Official Title: A Phase 2 Study to Assess the Safety and Efficacy of TGR-1202 (Umbralisib) in Patients with Chronic Lymphocytic Leukemia (CLL) who are Intolerant to Prior BTK or PI3K-DeltaInhibitor Therapy

NCT Number: NCT02742090

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Local Protocol #: Protocol TGR-1202-201-CLL

TITLE: A Phase 2 Study to Assess the Safety and Efficacy of TGR-1202 (Umbralisib) in Patients with Chronic Lymphocytic Leukemia (CLL) who are Intolerant to Prior BTK or PI3K-Delta Inhibitor Therapy

Sponsor:
TG Therapeutics, Inc.
2 Gansevoort Street, 9th Floor
New York, NY 10014
Tel: (212) 554-44847

IND Number:
Umbralisib (TGR-1202)
116,762

Study Chair:
[redacted] MD
[redacted]

Medical Monitor:
[redacted] MD
[redacted]
Tel: [redacted]

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

Version: 1.0	**Date:** 07 January 2016
Version: 2.0	**Date:** 04 July 2016
Version: 2.5	**Date:** 21 February 2017
Version: 3.0	**Date:** 13 March 2017
Version: 4.0	**Date:** 6 October 2017
Version: 5.0	**Date: 05 March 2019**

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the appropriate Institutional Review Boards/ Independent Ethics Committees under the condition that they keep it confidential.

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TGR-1202-201-CLL for issuance.

Protocol Title:	A Phase 2 Study to Assess the Safety and Efficacy of TGR-1202 (Umbralisib) in Patients with Chronic Lymphocytic Leukemia (CLL) who are Intolerant to Prior BTK or PI3K-Delta Inhibitor Therapy
Protocol Number:	TGR-1202-201-CLL
Study Drugs:	Umbralisib (TGR-1202)
IND Number:	**Umbralisib** 116,762
Date FINAL:	05 March 2019

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted] MD — [redacted] — [redacted]

Print Name — Signature — Date

STUDY CHAIR, Memorial Sloan Kettering Cancer Center

[redacted] MD — [redacted] — [redacted]

Print Name — Signature — Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted] — DocuSigned by: [redacted] 2009F1FD373C447... — [redacted]

Print Name — Signature — Date

[redacted] MS, MSF — [redacted] — [redacted]

Print Name — Signature — Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	**A Phase 2 Study to Assess the Safety and Efficacy of TGR-1202 (Umbralisib) in Patients with Chronic Lymphocytic Leukemia (CLL) who are Intolerant to Prior BTK or PI3K-Delta Inhibitor Therapy**
Protocol Number:	**TGR-1202-201-CLL**
IND Number:	**Umbralisib** 116,762
Date FINAL:	**05 March 2019**

I have read the attached protocol and agree that it contains all the necessary details for performing TGR-1202-201-CLL.

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

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

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Washington Clarification (2002).

Print Name	Signature	Date

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Version 2.0 (Dated 04 July 2016) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- Sponsor and study coordination address updated;
- Clerical corrections were made to Inclusion Criteria 6 and 7;
- Inclusion criteria #9 was changed from minimum 2 cm nodal lesion to 1.5 cm;
- Exclusion criteria 6 was further clarified for HBV and testing by PCR if required;
- Study schema in Section 4.1 was corrected;
- Table in Section 5 and footnotes were updated to change "weeks" to "cycles" as well as update a few clarifications needed in the Study Assessment and Treatment Schedule table;
- Section 6.2.1 was updated to mandate prophylaxis with anti-viral and PCP;
- Section 7 was updated based on the updated Investigator Brochure risks profile for TGR-1202;
- Section 8.3.1 was updated to clarify language for target lesion selection

Version 2.5 (Dated 21 February 2017) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- Inclusion criteria #8 was clarified to allow Growth Factor Support at any time during the study;
- Inclusion criteria #9 requiring measurable lymphadenopathy was deleted. Measurable disease is not required for protocol entry;
- Exclusion criteria #8 was clarified as prophylaxis with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy is required and not encouraged;
- Section 8.3.1 was updated to reflect the changes in Inclusion criteria #9 in respect to no measurable disease being required.

Version 3.0 (Dated 13 March 2017) of this Protocol is the third amendment to this clinical trial and contains the following modifications:

- Inclusion criteria #7 was changed from "...discontinued due to intolerance within 9 months..." to "...discontinued due to intolerance within 12 months..."
- CT scan assessments were changes from "at the completion of Cycles 3, 6, 9, 12 and every 3 cycles thereafter (+/- 7 day window)" to the following: "During the study period, patients will be evaluated for response by CT and/or MRI during Cycles 3, 6, 9, 12 and then at least every 6 cycles thereafter (+/- 14 day window)."

Version 4. 0 (Dated 06 October 2017) of this Protocol is the fourth amendment to this clinical trial and contains the following modifications:

- Inclusion criteria #7 has been clarified that discontinuation of the prior BTK or PI3K-delta inhibitor should be within 12 months of treatment initiation with TGR-1202, defined as Cycle 1/Day 1;
- Section 6.3.1 has been updated to provide additional guidance on dose delay/modifications for TGR -1202 and to include dose modifications for events of diarrhea and colitis.
- Section 7.1.1 has been updated to include the latest CAEPRS information for TGR-1202.

- Section 8.3.1 has been updated to remove the following statement to now require more accurate measurements of nodal target lesions: "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)."
- Appendix B has been updated to now require male patients to use highly effective contraception during the study period and for 30 days after.
- Updated throughout to acknowledge the generic name for TGR-1202: umbralisib
- Minor administrative updates and typographical errors were corrected throughout.

Version 5.0 (dated 5 March 2019) of this protocol is the fifth amendment to this clinical trial and contains the following modifications:

- Section 5.0 Study Assessment and Treatment Schedule updated to include:
  - The schedule for response evaluations updated to be performed during cycles 3, 6, 9, 12 and at least every 6 cycles for 24 cycles, then every 12 cycles thereafter or more frequent if warranted."
  - Updated to include CMV surveillance by PCR for all patients every 3 months while on study treatment
  - Updated with instruction to perform urine pregnancy test within 72 hours of Day 1 of each cycle and administer test with each drug dispensation after Cycle 6.
- Section 6.3.1 Dose Delay/Modification: Umbralisib has been updated to provide additional guidance on dose delay/modifications for umbralisib and provide clarification on the liver toxicity dose modifications guidelines
- Section 6 Treatment Plan has been updated to include:
  - Additional guidance for PJP and anti-viral prophylaxis
  - Revised to allow dose delays of any study medication for durations longer than 28 days to recover from toxicity
- Section 7.1.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs), has been updated to include the most recent adverse event information for umbralisib based on the Investigator's Brochure V6.0
- Section 10 Safety Reporting and Analysis, updated to reflect email address to submit SAE forms.
- Updated throughout to acknowledge the generic name for TGR-1202: umbralisib
- Updated throughout to update word patient to subject.
- Minor administrative updates and typographical errors were corrected throughout

