Official Title: A Phase 2 Study to Assess the Efficacy and Safety of TGR-1202 (Umbralisib) Monotherapy in Patients with Non-Follicular Indolent Non-Hodgkin's Lymphoma

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Local Protocol #: Protocol TGR-1202-202

TITLE:

A Phase 2 Study to Assess the Efficacy and Safety of TGR-1202 (Umbralisib) Monotherapy in Patients with Non-Follicular Indolent Non-Hodgkin's Lymphoma

Sponsor: TG Therapeutics, Inc.
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IND Number: **TGR-1202**
116,762

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Version: 1.0 **Date:** 4 April 2017

Version: 2.0 **Date**: 5 September 2017

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TGR-1202-202 for issuance.

Protocol Title: **A Phase 2 Study to Assess the Efficacy and Safety of TGR-1202 (Umbralisib) Monotherapy in Patients with Non-Follicular Indolent Non-Hodgkin's Lymphoma**

Protocol Number: TGR-1202-202

IND Number: **TGR-1202**
116,762

Date FINAL: 5 September 2017

STUDY CHAIR, [redacted] MD

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Date 12/4/17

SPONSOR CONTACTS, TG Therapeutics, Inc.

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Signature

12/4/2017
Date

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Print Name

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Signature

5 Dec 2017
Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	**A Phase 2 Study to Assess the Efficacy and Safety of TGR-1202 (Umbralisib) Monotherapy in Patients with Non-Follicular Indolent Non-Hodgkin's Lymphoma**
Protocol Number:	TGR-1202-202
IND Number:	**TGR-1202** 116,762
Date FINAL:	5 September 2017

I have read the attached protocol and agree that it contains all the necessary details for performing TGR-1202-202.

I will provide copies of the protocol and of the TGR-1202 (umbralisib) Investigator's Brochure, which was 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 TGR-1202, as well as the Standard of Care agents used in this trial, and the conduct of the study.

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

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

Print Name	Signature	Date

TABLE OF CONTENTS

Version 2. 0 (Dated 5 September 2017) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- Section 2.1 has been updated to include [redacted]
- Section 3.2 has been updated to broaden the Exclusion Criteria to include any significant cardiovascular disease within 6 months
- Sections 4.1, 6.5, and 8 have been updated to reflect the change in scan assessment schedule and to include response assessment for WM patients without nodal involvement. In addition, these sections have been updated to include the follow-up schedule for patients who discontinued from the study for reason other than disease progression.
- Updates on the Study Assessment and Treatment Schedule in Section 5
- Section 5.2.2 has been included to add Central Laboratory Assessments
- Section 6.2.1 has been updated to require treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy
- Section 6.3.1 has been updated to provide detailed guidance for TGR-1202 Dose Delays and Modifications
- Section 7.1.1 has been updated to include the latest CAEPRS information for TGR-1202.
- Appendix B has been updated for male patients to use highly effective contraception during the study period and for 30 days after.
- Updated throughout to acknowledge the tradename for TGR-1202: umbralisib
- Minor administrative updates and typographical errors were corrected throughout.

STUDY SYNOPSIS

Protocol no.	TGR-1202-202
Study Title	**A Phase 2 Study to Assess the Efficacy and Safety of TGR-1202 (Umbralisib) Monotherapy in Patients with Non-Follicular Indolent Non-Hodgkin's Lymphoma**
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Sites & Enrollment	This study will be carried out in up to 5 centers in the United States
Study Rationale	Relapsed and refractory indolent non-Hodgkin's lymphomas are difficult to treat with poor overall response rate and overall survival. Idelalisib, a PI3K delta inhibitor has been provided accelerated approval by the FDA to treat patients with relapsed follicular B-cell non-Hodgkin's lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. However up to 54% of the patients on Idelalisib experienced grade 3 or higher adverse events; with drug interruptions, due to toxicity in up to 20 % of the patients. Discontinuation or interruptions lead to response durations that were short lived and these patients frequently required continued therapy to control their disease. The purpose of this study is to evaluate the safety and efficacy of TGR-1202 in previously treated non-follicular indolent non-Hodgkin's lymphomas. TGR-1202 (umbralisib) is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. TGR-1202 is currently in a phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD. The selected phase 3 dose of TGR-1202 is 800 mg QD. In an integrated analysis of two phase I studies, 165 patients with non-Hodgkin's lymphoma were treated with TGR-1202, either alone or in combination with anti-CD20 therapy. AEs (all grades, all causality) included nausea, diarrhea, fatigue, headache, vomiting and cough being the most commonly reported events, the majority of which were Gr 1/2. The only Gr ≥3 AE in >10% of patients was neutropenia (18%). Notably, rates of transaminitis, pneumonitis, and colitis have been minimal. Of 17 evaluable indolent non-Hodgkin's lymphoma (iNHL) patients who were treated with TGR-1202, 9 (53%) patients achieved an objective response rate. Discontinuation due to an adverse event with TGR-1202 was reported in 8% of patients. Due to the differentiated safety profile, once-daily dosing and clinical activity in indolent NHL with TGR-1202, the primary aim of this study is to evaluate the overall response rate (ORR) and duration of response for TGR-1202 in patients with non-follicular indolent NHL.
Study Objectives	**PRIMARY OBJECTIVE**

