percentages will be the number of subjects with a non-missing assessment in a given treatment group within the analysis population of interest.

9.3 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population will consist of all subjects who were enrolled and have at least one post-treatment efficacy measurement. Primary efficacy analyses will be performed based on the ITT population.

The Safety Population will include all subjects who were enrolled and received at least one dose of study drug. All safety assessments including toxicity will be performed on the Safety Population.

The Per-Protocol Population (PP) will consist of all ITT subjects without a major protocol deviation. The criteria for a major protocol deviation will be determined and documented prior to data base lock. Subject exclusion from the PP population will also be determined and documented prior to database lock. Supportive analyses may be performed based on the PP population.

Furthermore, in the analyses/summaries, subjects will be assigned a treatment group based on the treatment they received on study UTX-TGR-304 prior to their entering of this Companion Study as appropriate.

9.4 SUBJECT DISPOSITION

The disposition of subjects includes the number and percentage of subjects for the following categories: subjects enrolled, subjects treated (safety population), subjects in the ITT population, subjects completed, and subjects discontinued from the study. The reasons for study discontinuation will also be summarized in this table. Only one primary reason for study discontinuation will be reported in the summary. However, all reasons will be presented in the listing. The disposition will be summarized by treatment group and overall.

A listing will present data concerning subject disposition.

9.5 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

9.6 MEDICAL HISTORY

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

9.7 EXTENT OF EXPOSURE

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

9.8 EFFICACY ANALYSES

All subjects included in the study must have a baseline tumor assessment within 30 days of Cycle 1/Day 1 and at least one post-treatment efficacy evaluation in order to be included in the efficacy analyses. Each subject will be assigned one of the following categories: 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).

9.8.1 PRIMARY EFFICACY VARIABLE

Overall response rate (ORR), where ORR = complete responses (CR) + partial response (PR), will be the primary efficacy variable. The overall response rate (ORR) and the 90% one-sided confidence interval of the rate will be estimated by treatment group, if appropriate (i.e., if sample sizes are sufficient) and overall.

CR and PR will be similarly analyzed as ORR.

9.8.2 SECONDARY EFFICACY VARIABLES

Progression free survival (PFS) is defined as the time from study entry to the first documentation of tumor progression or death due to any cause whichever comes first. For subjects previously on Arm A of Study UTX-TGR-304, PFS will be calculated from the date of randomization on Study UTX-TGR-304 to the first documentation of tumor progression or death due to any cause whichever comes first. This variable will be analyzed via Kaplan-Meier methodology. The median PFS will be estimated by treatment group, if appropriate (i.e., if sample sizes are sufficient) and overall.

MRD negativity rate is defined as the proportion of subjects who are MRD negative. This variable will be analyzed by the total number and percentage of subjects who are confirmed to achieve MRD negativity as per laboratory confirmation by treatment group and overall.

Duration of response is defined as the time from documentation of a response to treatment to the first documentation of tumor progression or death due to any cause whichever comes first. For subjects previously on Arm A of Study UTX-TGR-304, unless the subject's best overall response during study UTX-TGR-304 was stable disease, the duration of response will be determined from the first documented response on Study UTX-TGR-304. Duration of the response will be summarized using n (sample size), mean, standard deviation, median, minimum and maximum for the responders by treatment group and overall.

10 SAFETY REPORTING AND ANALYSIS

10.1 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 dose of the combination of ublituximab + umbralisib study drug actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated by treatment group and overall.

10.2 ADVERSE EVENT CHARACTERISTICS

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Expected AEs are defined as those described in the ublituximab Investigator Brochure and the umbralisib Investigator Brochure.

10.3 DEFINITIONS OF ADVERSE EVENTS

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 adverse event (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.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 is to be used for the grading of severity of symptoms and abnormal findings. For adverse events not covered by the NCI-CTCAE Version 4.0 grading system, the following definitions will be used:

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

10.4 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.

AEs that occur after informed consent but before first dosing of study medication will not be summarized but will be listed.