STUDY SYNOPSIS

Protocol no.	TGR-1202-201-CLL
Study Title	A Phase 2 Study to Assess the Safety and Efficacy of TGR-1202 in Patients with Chronic Lymphocytic Leukemia (CLL) who are intolerant to Prior BTK or PI3K-Delta Inhibitor Therapy
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
IND #	Umbralisib (TGR-1202): 116,762
Study Chair	[redacted], MD [redacted]
Study Sites & Enrollment	• This study will be carried out in up to 20 centers in the United States • Enrollment is expected to take approximately 12 months
Study Rationale	Although kinase inhibitor (KI) therapies are generally well tolerated in CLL there is a small subset of patients (upwards of 12%) who discontinue therapy due to toxicity and a larger subset who require dose interruption due to toxicity (upwards of 30%). Discontinuation or interruptions lead to response durations that are short lived and these patients frequently require continued therapy to control their disease. The purpose of this study is to evaluate the safety and efficacy of umbralisib in previously treated chronic lymphocytic leukemia (CLL) patients who are intolerant to prior BTK or PI3K-delta inhibitor therapy. Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. Umbralisib is currently in a Phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD. In the Phase I study, 20 CLL patients have been treated with umbralisib. AEs (all grades, all causality) included nausea, diarrhea, fatigue, headache, vomiting and cough being the most commonly reported events, the majority of which were Gr1/2. The only Gr≥3 AE in >10% of patients was neutropenia (11%). Of 16 evaluable CLL patients, 14 (88%) achieved a nodal PR (median nodal ↓ of 76%), of which 10 (63%) achieved a PR per Hallek 2008 criteria. Discontinuation due to an adverse event with umbralisib was reported in less than 5% of patients. The importance of dose intensity in patients treated with ibrutinib is highlighted in the RESONATE study (ibrutinib vs. ofatumumab) where lower dose intensity was associated with an inferior progression free survival (PFS). Missing as few as 8 consecutive days of ibrutinib monotherapy resulted in an inferior PFS. The kinase inhibitor intolerant patient population is therefore a

	unique CLL patient population in that they have at least SD to kinase inhibitor therapy however, clinically cannot continue with an active medication due to toxicity. This represents a population at risk for inferior outcomes and one that requires distinct study apart from patients who progress while receiving kinase inhibitor therapy. Additionally, there have been no studies reported to date that address the important question of sequencing kinase inhibitor therapies. Fortunately, kinase inhibitor therapies in CLL appear to have somewhat unique and non-over lapping toxicity profiles. In patients treated with the combination of idelalisib-rituximab, at least one serious adverse event occurred in 40% of patients in which the most common serious adverse events being pneumonia, pyrexia, and febrile neutropenia. Unique toxicities observed include colitis (grade ≥ 3, 5%), pneumonitis (grade ≥ 3, 4%), and transaminitis (grade ≥ 3, 8%). In patients treated with ibrutinib, the most common grade ≥ 3 serious adverse events were pneumonia (10%), bacteremia (5%), cellulitis (5%), sinusitis (5%), and atrial fibrillation (4%). Due to the differentiated safety profile, once-daily dosing and clinical activity in CLL with umbralisib, the primary aim of this study is to evaluate the progression-free survival of umbralisib in patients who are intolerant to prior BTK or PI3K-delta inhibitor therapy.
Study Objectives	**PRIMARY OBJECTIVE** • To determine the progression free survival of umbralisib in patients who were intolerant to prior BTK and/or PI3K-delta inhibitors. **KEY SECONDARY OBJECTIVES** • To evaluate the overall response rate (CR + PR) and duration of response of umbralisib in patients who were intolerant to prior BTK and/or PI3K-delta inhibitors. • To evaluate Time to Treatment Failure with umbralisib as compared to the prior kinase inhibitor therapy in patients with CLL. • To evaluate the safety profile of umbralisib as compared to the safety profile of the prior kinase inhibitor therapy in patients with CLL.
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Confirmed diagnosis of CLL as per the iwCLL (Hallek 2008) criteria[6] 2. CLL warranting therapy as per investigator discretion. 3. Patients must be off prior BTK and/or PI3K-delta inhibitor for at least 14 days following discontinuation without documented disease progression. This is to ensure the reason for discontinuation was intolerance, not disease progression as listed below, # 4 - 7. Patient may sign consent during the washout period. 4. For ibrutinib/BTK patients who experience related hematologic and non-hematologic toxicities and discontinue therapy (see bullet 7). Non-hematologic toxicities are limited to: Atrial fibrillation, Hypertension, Bleeding, Arthralgia, Rash, Diarrhea, Infection, Pneumonitis.

	5. For idelalisib/duvelisib patients who experience related hematologic and non-hematologic toxicities and discontinue therapy (see bullet 7). Non-hematologic toxicities are limited to: Pneumonitis, Transaminitis, Rash, Colitis, and Infection. 6. Other grade ≥ 2 non hematologic toxicities not listed in 4 or 5, despite dose interruption and/or reduction, and defined by the treating investigator as "intolerant", will be evaluated individually by the study chair as part of eligibility criteria as part of the screening process. 7. Prior therapy with a BTK inhibitor (ibrutinib, ACP-196, other) or a PI3K-delta inhibitor (idelalisib, duvelisib, other), which was discontinued due to intolerance, within 12 months of the time of treatment initiation with umbralisib (Cycle 1/Day 1). a. Intolerance defined as unacceptable toxicity where in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of one of the following: i. ≥ 2 Grade ≥ 2 non-hematological toxicities (see list above, #4-6) as a cause of discontinuation, and/or; ii. ≥ 1 Grade ≥ 3 non-hematological toxicity (see list above, #4-6), and/or; iii. ≥ 1 Grade 3 neutropenia with infection or fever, and/or; iv. Grade 4 hematological toxicities, AND the toxicities persistent to the point that the investigator chose to discontinue therapy due to toxicity / not progression. v. Toxicity must resolve to ≤ grade 1 prior to umbralisib dosing. 8. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) ≥ 1,000/ platelet count ≥ 30,000. Growth factors are permitted at any time during the study. b. Total bilirubin ≤1.5 times the upper limit of normal (ULN) c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement d. Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault or MDRD formula, 24 hour urine Cr clearance also acceptable) 9. ECOG performance status ≤ 2 10. Male or female ≥ 18 years of age 11. Ability to swallow and retain oral medication 12. Female patients who are not of child-bearing potential and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. 13. Willingness and ability to comply with trial and follow-up procedures, and give written informed consent
Exclusion Criteria	Patients who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Patients receiving a BTK or PI3K-delta inhibitor within 14 days of Cycle 1/Day 1.

	a. Corticosteroid therapy started at least 7 days prior to study entry (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted 2. Disease progression as defined by IWCLL (Hallek 2008) criteria as the indication for discontinuation on or within 14 days with a prior BTK or PI3K delta inhibitor. 3. Treatment with prior umbralisib. 4. Prior autologous stem cell transplant within 3 months. Prior allogeneic hematologic stem cell transplant within 1 year and excluded if there is active graft versus host disease. 5. Anaphylaxis to prior kinase inhibitor therapy. 6. Evidence of chronic active Hepatitis B (HBV, not including patients 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 is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by DNA (PCR) - See Appendix D. 7. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation / Hodgkin Lymphoma) 8. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infection of skin or nails. 9. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) – See Appendix C b. Myocardial infarction within 6 months of enrollment c. QTcF >470 msec d. Angina not well-controlled by medication e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of enrollment 10. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry. 11. Women who are pregnant or lactating.
Study Design	This study is designed as a Phase 2, multicenter, single-arm trial to evaluate umbralisib in patients who discontinue a BTK or a PI3K-delta inhibitor due to intolerance. Approximately 55 patients, who have discontinued prior therapy with a BTK or PI3K-delta inhibitor due to intolerance, may be enrolled at approximately 20 sites in the US. Planned analysis will include approximately 50 evaluable patients assuming a 10% discontinuation rate. **<u>Enrollment</u>**

	Following Screening, qualified patients will be enrolled via an IWRS and receive the following: • Umbralisib at 800 mg once daily During the study period, all patients will be evaluated for response by CT and/or MRI during Cycles 3, 6, 9, 12 and then at least every 6 cycles for 24 cycles, then every 12 cycles thereafter. Patients will be treated until disease progression, unacceptable toxicity or the end of the study. Upon the end of the study, patients without disease progression may be transitioned to an open label compassionate use study.
Statistics	We will plan to enroll approximately 55 subjects, and assuming 10% attrition, we will have approximately 50 subjects remaining for analysis. Enrollment is expected to be completed in approximately 12 months with 24 months follow up. The sample provides 82% power to detect a 12- month median survival versus an 8 month median representing the null hypothesis, using a one-sided one-sample log-rank test with a 5% type 1 error. The number of treatment interruptions and dose reductions will also be evaluated between the prior therapy with a BTK or PI3K-delta inhibitor compared to umbralisib. Safety will be examined on an ongoing basis while the study is being conducted. Adverse events will be recorded as per CTCAE v4.0, and be compared for umbralisib to the prior treatment if data available.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Definitions of Terms	
AE	Adverse Event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BM	Bone Marrow
BTK	Bruton's Tyrosine Kinase
Ca	Calcium
CBC	Complete Blood cell Count
Cl	Clearance
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
Cmax	Maximum Concentration
CR	Complete Response
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebro-Vascular Accident
D, d	Day
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRG	Data Review Group
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCR	Fludarabine, Cyclophosphamide, Rituximab
FISH	Fluorescence in-situ hybridization
GCP	Good Clinical Practice
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
ITT	Intent-to-treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LD	Longest Diameter
LDH	Lactate dehydrogenase
LPD	Longest Perpendicular Diameter
LTFU	Long-Term Follow Up
MDS	Myelodysplastic Syndrome
MPD	Myeloproliferative Disorder
MRD	Minimum Residual Disease