	• To evaluate the overall response rate (CR + PR + VGPR + MR) and duration of response of TGR-1202 in patients with relapsed or refractory non-follicular indolent non-Hodgkin's lymphoma. **KEY SECONDARY OBJECTIVES** • To determine the progression free survival of TGR-1202 in patients with relapsed or refractory non-follicular indolent non-Hodgkin's lymphoma • To evaluate Time to Treatment Failure with TGR-1202 • To evaluate the safety profile of TGR-1202 [redacted]
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Histologically confirmed diagnosis of B-cell non-follicular indolent non-Hodgkin's Lymphoma meeting at least one of the two following requirements: a. World Health Organization 2008 classification criteria warranting therapy as per investigator discretion for histologies limited to splenic marginal zone lymphoma (SMZL), nodal marginal zone lymphoma (NMZL), or extra-nodal marginal zone lymphoma (ENMZL), and lymphoplasmacytic lymphoma. b. Presence of $CD20^+$ lymphoplasmacytic lymphoma involving the bone marrow, positive serum immunofixation for monoclonal IgM and at least one criteria for initiation of treatment as per Consensus panel of International Workshops on Waldenstrom's macroglobulinemia. 2. Relapsed or refractory after at least one prior treatment regimen, with no limit on prior therapies. 3. At least 1 measurable disease lesion >1.5 cm in at least one diameter by CT/CT-PET or magnetic resonance imaging (MRI) in an area of no prior radiation therapy, or in an area that was previously irradiated that has documented progression. a. Exception included for Waldenstrom's macroglobulinemia patients without nodal involvement. 4. Waldenstrom's macroglobulinemia patients must have measurable quantitative IgM monoclonal protein greater than normal value. 5. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) > 1,000 / platelet count > 50,000. 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) 6. ECOG performance status ≤ 2 7. Male or female ≥ 18 years of age 8. Ability to swallow and retain oral medication 9. 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. 10. 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 cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1/Day 1. 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. Refractory to idelalisib, duvelisib, or any drug that specifically inhibits phosphoinositide-3-kinase (PI3K). 3. Prior autologous stem cell transplant within 6 months. Prior allogeneic hematologic stem cell transplant is excluded. 4. 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. 5. Known histological transformation to an aggressive lymphoma 6. Known Central Nervous System (CNS) lymphoma; patients with symptoms of CNS disease must have a negative CT scan and negative diagnostic lumbar puncture. 7. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infection of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. 8. 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. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization c. QTc Interval >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

	9. 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. 10. Women who are pregnant or lactating.
Efficacy Endpoints	**Overall response rate (ORR)** ORR is defined as sum of CR, PR, VGPR and MR rates. **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 (Cheson et al., 2014 and Owen et al 2013). **Complete Response (CR) Rate** CR rate is defined as the proportion of patients who achieve a CR. **Very Good Partial Response (VGPR) Rate** VGPR rate is defined as the proportion of patients who achieve a VGPR. Applicable only for patients with WM. **Partial Response (PR) Rate** PR rate is defined as the proportion of patients who achieve a PR. **Minor Response (MR) Rate** MR rate is defined as the proportion of patients who achieve a MR. Applicable only for patients with WM. **Duration of Response (DOR)** Duration of response is defined as the time from documentation of a response to treatment to the first documentation of tumor progression or death due to any cause, whichever comes first. **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.
Safety Endpoints	All Adverse Events (AE's) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v4.0.
Study Design	Study TGR-1202-202 (umbralisib) is designed as a Phase 2 trial to evaluate the efficacy and safety of TGR-1202 monotherapy in patients with non-follicular indolent non-Hodgkin's lymphoma. Patients are required to have non-follicular