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.

10.5 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.

10.5.1 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 – ublituximab + umbralisib). 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 treatment spanning 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.

10.5.2 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 4.0 when applicable. Subject incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

10.5.3 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 (either ublituximab and/or umbralisib). 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.

10.6 SERIOUS ADVERSE EVENTS

10.6.1 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,
- 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 may 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. 2008, 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
- Admissions to receive protocol defined therapy

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.

10.6.2 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 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 (or Sponsor designee) as outlined in the Safety Monitoring Plan.

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. The detailed SAE reporting process will be provided to the sites in the Safety Monitoring Plan.

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).

10.7 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).

10.8 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.

10.9 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 subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

10.9.1 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.

10.9.2 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.

10.9.3 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 be recorded on the appropriate study eCRF and reported on the Adverse Event page of the eCRF, i.e. are exempted from expedited reporting. 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.

10.9.4 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 10.6.1.

10.9.5 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.

10.9.6 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 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 (ublituximab and/or umbralisib) that is symptomatic, 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/Second Primary Malignancy

Any secondary/second primary malignancy 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.

11 CLINICAL DATA COLLECTION AND MONITORING

11.1 SITE MONITORING PLAN

A Sponsor representative or designee will have made a site visit to each institution within 6 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 or a teleconference will be performed to review investigator responsibilities, the protocol, and its requirements with the Investigator(s). During the initiation, the case report forms (CRFs)/ eCRF's 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 CRFs, and individual subject medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected CRF 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, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet the Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

12 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial 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).

12.1 IRB/IEC APPROVAL

The trial protocol, ICF, IB, available safety information, subject documents (e.g., trial 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/IEC for ethical review and approval prior to the trial start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB/IEC trial review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/IEC 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/IEC.

If applicable, the PI will notify the IRB/IEC **within 90 days** of the end of the trial, or if the trial 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.

12.2 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 trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

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

12.3 INSURANCE AND INDEMNITY

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

12.4 INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial 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/IEC that is responsible for review and approval of the trial. 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 trial, each prospective candidate will be given a full explanation of the trial. 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 trial, the candidate will be asked to give consent to participate in the trial 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, including the subject's signature, will be provided by the investigator to the subject.

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

12.5 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 trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects in this trial;
- 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 trial 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 trial;
- 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 trial 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 trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify subjects on the CRF 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 CRF 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.

12.6 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.

12.7 FINANCIAL INFORMATION

The finances for this trial 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.

13 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

13.1 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 trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB/IEC at the investigator's facility for the board's approval.

Amendments specifically involving change to trial 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/IEC at the Investigator's facility.

The amendment will be submitted formally 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 trial 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 trial design or the potential risks to the subjects, their consent to continue participation in the trial should be obtained.

13.2 DOCUMENTATION REQUIRED TO INITIATE TRIAL

Before the trial may begin, documentation required by FDA regulations must be provided by the Investigator. The required documentation should be submitted to the Sponsor.

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

- A signature-authorized protocol and contract;
- A copy of the official IRB/IEC approval of the trial and the IRB/IEC members list;
- Current Curricula Vita for the principal investigator and any associate investigator(s) who will be involved in the trial;

- Indication of appropriate accreditation for any laboratories to be used in the trial 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/IEC-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 trial 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 trial may start, in accordance with ICH E6 and Sponsor SOPs, will be available before any trial sites are initiated.

13.3 TRIAL DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the subject's CRF 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 CRF 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 trial staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-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 trial 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, copies of completed CRFs, IRB/IEC approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial 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 CRF 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/IEC 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 trial-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 CRFs, 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 trial-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the trial, the sponsor and/or its representative should be prospectively notified. The trial 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 trial files will be maintained by the Sponsor or its representative throughout the trial and will be transferred to the Sponsor at the conclusion of the trial.

13.4 DATA COLLECTION

The trial CRF is the primary data collection instrument for the trial. A case report form (CRF/eCRF) 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 trial.