Abbreviations and Definitions of Terms	
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NHL	Non-Hodgkin's Lymphoma
OS	Overall survival
ORR	Overall Response Rate
PCR	Polymerase Chain Reaction
PE	Physical Examination
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PK	Pharmacokinetic
PPD	Perpendicular Diameters
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
SPD	Sum of the Products
SUV	Standardized Uptake Value
t1/2	Half-Life of Elimination
TTR	Time to response
ULN	Upper limit of normal
V	Visit
Vd	Volume of distribution
WHO	World Health Organization

1 INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

In the US, an estimated 14,620 new cases of Chronic Lymphocytic Leukemia (CLL) will be reported in 2015 with deaths totaling 4,650 due to the disease according to American Cancer Society estimates (American Cancer Society, 2015). 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). Patients with 17p deletion show higher resistance to conventional chemotherapies as well as shorter duration of survival than non 17p deletion patients. Patients with 11q deletion have been associated with marked lymphadenopathy (Hallek M, 2008). Patients with P53 gene mutations are associated with an adverse clinical outcome (Lin 2002).

Recently the BTK inhibitor, ibrutinib and the PI3K delta inhibitor, idelalisib were approved by the FDA for the treatment of patients with CLL in the relapsed or refractory setting. Although kinase inhibitor (KI) therapies are generally well tolerated in CLL there is a sizable subset of patients (upwards of 12%) who discontinue therapy due to toxicity and a larger subset who require dose interruption due to toxicity (upwards of 30%). Discontinuation or interruptions lead to response durations that are shorter lived. Additionally, these patients frequently require continued therapy to control their disease. Therefore, there is a consensus in the CLL community that frequent treatment interruptions or dose reductions may lead to inferior outcomes. The importance of dose intensity in patients treated with ibrutinib is highlighted in the RESONATE study (ibrutinib vs. ofatumumab) where lower dose intensity was associated with an inferior progression free survival (PFS).[1,2] Missing as few as 8 consecutive days of ibrutinib monotherapy resulted in an inferior PFS.[2]

Fortunately, kinase inhibitor therapies in CLL appear to have somewhat unique and non over lapping toxicity profiles. In patients treated with the combination of idelalisib-rituximab, at least one serious adverse event occurred in 40% of patients with the most common serious adverse events being pneumonia, pyrexia, and febrile neutropenia. Unique toxicities of idelalisib include colitis (grade ≥ 3, 5%), pneumonitis (grade ≥ 3, 4%), and transaminitis (grade ≥ 3, 8%). In patients treated with ibrutinib, the most common grade ≥ 3 serious adverse events were pneumonia (10%), bacteremia (5%), cellulitis (5%), sinusitis (5%), and atrial fibrillation (4%).[5]

We have selected umbralisib to study in the patient population due to its seemingly non- overlapping toxicity profile with agents such as ibrutinib and idelalisib.

1.2 UMBRALISIB

Umbralisib is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K.[3] Umbralisib is currently in a Phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD.

In a Phase I study, 20 CLL patients were treated with umbralisib. AEs (all grades, all causality) included nausea, diarrhea, fatigue, headache, vomiting and cough being the most commonly reported

events, the majority of which were Gr1/2. The only Gr≥3 AE in >10% of patients was neutropenia (11%). Of 16 evaluable CLL patients, 14 (88%) achieved a nodal PR (median nodal ↓ of 76%), of which 10 (63%) achieved a PR per Hallek 2008 criteria. Discontinuation due to an adverse event with umbralisib was reported in less than 5% of patients.[4]

1.2.1 PRE-CLINICAL DEVELOPMENT OF TGR-1202

The potency of TGR-1202 against the human and mouse δ isoform of PI3K was evaluated in a homogeneous time resolved fluorescence (HTRF) based enzyme assay in the presence of ATP at its Km value (100 µM) (11). Selectivity over the other three isoforms, namely, α, β, and γ was also determined ([redacted] 2011) ([redacted] AKT phosphorylation in THP-1 cells. Study Report IVT-5264-APT-08, 2011) ([redacted] AKT phosphorylation in MOLT-4 cells. June Study Report IVT-5264-APM-10, 2011).

Data demonstrated the specificity of TGR-1202 towards PI3Kδ with >1000, 50 and 48-fold selectivity over α, β, and γ, respectively in an enzyme based assay, indicating that the primary mode of action of this compound is via inhibition of the δ isoform.

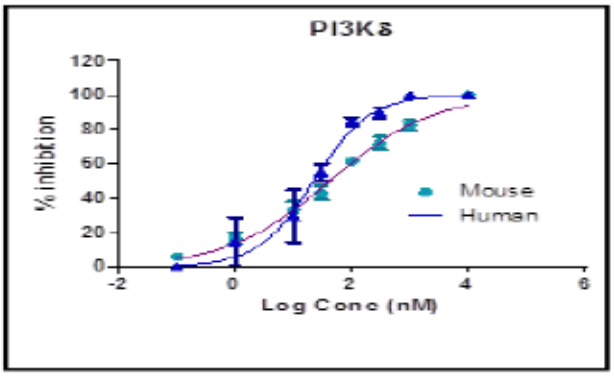


FIGURE 1: TGR-1202 POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

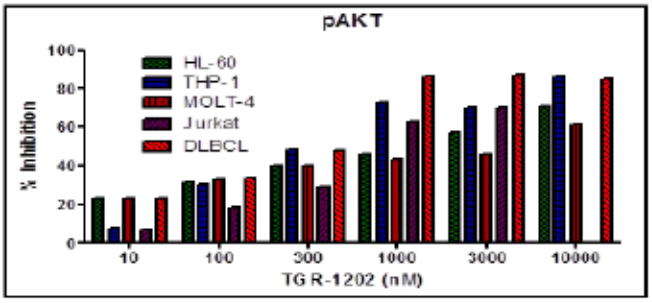
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

Proliferation of immortalized leukemic cells representative of various indications was determined by a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (17). Cells were incubated with TGR-1202 for different time-periods (72 -96 h) based on their doubling time. Data demonstrated the ability of TGR-1202 to inhibit leukemic cell proliferation albeit with different potencies based on the cell type.

Overall, a 50% growth inhibition for majority of B, T, and monocytic cell lines was achieved at a concentration between 0.5 -7.5 µM of TGR-1202.

Subsequent to cell viability, the effect of TGR-1202 on AKT phosphorylation (12, 13, 14, 15, 16) was determined. AKT, a serine threonine kinase mediates the downstream effects of PI3K activity and modulates several cell processes including survival and growth. Reduction of phosphorylated AKT by TGR-1202 in representative cell lines was determined by Western blotting using a phospho-AKT (Ser473) antibody.

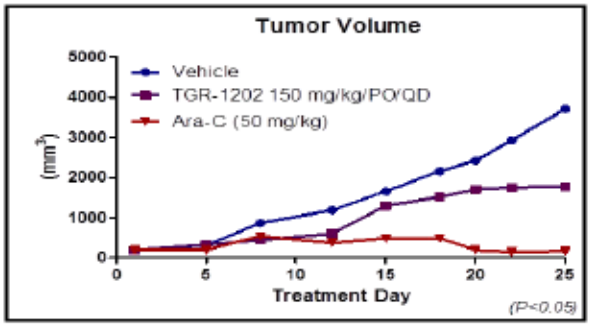
FIGURE 2: REDUCTION OF PAKT BY TGR-1202 IN CELL LINES BY WESTERN BLOTTING



1.2.1.1.1 IN-VIVO ACTIVITY

In vivo efficacy of TGR-1202 was confirmed in a subcutaneous mouse MOLT-4 xenograft model. Oral administration of 150 mg/kg/QD over a 25-day period resulted in a significant delay in tumor growth.