	indolent non-Hodgkin's lymphoma that is relapsed or refractory following at least one prior standard therapy regimen, without limit on prior therapies. **Enrollment** Following Screening, qualified patients will be administered TGR-1202 (umbralisib) monotherapy at 800 mg QD. During the study period, all patients will be evaluated for response by CT, PET-CT and/or MRI every 3 cycles. For patients with WM without nodal involvement, response will be assessed by quantitative monoclonal IgM protein every 3 cycles. The best clinical response as well as disease progression will be determined by local investigator. Patients will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression. All enrolled subjects will be treated for at least 6 months, after which time the study may end.
Dosing Regimen (Cycle = 28 days)	**TGR-1202 (umbralisib):** • TGR-1202: Orally (800 mg) daily starting on Day 1 of Cycle 1.
Study Drugs	TGR-1202 is a highly specific and orally available PI3K delta (δ) inhibitor available in 200 mg tablets, supplied by TG Therapeutics, Inc.
Statistical Considerations	Sample Size: Up to 20 MZL patients and up to 20 WM patients may be enrolled in the study. The safety population will include all patients who take at least one dose of study medication. The safety analysis will be based on the safety population. The mITT (modified Intent to Treat) population will include all safety patients who have provided at least some post-baseline efficacy measures. The efficacy assessments will be based on the mITT population. In general, the safety and efficacy date will be presented by histology type (MZL and WM) as well as combined.

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
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
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FL	Follicular Lymphoma
GCP	Good Clinical Practice
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
ITT	Intent-to-treat
IWNHL	International Workshop on Non-Hodgkin's Lymphoma
IV	Intravenous
LD	Longest Diameter
LDH	Lactate dehydrogenase
LPD	Longest Perpendicular Diameter
LTFU	Long-Term Follow Up
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal Zone Lymphoma
NHL	Non-Hodgkin's Lymphoma
OS	Overall survival
ORR	Overall Response Rate

Abbreviations and Definitions of Terms	
PCR	Polymerase Chain Reaction
PE	Physical Examination
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PK	Pharmacokinetic
PPD	Perpendicular Diameters
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
TTF	Time to treatment failure
TTR	Time to response
ULN	Upper limit of normal
V	Visit
Vd	Volume of distribution
VGPR	Very Good Partial Response
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia

1 INTRODUCTION

1.1 INDOLENT NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphomas are a heterogeneous group of disorders with different pathophysiology, histology and clinical course. The indolent non-Hodgkin's lymphomas (iNHL) are a subset of B-cell Non-Hodgkin's Lymphomas characterized by prolonged median survival with a long relapsing and remitting clinical course. These indolent lymphomas are slow growing, spread slowly with few presenting symptoms. Follicular lymphoma grades I-IIIa tend to be slow growing and are the most prevalent lymphoma in this disease group. The remainder of indolent lymphomas are non- follicular indolent lymphomas comprising of small lymphocytic lymphoma, marginal zone B- cell lymphoma (nodal, splenic and extra nodal) and lymphoplasmacytic lymphoma/ Waldenstrom's macroglobulinemia[1] .

In the US, there are an estimated 16000 new cases of non-follicular indolent lymphomas diagnosed every year. Indolent non-Hodgkin's lymphoma is a disease of the older population with the median age of diagnosis varying from 65 to 72 years. The average median survival for non–follicular indolent non-Hodgkin's lymphomas is 10 – 15 years (SEER Stat Fact Sheets: Non-Hodgkin's Lymphoma. Bethesda, MD: National Cancer Institute; 2013) For a disease with such a protracted course the goal of management has been to maintain a good quality of life and initiate treatment only when the patients become symptomatic. A wait and watch approach is used till the disease becomes symptomatic. [2]The foundation of treatment for indolent non-Hodgkin's lymphomas is chemoimmunotherapy (mainly CD-20 antibody like rituximab) used alone or in combination with chemotherapy consisting of anthracycline, alkylating and purine analogues for use as a first line agent and in relapsed or refractory disease. [3,4] The response rate and progression free survival of Rituximab monotherapy or combination therapy is reassuring however as many as 20-30% patients relapse within 3 years of treatment with first-line chemoimmunotherapy.[5–7] Relapsed or refractory iNHL have poor overall survival. Furthermore, the responses to second line therapies are inferior suggesting a need for better salvage therapy after first line therapies