In order to maintain confidentiality, only trial number, subject number, initials and date of birth will identify the subject in the CRF. 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.

13.5 TRIAL MONITORING, AUDITING, AND INSPECTING

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

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, 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.

13.6 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 trial 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 trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial.

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

The financial disclosure information will be provided to the Sponsor prior to trial participation from all PIs and Sub-Investigators who are involved in the trial 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.

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15 APPENDIX A – IWCLL RESPONSE CRITERIA

Chronic Lymphocytic Leukemia Response Definition (Hallek et al. 2008)

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

Complete Response: (CR)	***CR requires all of the following criteria as assessed at least 2 months after completion of therapy:*** 1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/µL). 2. Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by physical examination. 3. No hepatomegaly or splenomegaly by physical examination and CT. 4. Absence of constitutional symptoms. 5. Blood counts above the following values: • Neutrophils >1.5 x 10^9/L (1500/µL) without need for exogenous growth factors. • Platelets >100 x 10^9/L (100 000/µL) without need for exogenous growth factors. • Hemoglobin >110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin. **For patients in clinical trials, a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed above a-e demonstrate that a CR has been achieved.** To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician. In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry or by immunohistochemistry. **A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR (including the marrow examinations described above) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity.** We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (described above) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual or with noncytopenic CR.

Chronic Lymphocytic Leukemia Response Definition (Hallek et al. 2008) (continued)

Partial Response: (PR)	***To define a PR (partial remission): at least two of the criteria of Group A plus one of the criteria of Group B have to be met. The parameters below should be documented for no less than 2 months. Constitutional symptoms persisting for >1 month should be recorded.*** ***Group A*** a. Decrease in the number of blood lymphocytes by 50% or more from the value before therapy. b. Reduction in lymphadenopathy (by PE and CT scans) as defined by the following: • A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy. • No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant. c. Reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan. ***Group B*** d. Blood count should show one of the following: • Neutrophils >1.5 x 10^9/L (1500/μL) without need for exogenous growth factors. • Platelet count >100 x 10^9/L (100 000/μL) or 50% improvement over baseline without need for exogenous growth factors. • Hemoglobin >110 g/L (11.0 g/dL), or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

Chronic Lymphocytic Leukemia Response Definition (Hallek et al. 2008) (continued)

Progressive Disease: ***(PD)***	***Progressive disease during or after therapy is characterized by at least one of the following:*** a. Lymphadenopathy: Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed: • Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. • An increase by 50% or more in greatest determined diameter of any previous site. b. An increase in the previously noted enlargement of the liver or spleen by 50% or more, or the de novo appearance of hepatomegaly or splenomegaly. c. An increase in the number of blood lymphocytes by 50% or more, with at least 5000 B-lymphocytes per µL. d. Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy. e. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL • *During therapy:* Cytopenias may occur as a side effect of many therapies. During therapy, cytopenias cannot be used to define disease progression. • *After treatment:* The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by >20 g/L (2 g/dL) or to <100 g/L (10 g/dL), or by a decrease of platelet counts by >50% or to <100 x 10^9/L (100,000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.
Stable Disease: ***(SD)***	Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a non-response).

Source: Hallek M, Cheson BD, Catovsky D, et al. 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. 2008;111:5446-56.

16 APPENDIX B - CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least 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 Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use effective contraception during the study and for 4 months after stopping treatment. If a women of child-bearing potential was on treatment arm B (obinutuzumab arm) from trial UTX-TGR-304, effective contraception should continue to be used for 18 months after the last treatment dose of obinutuzumab. Effective contraception is defined as:

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 women of childbearing potential:

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

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

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, and for an additional 4 months after study drug discontinuation, and should not father a child in this period.

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 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 should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to TG Therapeutics Inc. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug and reported by the investigator to TG Therapeutics Inc. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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.

17 APPENDIX C – 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

www.cdc.gov/hepatitis