FIGURE 3: TGR-1202 IN VIVO EFFICACY



1.2.1.1.2 TOXICOLOGY

To assess the safety and toxicity of TGR-1202 a 28-day repeat dose study with a 14-day recovery period was conducted in CD-1 mice and beagle dogs, to evaluate the potential reversibility of findings and to support the use in humans. TGR-1202 was administered orally in order to mimic the planned mode of clinical administration.

Once daily oral administration of TGR-1202 was tolerated in mice at free base dose levels of 50 and 150 mg/kg/day. Increases in liver weights, microscopic findings in the liver and the increases in serum cholesterol, and female only ALT, AST, and GGT levels were observed at 750 mg/kg/day of free base (the highest dose tested) and were considered adverse. The no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg/day in mice.

Once daily oral administration by capsule of TGR-1202 was well tolerated in dogs at levels of 50 and 150 mg/kg/day. The gastrointestinal tract, based on clinical signs, was the target organ system. Based on effects on body weight and the incidence and severity of emesis and diarrhea, the NOAEL was considered to be 150 mg/kg/day (114.5 mg/kg/day as free base) in this species.

Refer to the Umbralisib Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

1.2.2 CLINICAL DEVELOPMENT OF UMBRALISIB

1.2.2.1 SINGLE-AGENT IN PATIENTS WITH RELAPSED OR REFRACTORY HEMATOLOGIC MALIGNANCIES

Umbralisib is under evaluation in an ongoing single-agent Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies (Burris et al, ASH 2014). Fifty-five patients were enrolled and eligible for safety evaluation, with 43 patients evaluable for efficacy. The median age was 62 years (range 22-82), 73% male and 18/55 enrolled patients had a diagnosis of CLL. Among all patients the median number of prior therapies was 3, with 80% receiving prior rituximab-based chemotherapy. Other histological diagnoses included; FL (n=15), HL (n=9), DLBCL (n=7), MCL (n=2), MZL (n=2), HCL and WM (n=1 each). The majority of patients had an ECOG of 1 and 51% received 3 or more prior therapies.

Patients have been enrolled in a 3+3 dose-escalation design starting at 50 mg QD with subsequent cohorts evaluating doses as high as 1800 mg QD. In an effort to further improve the oral bioavailability of umbralisib, the particle size of the drug product was reduced through a micronization process, resulting in greater absorption when tested in a bioequivalence crossover study in healthy subjects (see Section 1.2.2.2 Healthy Subject Pharmacokinetic Studies below). This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1200 mg QD, with no maximum tolerated dose (MTD) reached. Intra-patient dose escalation rules have allowed patients enrolled into the study in early cohorts to increase their dose of umbralisib as subsequent higher cohorts have cleared safety evaluation.

A dose-dependent response has been observed with umbralisib, with a dose of 800 mg or higher of the initial formulation or any dose of the micronized formulation producing significant nodal reductions among CLL patients. Of the 14 evaluable CLL patients treated at or above this therapeutic threshold, 93% have achieved a nodal partial response, and nodal reductions show an improvement with time on umbralisib with a median time on study of 6 months. Adverse events observed amongst all 55 patients included diarrhea, nausea, fatigue, cough, anorexia, headache, vomiting, rash, neutropenia, constipation, dyspnea, and thrombocytopenia. One DLT event of Grade 3 rash was observed at the 800 mg dose level of the initial formulation, which necessitated enrollment of an additional 3 patients. The Grade 3 rash resolved upon suspension of umbralisib and concomitant medications and did not recur upon re-challenging the patient at 800 mg QD. See the umbralisib investigators brochure for a complete overview of the umbralisib side effect profile.

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

Overall, umbralisib was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts with 800 mg QD selected as the Phase 2 dose in patients with CLL. Dose expansion in the Phase 1 study continues.

1.2.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

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

1.2.2.2.1 TGR-1202-PK101: FOOD EFFECT

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

The statistical comparisons of TGR-1202 pharmacokinetic parameters under fasted and fed condition are shown below.

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Fasting	Fed		
AUC_{0-t} (ng·hr/mL)	6029.87	962.02	160.73	140.25 – 184.21
AUC_{0-inf} (ng·hr/mL)	8391.35	14047.17	167.40	141.59 – 197.92
C_{max} (ng/mL)	176.78	483.15	273.31	234.04 – 319.17

Food increased both the extent and rate of exposure of TGR-1202. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure increased by 61% and 67%, respectively, when TGR-1202 was administered under fed conditions compared to fasting conditions. The peak plasma levels of TGR-1202 increased by over 173% when TGR-1202 was administered with food.

Using these mean values, a 334 mg oral dose of TGR-1202 under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of TGR-1202 under fed conditions in terms of exposure based on AUC_{0-inf}.

1.2.2.2.2 TGR-1202-PK102: FORMULATION EFFECT

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

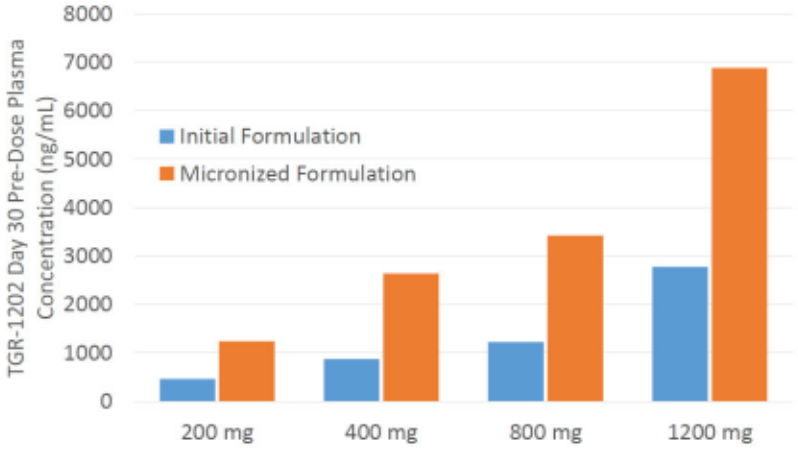
The statistical comparison of the micronized 200 mg drug product formulation versus the original 200 mg drug product formulation are shown below:

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

The micronized drug product formulation increased both the extent and rate of exposure of TGR-1202 under fasted conditions. The extent (AUC_{0-t}) and total extent (AUC_{0-inf}) of exposure both increased by 60%, respectively, following administration of the modified drug product formulation relative to original drug product formulation. The Peak plasma (C_{max}) levels of TGR-1202 increased by over 124% following administration of the micronized drug product formulation relative to original drug product formulation under fasted conditions.

Using these mean values, a 320 mg oral dose of TGR-1202 in the original formulation under fasted condition can be extrapolated to be equivalent to an oral dose of 200 mg of the original formulation TGR-1202 under fasted conditions in term of exposure based on AUC_{0-inf}.

The improved exposure seen with the micronized formulation of TGR-1202 was confirmed in patients in the Phase 1 dose escalation as well. The chart below illustrates the pre-dose plasma concentrations of TGR-1202 on Day 1 of Cycle 2 in patients administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state:



1.3 RATIONALE FOR THE PHASE 2 TRIAL

A retrospective analysis of 123 patients who discontinued prior kinase inhibitor (KI) therapy across 10 large US cancer centers was conducted. Investigators identified 123 patients who discontinued either ibrutinib or idelalisib (ibrutinib=93/idelalisb=30). Interestingly, 10% and 32% of ibrutinib (5% 140 mg, 5% 280 mg daily) and idelalisib patients (32% 100 mg BID), respectively, were initiated at doses less than FDA labeled dose. Further, 23% and 42% of ibrutinib (Ibr) patients and 30% and 65% idelalisib (Ide) patients had doses modified or held, respectively, prior to discontinuation. For patients who discontinued KI therapy, the median time on KI was 5 months. The most common reasons for KI discontinuation were toxicity (58% Ibr, 60% Ide), CLL progression (24% Ibr, 30% Ide), and RT DLBCL (8% Ibr, 7% Ide) *(Mato et al, Abstract 80707, ASH 2015).*

The "kinase inhibitor intolerant" patient population is therefore a unique CLL patient population in that they have at least SD to kinase inhibitor however, clinically cannot continue with therapy due to treatment related toxicity. This represents a population at risk for inferior outcomes and one that requires distinct study apart from patients who progress while receiving kinase inhibitor therapy. Additionally there have been no prospective studies reported to date that address the important question of sequencing kinase inhibitor therapies.