Recently the FDA provided accelerated approval for the PI3K inhibitor, idelalisib to treat patients with relapsed follicular B-cell non-Hodgkin's lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. This was based on a randomized clinical trial involving 123 patients which showed an overall response rate of 57% and a median progression free survival of 11 months. However up to 54 % of patients in the clinical trial experienced a grade 3 or higher adverse event, with discontinuation of idelalisib in 20 % of the patients. Some of the most frequently reported adverse events of grade 3 or higher were diarrhea (in 13% of the patients), pneumonia (in 7%), and dyspnea (in 3%). Discontinuation or interruptions led to response durations that were shorter lived.[8] Another clinical trial involving idelalisib for treatment of CLL showed a similar adverse effect profile. Given the increasing rate of adverse effects including death, FDA has placed six clinical trials on hold for patients receiving idelalisib for chronic lymphocytic leukemia, small lymphocytic lymphoma and indolent non-Hodgkin's lymphoma.

Given an improved tolerability profile observed to date, we have selected TGR-1202(umbralisib) to study in patients with relapsed/refractory non-follicular indolent non-Hodgkin's lymphomas.

1.2 TGR-1202 (UMBRALISIB)

TGR-1202 (umbralisib) is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma isoforms. The PI3Ks are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies. TGR-1202 has demonstrated safety and efficacy in ongoing Phase I clinical trials in patients with a wide variety of relapsed or refractory hematologic malignancies.

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] 2011a, 2011b).

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.

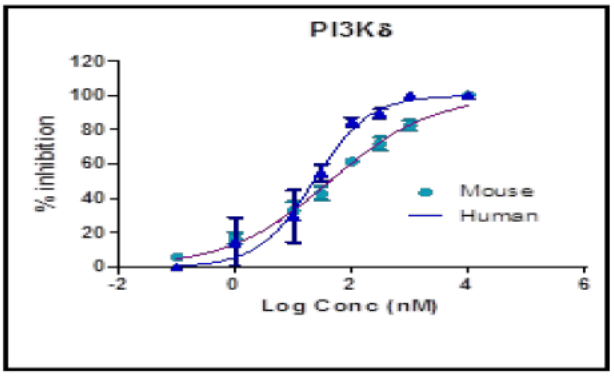


FIGURE 1: TGR-1202 POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

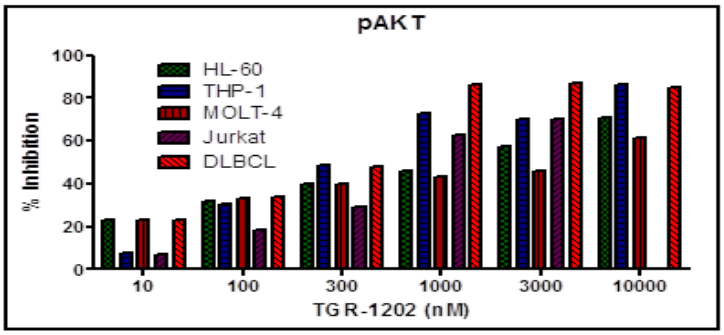
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

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.

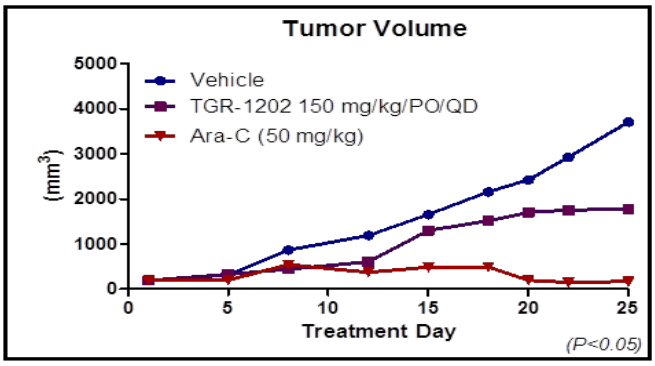
FIGURE 2: REDUCTION OF PAKT BY TGR-1202 IN CELL LINES BY WESTERN BLOTTING



1.2.1.1 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



1.2.1.2 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 TGR-1202 Investigator's Brochure (IB) for detailed information on toxicology studies conducted to date.

1.2.2 CLINICAL DEVELOPMENT OF TGR-1202

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

TGR-1202 was evaluated in a Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies (O'Connor et al, ASH 2015). As of the latest cutoff date for this study of December 2015, 81 patients were enrolled and eligible for safety evaluation, with 63 patients evaluable for efficacy. The median age was 65 years (range 22-85), 53/28 male and 14/81 enrolled patients had a diagnosis of DLBCL. Among all patients, the median number of prior therapies was 3 (range, 1-14), with 57% of patients having 3 or more prior therapies and 49% refractory to their immediate prior therapy.