The purpose of this study is to evaluate the safety and efficacy of umbralisib in previously treated chronic lymphocytic leukemia (CLL) patients who are intolerant to prior BTK or PI3K-delta inhibitor therapy. This study will evaluate the progression-free survival of umbralisib in patients who are intolerant to prior KI therapy which is required to be a BTK (ie. ibrutinib) or PI3K-delta inhibitor (idelalisib, duvelisib, etc).

2 OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PRIMARY OBJECTIVE

- **To determine the progression free survival of umbralisib in patients who were intolerant to prior BTK and/or PI3K-delta inhibitors.**

KEY SECONDARY OBJECTIVES

- **To evaluate the overall response rate (CR + PR) and duration of response of umbralisib in patients who were intolerant to prior BTK and/or PI3K-delta inhibitors.**
- **To evaluate Time to Treatment Failure with umbralisib as compared to the prior kinase inhibitor therapy in patients with CLL.**
- **To evaluate the safety profile of umbralisib as compared to the safety profile of the prior kinase inhibitor therapy in patients with CLL.**

2.2 EFFICACY ENDPOINTS

Progression-free survival (PFS)

PFS is defined as the interval from Cycle 1/Day 1 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.

Time to treatment failure (TTF)

TTF is defined as a composite endpoint measuring time from Cycle 1/Day 1 to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

Overall response rate (ORR)

ORR is defined as sum of CR and PR rates.

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

Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

3.1 INCLUSION CRITERIA

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

1. **Confirmed diagnosis of CLL as per the iwCLL (Hallek 2008) criteria**
2. **CLL warranting therapy as per investigator discretion.**
3. **Patients must be off prior BTK and/or PI3K-delta inhibitor for at least 14 days following discontinuation without documented disease progression. This is to ensure the reason for discontinuation was intolerance, not disease progression as listed below, # 4 - 7. Patients may sign consent during the washout period.**
4. **For ibrutinib/BTK patients who experience related hematologic and non-hematologic toxicities and discontinue therapy (see bullet 7). Non-hematologic toxicities are limited to: Atrial fibrillation, Hypertension, Bleeding, Arthralgia, Rash, Diarrhea, Infection, Pneumonitis.**
5. **For idelalisib/duvelisib patients who experience related hematologic and non-hematologic toxicities and discontinue therapy (see bullet 7). Non-hematologic toxicities are limited to: Pneumonitis, Transaminitis, Rash, Colitis, and Infection.**
6. **Other grade ≥ 2 non-hematologic toxicities not listed in 4 or 5, despite dose interruption and/or reduction, and defined by the treating investigator as "intolerant", will be evaluated individually by the study chair as part of eligibility criteria as part of the screening process.**
7. **Prior therapy with a BTK inhibitor (ibrutinib, ACP-196, other) or a PI3K-delta inhibitor (idelalisib, duvelisib, other) which was discontinued, due to intolerance, within 12 months of the time of treatment initiation with umbralisib (Cycle 1/Day 1).**
    a. **Intolerance defined as unacceptable toxicity where in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of one of the following:**
        i. **≥ 2 Grade ≥ 2 non-hematological toxicities (see list above, #4-6) as a cause of discontinuation, and/or;**
        ii. **≥ 1 Grade ≥ 3 non-hematological toxicity (see list above, #4-6), and/or;**
        iii. **≥ 1 Grade 3 neutropenia with infection or fever, and/or;**
        iv. **Grade 4 hematological toxicities, AND the toxicities persistent to the point that the investigator chose to discontinue therapy due to toxicity / not progression.**
        v. **Toxicity must resolve to ≤ grade 1 prior to umbralisib dosing.**
8. **Adequate organ system function, defined as follows:**
    a. **Absolute neutrophil count (ANC) ≥ 1,000 / platelet count ≥ 30,000. Growth factors are permitted at any time during the study.**
    b. **Total bilirubin ≤1.5 times the upper limit of normal (ULN)**
    c. **Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x the ULN if known liver involvement**
    d. **Calculated creatinine clearance >30 mL/min (as calculated by the Cockcroft-Gault or MDRD formula, 24- hour urine Cr clearance also acceptable)**
9. **ECOG performance status ≤ 2**
10. **Male or female ≥ 18 years of age**
11. **Ability to swallow and retain oral medication**

12. Female patients who are not of child-bearing potential and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1.
13. Willingness and ability to comply with trial and follow-up procedures, and give written informed consent.

3.2 EXCLUSION CRITERIA

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

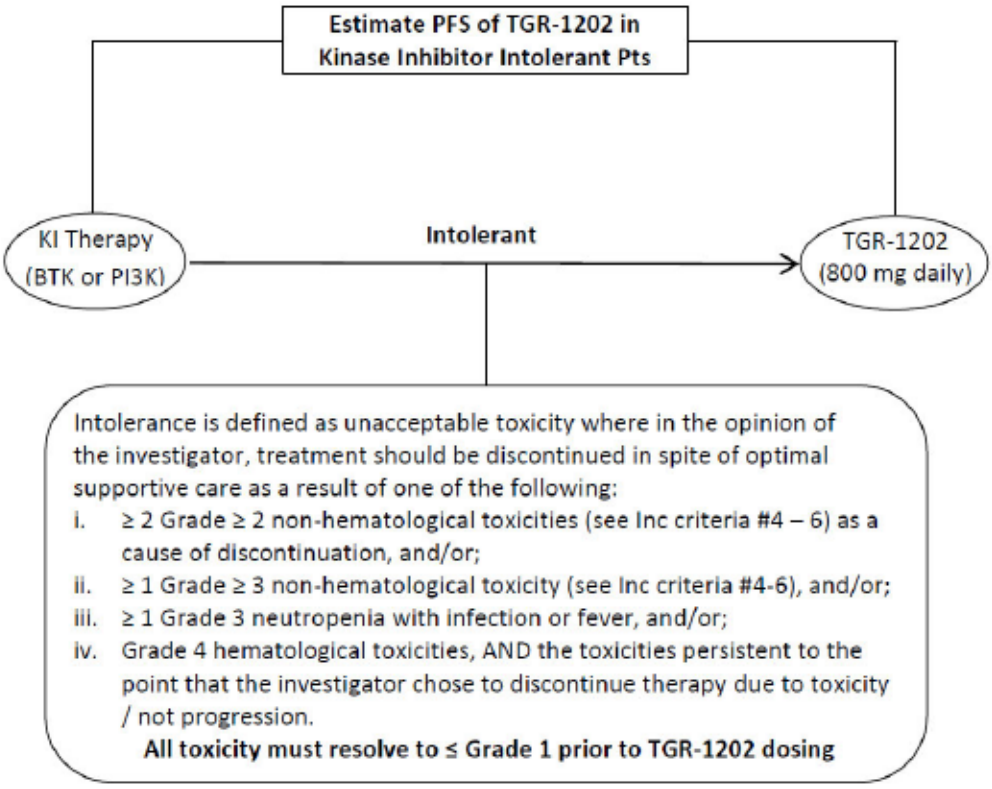
1. Patients receiving a BTK or PI3K-delta inhibitor within 14 days of Cycle 1/Day 1.
   a. Corticosteroid therapy started at least 7 days prior to study entry (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
2. Disease progression as defined by IWCLL (Hallek 2008) criteria as the indication for discontinuation on or within 14 days with a prior BTK or PI3K-delta inhibitor.
3. Prior treatment with umbralisib.
4. Prior autologous stem cell transplant within 3 months. Prior allogeneic hematologic stem cell transplant within 1 year and excluded if there is active graft versus host disease.
5. Anaphylaxis to prior kinase inhibitor therapy.
6. Evidence of chronic active Hepatitis B (HBV, not including patients 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 is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by DNA (PCR) - See Appendix D.
7. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation / Hodgkin Lymphoma).
8. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infection of skin/nails.
9. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
   a. Symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV) – See Appendix C
   b. Myocardial infarction within 6 months of enrollment
   c. QTcF >470 msec
   d. Angina not well-controlled by medication
   e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of enrollment.
10. Malignancy within 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer and PSA <1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry.
11. Women who are pregnant or lactating.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This study is designed as a Phase 2, multicenter, single-arm trial to evaluate the PFS of umbralisib in CLL patients requiring therapy who are intolerant to prior kinase inhibitor therapy. Up to 55 patients who have discontinued their prior therapy with a BTK or PI3K-delta inhibitor due to intolerance, may be enrolled.

Study Schema



4.2 REGISTRATION/ENROLLMENT

Following Screening, qualified patients will receive the following:

- **Umbralisib at 800 mg once daily**

Investigators will use an interactive web response system (IWRS) to enroll patients to study TGR-1202-201. Upon entering patient information into the IWRS, investigators will receive a unique patient identifier. This confirmation must be received by the site prior to dispensing study drug to the participant. Further details about the patient registration process using the IWRS system will be outlined in the Study Manual.

During the study period, all patients will be evaluated for response by CT and/or MRI during Cycles

3, 6, 9, 12 and at least every 6 cycles for 24 cycles, then every 12 cycles thereafter or more frequent if warranted
(+/- 14 day window). Patients will be treated until disease progression, unacceptable toxicity, or the end of the study. Upon the end of the study, patients without disease progression may be transitioned to an open label compassionate use study.

4.3 STUDY SITES

Up to 20 centers in the United States may be asked to participate in this study. Enrollment is expected to be completed in approximately 12 months.

4.4 DISCONTINUATION FROM STUDY TREATMENT

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

- Disease progression
- Intolerable toxicity related to study drug
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the patient 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

Patients who discontinue from study treatment (for reasons other than progressive disease) should continue to be followed for progression as per the Study Assessment Table.

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

All patients 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 patient's medical records and as a comment on the eCRF.

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Error! Reference source not found.The Table below lists study assessments that should be performed at each study visit.

STUDY ASSESSMENTS AND TREATMENT SCHEDULE

All cycles are 28 days	Screening	Cycle 1[1]			Cycles 2 - 6[2]	> Cycle 6[3]	EOT	30 day F/U
	D-30 to D0	D1	D8	D15	D1	Every 3 cycles		
Informed Consent	X							
Medical History	X							
ECOG Performance Status	X	X			X	X	X	
Physical Examination/Vitals (Weight, Temp, BP, HR, RR)	X	X	X	X	X	X	X	
EKG (QtcF)	X							
Serology HCV, HBV, CMV	X[4]							
CMV surveillance					C3&6	X[5]		
Hematology	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	
CT Imaging (neck, chest, abdomen, pelvis)	X[6]	During Cycles 3, 6, 9, 12 and at least every 6 cycles for 24 cycles, then every 12 cycles thereafter or more frequent if warranted (+/- 14 days)					X[7]	
Serum Pregnancy Test	X[8]							
Urine Pregnancy Test[9]					X	X		
Collect Buccal Swab for Somatic DNA[10]	X							
Correlative Labs (PB)[10]	X				Cycle 2		Disease progression	
Peripheral Blood[11]	X							
Umbralisib		Daily Days 1 – 28						
Bone Marrow Biopsy[12]	X							
AE Assessment		X	X	X	X	X	X	X[13]
Con med Assessment		X	X	X	X	X	X	

[1] Physical Exam, Vitals, ECOG, treatment administration, AEs, conmeds, hematology, serum chemistry visit days have +/- 1 day window. Assessments must be done within the specified window, but only prior to initiation of next cycle.
[2] Physical Exam, Vital Signs, ECOG PS, treatment administration, AEs, conmeds, hematology, serum chemistry visit days have +/- 3 day window in Cycles 2 - 6. Assessments must be done prior to treatment administration. Assessments must be done within the specified window, but only prior to initiation of next cycle.
[3] Physical Exam, Vital Signs, ECOG PS, treatment administration, AEs, conmeds, hematology, serum chemistry visit days have +/- 7 day window for Cycles > 6. Assessments must be done prior to treatment administration. Assessments must be done within the specified window, but only prior to initiation of next cycle.
[4] Serum virology to include HBsAg, HBsAb, HBc antibody, HCV antibody and CMV. If HBc antibody, HCV antibody or CMV is positive, subjects must be evaluated for the presence of active HBV, HCV or CMV by DNA (PCR).
[5] 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] Baseline CT scan within 30 days prior to Cycle 1/Day 1; then during cycles 3, 6, 9, 12 and at least every 6 cycles for 24 cycles, then every 12 cycles thereafter or more frequent if warranted (+/- 14 days). CT imaging should be performed at EOT visit if it hasn't been completed within past 30 days.
[7] If discontinued due to reasons other than progression, follow up every 3 months on status of disease progression. Patients who discontinue from study treatment after cycle 12 (for reasons other than disease progression) should be followed for progression, approximately every 6 months for 24 months then every 12 months or more frequent if warranted.
[8] Serum pregnancy test within 72 hours prior to starting treatment on Cycle 1 / Day 1.
[9] Urine pregnancy test within 72 hours of Day 1 of each cycle. Administer test with each drug dispensation after Cycle 6.
[10] Peripheral Blood (screening, Cycle 2/Day 1 and at disease progression) and buccal swab (screening only) samples for correlative analyses. See lab manual.
[11] Additional peripheral blood sample will be collected at screening only and analyzed at central lab for high-risk cytogenetics as well as BTK/PI3K resistance and activating mutations/deletions of prognostic value.
[12] Bone Marrow aspirate/ biopsy performed at baseline at the discretion of investigator to evaluate cytopenias. Bone marrow to be repeated if patient meets clinical criteria for CR to confirm this finding, as per iwCLL criteria.
[13] Subjects who discontinue study drug should have a follow up visit or telephone call to assess for AEs. This should be done 30 days (+/- 7 days) after the last dose of study drug. In addition, SAEs will be reported for 30 days after the last dose of study drug.

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

5.1.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include (within 30 days of Cycle 1/Day 1):

Hematologic Profile		
Hematocrit	Neutrophils	Platelet count
Hemoglobin	Lymphocytes	Absolute lymphocyte count
Erythrocyte count	Monocytes	Leukocyte count
Basophils	Eosinophils	Absolute neutrophil count
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 and Serum Chemistry windows as follows:

- Cycle 1: - 1 day window
- Cycles 2 – 6: - 3 day window
- > Cycle 6: - 7 day window

2. Serum β-HCG test.
3. Serum Virology to include HBsAG, HbSAb, HBc antibody, HCV antibody, and CMV. If HBc antibody, HCV antibody or CMV are positive the subject must be evaluated for the presence of active HBV, HCV or CMV by DNA (PCR) - See Appendix D.
4. Baseline bone marrow aspirate/ biopsy (if indicated or warranted).
5. CMV surveillance every 3 months by PCR. CMV surveillance will discontinue 30 days after last dose of umbralisib, or as otherwise clinically indicated per investigator discretion.

5.1.2 CENTRAL LABORATORY ASSESSMENTS

See Study Lab Manual for full Central Lab details (collection, preparation, shipping, etc.)

- Peripheral Blood sample at screening, Cycle 2/Day 1 and at disease progression, will be collected, shipped and stored at [redacted] for correlative analyses. See Study/Lab Manual for details.
- An additional peripheral blood sample will be collected at screening only and analyzed by at central lab for cytogenetics (17p del, 11q del, p53 mutation) and BTK/PI3K resistance and activating mutations/deletions of prognostic value. In addition, a Buccal Swab will be collected at screening only and sent to central lab for analysis (See Study/Lab Manual).

6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

Treatment will be administered on an outpatient basis in 4-week (28 day) cycles.

Umbralisib

- 800 mg umbralisib once daily until removal from study
- Patient diary will be utilized to document missed doses of study drug

6.2 AGENT ADMINISTRATION

Umbralisib will be self-administered orally, all on an outpatient basis.

6.2.1 GUIDELINES FOR ADMINISTRATION OF UMBRALISIB

- *Method of Administration:* Umbralisib will be administered orally once daily with food
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Anti-microbial prophylaxis:* Subjects are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PJP) and antiviral therapy prior to Cycle 1 Day 1. Choice of PJP and anti-viral prophylaxis therapy is per investigator discretion and institutional standard of care, with the following as recommendations:
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
    - *PJP Prophylaxis:* Dapsone 100 mg daily or equivalent.

    If anti-viral or anti-bacterial prophylaxis is not tolerated, alternating to a different prophylactic agent, reducing the dose or modifying the schedule for the prophylactic agent, or discontinuing prophylaxis is at the discretion of the investigator. Final choice of PJP and anti-viral prophylaxis therapy is per investigator discretion.
- *Pre-medications:* None

Umbralisib will be dispensed at the sites by the Pharmacist of authorized designee. 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 approximately the same time each day with food (within 30 minutes of a meal). Subjects should be instructed to swallow the tablets whole. Do not chew or crush umbralisib.

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

6.2.1.1 DISPENSING OF UMBRALISIB

Before dispensing, the Pharmacist or authorized designee 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. For the purpose of drug accountability and dosing, a drug diary will be utilized. Any error in drug administration should be recorded (e.g., missed dose) in the eCRF.

The Pharmacist or authorized designee 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.

6.2.2 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that subject has:

- No intolerable toxicities related to study drug.
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

6.3 DOSING DELAYS AND MODIFICATIONS

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**Error! Hyperlink reference not valid.**) 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 and are per investigator discretion. Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. Delay of study drug is allowed for recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level.

If greater than 2-cycle drug delay is necessary for recovery of toxicities, you may contact TG Therapeutics prior to re-initiating study drug with any questions. If a subject discontinues study drug due to toxicity, the subject should continue to be followed for progression as described in the Study Assessments and Treatment Schedule. If a subject withdraws consent or has documented progression, an end of study visit should be completed.

Subjects should be re-educated if a dose modification occurs, to ensure they are aware of the revised number of study drug tablets. The IWRS system should be updated in the event of dose delays and/or modifications in IWRS. Contact sponsor with questions regarding dose delay and/or modification.

6.3.1 DOSE DELAY/MODIFICATIONS: UMBRALISIB

TABLE 1: 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	Stop all therapy and hold until complete resolution. Restart umbralisib at one lower dose level. If recurrence after re-challenge, discontinue all treatment therapy.
Grade ≥ 3	Discontinue all therapy
***For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-viral prophylaxis is required at start of therapy.**	
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.
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. Consider supportive care. **NOTE:** If persistent grade 2 diarrhea, despite supportive care, delay umbralisib until ≤ grade 1. If recurrence after rechallenge, resume at full dose or next lower dose level at discretion of the investigator.
Diarrhea Grade ≥ 3	Withhold umbralisib until Grade ≤ 2. Administer supportive care. 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
Liver Injury (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 (prednisone 0.5-1 mg/kg/day or equivalent, per investigator discretion)**
	• Monitor labs at least weekly until Grade 1
	• Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off.
	  ○ If liver toxicity recurs to Grade 2 once off steroids, re-initiate steroids with 10 mg per week taper until off.
	  ○ Consider withholding umbralisib.

Grade ≥3	• Hold umbralisib • Assess Concomitant Medications and Risk Factors* • Begin/continue supportive care (0.5-1 mg/kg/day or equivalent, per investigator discretion)** • Monitor labs at least weekly until Grade 1 • Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off • Resume umbralisib at next lower dose level when Grade ≤1
* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc. **Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc. Important: Before initiating steroids, check for viral hepatitis or CMV infection.	

Study Drug Dose Reduction Recommendations

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

A maximum of 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 ORDERING UMBRALISIB

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

Upon receipt of treatment supplies, the Pharmacist or authorized designee should update the accountability forms for umbralisib. If any abnormality on the supplied bottles (umbralisib) is observed, the Pharmacist or authorized designee must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

6.5 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.
- Patient 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.

- Study drug will be made available to responding subjects for a total of three years from initiation of therapy. If umbralisib becomes commercially available during the active period on study, an attempt will be made to obtain this agent through commercial insurance. If coverage is not available, it will be provided for a period of three years as stated above.

During the study period, subjects will be evaluated for response by CT and/or MRI during Cycles 3, 6, 9, 12 and then at least every 6 cycles for 24 cycles then every 12 cycles thereafter (+/- 14 day window). 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 and have not progressed should continue to be followed for progression, if agreeable, approximately every 3 months. If the subject discontinues after cycle 12 for reasons other than disease progression, they should continue to be followed for progression approximately every 6 months for 24 cycles then every 12 cycles thereafter (+/- 14 day window).

7 STUDY MEDICATION OVERVIEW AND SAFETY

7.1 UMBRALISIB

Chemical Name:	Umbralisib tosylate
Other Names:	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:	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.

7.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in subjects treated with single agent umbralisib and were considered at least possibly related to the study medication. The preliminary safety data as of May 1, 2018 is provided for a total of 136 subjects exposed to single agent umbralisib with a maximum follow up of 5+ years. See the latest umbralisib Investigator's Brochure for updated safety information.

VERY COMMON (≥10%)

Blood and Lymphatic System Disorders: neutropenia

Gastrointestinal Disorders: nausea, diarrhoea, vomiting

General Disorders and Administration Site Conditions: fatigue

7.1.1.1 COMMON (≥ 2% - < 10%)

Blood and Lymphatic System Disorders: anaemia, thrombocytopenia, leukocytosis, lymphocytosis

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: vision blurred

Gastrointestinal Disorders: constipation, abdominal pain, abdominal distension, dyspepsia, colitis, dry mouth

General Disorders and Administration Site Conditions: pyrexia, oedema peripheral

Infections and Infestations: pneumonia, oral candidiasis

Injury, Poisoning and Procedural Complications: contusion

Investigations: weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased

Metabolism and Nutrition Disorders: decreased appetite, dehydration, hyperglycaemia, hypokalaemia, hypophosphataemia

Musculoskeletal and Connective Tissue Disorders: muscle spasms, pain in extremity

Nervous System Disorders: dizziness, headache, dysgeusia, tremor

Psychiatric Disorders: insomnia

Respiratory, Thoracic and Mediastinal Disorders: cough

Skin and Subcutaneous Tissue Disorders: rash maculo-papular, alopecia, night sweats, pruritus, rash

8 MEASUREMENT OF EFFECT

During the study period, all subjects will be evaluated for response by CT and/or MRI during Cycles 3, 6, 9, 12 and then at least every 6 cycles for 24 cycles, then every 12 cycles thereafter or more frequent if warranted. All efficacy assessments have a +/- 14- day window. The determination of response and progression will be based on IWCLL criteria (Hallek M, 2008).

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 30 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. If IV contrast is not used at baseline, then it should not be used with subsequent response assessments to maintain consistency.

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 not be performed with contrast, unless medically contraindicated.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification.

8.2 RESPONSE REVIEW

The review of radiographic and clinical data by the study investigators will be performed on an ongoing basis. De-identified images should be available if the Sponsor requests to confirm any objective response observed.

8.3 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

8.3.1 TARGET LESIONS

At baseline, up to 6 lymph nodes should be selected as target lesions (if measurable disease is present) 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 should be measured and recorded at baseline and as per the study assessment schedule. The cross-sectional dimensions (the largest cross-sectional diameter, i.e., the LD × LPD) will be recorded (in cm) for each target lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each target lesion and the sum of the products (SPD) (in cm^2) for all target lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a measurable nodal target lesion if it is > 1.5 cm in long axis diameter and > 1.0 cm in short axis diameter.

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.

8.3.2 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.

8.3.3 NON-TARGET LESIONS

Any other measurable and abnormal nodal lesions not selected for quantitation as target lesions may be considered non-target lesions. In addition, non-measurable evidence of CLL 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".

8.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized as CR, PR, PR-L, 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.

8.5 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 (if applicable)
- 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 hypo cellular bone marrow related to prior or ongoing drug toxicity (not to CLL) will be considered as a CR with incomplete marrow recovery (CRi).

8.6 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 (if applicable)
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 8.3.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 8.3.2
  - 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)

The proportion of subjects who achieve a PR with lymphocytosis will be recorded.[7]

8.7 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

8.8 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 (if applicable)
  - 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 (if applicable)
  - 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

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

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

Worsening of disease during temporary interruption of study treatment (e.g., for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL progression, then the date of progression should be the time point at which progression was first objectively documented.

8.9 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.

8.10 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.[7]

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE

[redacted]

9.2 GENERAL ANALYSIS CONVENTION

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher and all hypothesis tests will be conducted at a two-sided significance level of 0.05.

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries will be presented. The data listings will include all available efficacy and safety data.

9.3 STUDY POPULATIONS

Two study populations, intent-to-treat (ITT) and safety populations, are pre-defined for this study. The ITT population will include all enrolled subjects who provide some efficacy assessments and the safety population will include all subjects who take at least one dose of study medication. The efficacy analyses will be based on ITT population and the safety analyses will be based on the safety population.

9.4 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.

9.5 MEDICAL HISTORY

Medical history will be captured at the Screening visit.

9.6 EXTENT OF EXPOSURE

The dose (mg) of study drugs administered, the total number of doses of study drug, 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.

9.7 EFFICACY ANALYSES

Each subject will be assigned to 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 8) unknown (not assessable, insufficient data).

Many of the efficacy measures will be based on disease assessments. The best clinical response as well as disease progression will be determined by the treating investigator. Scans should be kept on file in cases where independent review or confirmation may be warranted. Definitive disease progression will be based on standard criteria (Hallek et al. 2008, Appendix A – CLL Response Definition) occurring for any reason (e.g., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis.

Subjects will be treated until disease progression, unacceptable toxicity or the end of the study. Upon the end of the study, subjects without disease progression may be transitioned to an open label compassionate use study.

9.8 MISSING VALUE HANDLING PROCEDURES

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates may vary depending upon the parameter.

9.9 STATISTICAL ANALYSES

9.9.1 PRIMARY EFFICACY VARIABLE - PFS

The primary efficacy outcome is progression-free survival (PFS). Time to progression event "Survival" curve will be presented using Kaplan-Meier method. Median time to event and the 95% confidence interval of the median times will be presented, if estimable. Median time to event will be tested against the null hypothesis value using a one-sample (one-sided) log-rank test.

PFS is defined as the interval from Cycle 1/Day 1 to the earlier of the first documentation of definitive disease progression or death from any cause.

9.9.2 SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes will include:

- Overall Response Rate (ORR)
- Time to Treatment Failure (TTF)
- Duration of Response (DOR)

9.9.2.1 OVERALL RESPONSE RATE

Overall Response Rate (ORR) will be determined according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (Hallek et al. 2008).

We will estimate Overall Response Rate (ORR), is defined as percent of subjects who achieve CR or PR. We will also estimate exact 95% confidence intervals for the response rates. These will be followed by additional logistic regression analyses model to adjust for demographic and baseline parameters.

9.9.2.2 TIME TO TREATMENT FAILURE

Time to Treatment Failure (TTF) is defined as a composite endpoint measuring time from Cycle 1/Day 1 to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Estimates of median TTF will be made using Kaplan-Meier methods.

9.9.2.3 DURATION OF RESPONSE

Duration of response (DOR) 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. This variable will be summarized. Estimates of median DOR will be made using Kaplan-Meier methods.

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 umbralisib study drug actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

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 umbralisib Investigator Brochure.

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.

10.3 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 (Cycle 1/Day 1) and through the end of the study or up through 30 days (+/-7 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.

10.4 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.

10.4.1 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 – 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 umbralisib treatment spanning from Cycle 1/Day 1 until 30 calendar days (+/-7 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.

10.4.2 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.

10.4.3 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 (+/-7 days) after discontinuation or completion of protocol-specific treatment (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.

10.5 SERIOUS ADVERSE EVENTS

10.5.1 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,**
- **immediately life-threatening,**
- **requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization,**
- **results in persistent or significant disability/incapacity, and/or**
- **causes a congenital anomaly/birth defect.**

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or 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 and is an unexpected event. SUSAR reporting is encompassed within SAE reporting guidelines as defined in this section.

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

- **Emergency Department or Emergency Room**
- **Outpatient or same-day surgery units**
- **Observation or short-stay unit**
- **Rehabilitation facility**
- **Hospice or skilled nursing facility**
- **Nursing homes, Custodial care or Respite care facility**

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a serious adverse event to the Sponsor.

10.5.2 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 Cycle 1/Day 1 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) at safety-inbox.biotech@iqvia.com within 24 hours of the first knowledge of the event by the treating physician or research personnel.

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When an SAE is reported to the sponsor or designee, the same information should be entered on the eCRF within 24 hours (1 business day). Transmission of the SAE report should be confirmed by the site personnel submitting the report.

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

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

10.6 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).

10.7 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.

10.8 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.

10.8.1 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.

10.8.2 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.

10.8.3 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 will not be reported as an Adverse Event. 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.

10.8.4 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 10.5.1.

10.8.5 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.

10.8.6 PROTOCOL-DEFINED SERIOUS ADVERSE EVENTS

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

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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

must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a subject may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the subject must not receive any study drug(s), and must be discontinued from the study.

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

If a subject becomes pregnant while enrolled in the study, an SAE form should be completed and submitted to the Sponsor. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.

Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting.

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment (umbralisib), 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 vs. Second Primary Malignancy

Any secondary (occurring as a direct result as study drug administered, including but not limited to MDS) or second primary (unrelated, new cancer, including but not limited to MDS and MPD) malignancy event must be reported 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 12 months prior to initiating the protocol to inspect the drug storage area, and fully inform the Investigator of his/her responsibilities for studies and the procedures for assuring adequate and correct documentation.

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

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

11.2 AMENDMENTS TO THE PROTOCOL

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

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

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

The amendment will be submitted 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 Ethics Committee and/or FDA and Competent Authority approval may include the following:

- Change to study design
- Risk to subject

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

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the subjects, their consent to continue participation in the study should be obtained.

11.3 CURRICULA VITAE AND FINANCIAL DISCLOSURES

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

11.4 DATA OWNERSHIP AND PUBLICATION

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

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

All manuscripts, abstracts, or other presentation materials generated by site investigators must be reviewed and approved by the Sponsor prior to submission.

12 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

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

12.1 IRB APPROVAL

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

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

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

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

Safety updates for 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 study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

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

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the investigator to the subject.

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

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 study, the subject should be informed of following:

- What protected health information (PHI) will be collected from subjects in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the study;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

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

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory

authorities and the IRB direct access to review the subject's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify subjects on the eCRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Subject names or addresses will not be entered in the eCRF or database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

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

13 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

13.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

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

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

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

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

13.2 STUDY DOCUMENTATION AND STORAGE

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

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

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Site Study File/SSF or ISF) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 13 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, IRB approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

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

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

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

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

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

13.3 DATA COLLECTION

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

In order to maintain confidentiality, only study number, subject number, initials and date of birth will identify the subject in the eCRF. If the subject's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the subject number and subject's initials. The investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

13.4 STUDY MONITORING, AUDITING, AND INSPECTING

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

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities and the sponsor or its representative(s).

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

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

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

Accurate and reliable data collection will be ensured by verification and cross check of the eCRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

13.6 DISCLOSURE AND PUBLICATION POLICY

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

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

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

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

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

All manuscripts, abstracts, or other presentation materials generated by site investigators must be reviewed and approved by the Sponsor prior to submission.

[redacted]

14 REFERENCES

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15 APPENDIX A – CLL RESPONSE DEFINITION

Assessment of response will follow the guidelines published by 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:*** a. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/µL). b. Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by physical examination. (if applicable) c. No hepatomegaly or splenomegaly by physical examination and/or CT. d. Absence of constitutional symptoms. e. Blood counts above the following values: a. Neutrophils >1.5 x 10^9/L (1500/µL) without need for exogenous growth factors. b. Platelets >100 x 10^9/L (100 000/µL) without need for exogenous growth factors. c. Hemoglobin >110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin. **For patients in clinical studies, 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 studies 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 studys, 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 (if applicable): • 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. ***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 highly effective contraception during the study and for 30 days after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 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 or urine pregnancy test ≤ 72 hours prior to initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring, must use condoms during treatment and for 30 days after discontinuation of the study drug. They 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 – NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

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

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

Interpretation of Hepatitis B Serologic Test Results

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

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

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

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

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

www.cdc.gov/hepatitis