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 TGR-1202, 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). Additionally, a healthy subject food effect study as well as data from the patients in the fed-state expansion cohorts revealed increased exposure in the fed state. As a result of these improvements, dose-escalation has proceeded using the micronized formulation in a fed state. 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 TGR-1202 as subsequent higher cohorts have cleared safety evaluation. A dose-dependent response has been observed with TGR-1202 (ASCO 2013), 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 17 CLL patients treated at ≥800mg, 94% have achieved a nodal partial response, and nodal reductions show an improvement with time on TGR-1202 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 TGR-1202 and concomitant medications and did not recur upon re-challenging the patient at 800 mg QD. See Section 7.1.1 [redacted] for a complete overview of the TGR-1202 side effect profile.

1.2.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

In parallel with the Phase I 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 I drug-food interaction study with a single 200 mg oral dose of TGR-1202 in healthy volunteers followed by a second single dose Phase I 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-1202concentration 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	9962.02	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:

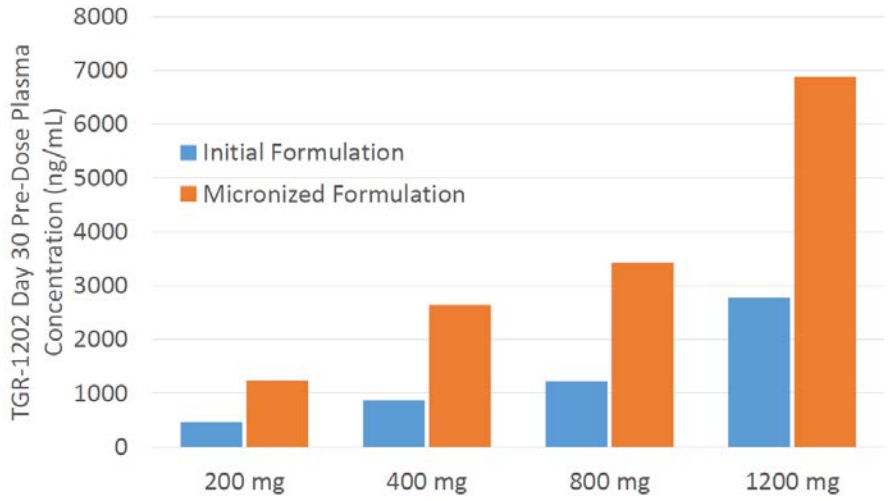
Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
AUC_{0-t} (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95
AUC_{0-inf} (ng·hr/mL)	7715.67	12378.19	160.43	146.49 – 175.70
C_{max} (ng/mL)	166.20	371.70	223.65	202.33 – 247.20

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 $AUC_{0\text{-}inf}$.

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 RECOMMENDED PHASE 2 DOSE OF TGR-1202

In this Phase 2 study, 800 mg dose of TGR-1202 will be orally administered under fed conditions using the micronized drug product formulation. The two Phase I pharmacokinetic studies have elucidated that:

- The systemic exposure to TGR-1202 increases approximately 67% based on total extent ($AUC_{0\text{-}inf}$) under fed condition; and
- The systemic exposure to TGR-1202 increases approximately 60% based on the modified drug product formulation when compared to the original drug product formulation.

To evaluate the improvement in the absorption of TGR-1202 with the modified drug product formulation under fed condition, the Phase I dose-escalation study with TGR-1202 includes the following dose groups:

- Administration of original drug product formulation under fasted and fed conditions; and
- Administration of the modified drug product formulation under fed conditions.

Based on the results from the completed Phase 1 dose-escalation study and the two Phase I pharmacokinetics studies in healthy volunteers, a dose of 800 mg of TGR-1202 using the modified drug product formulation under fed condition was selected.

1.4 RATIONALE FOR PHASE 2 STUDY

Based on the success of Phase I trials of PI3K inhibitor idelalisib in patients with iNHL Gopal et al performed a Phase 2 randomized clinical trial involving 123 patients with relapsed and refractory iNHL with prior rituximab and alkylator based therapy. After a median follow-up of 9.7 months, the median time to a response was 1.9 months, the median duration of response was 12.5 months, and the median progression-free survival was 11 months. The response rate was 57% (71 of 125 patients), with 6% meeting the criteria for a complete response. However up to 54 % of patients in the clinical trial experienced a grade 3 or higher adverse event, with discontinuation of idelalisib in 20 % of the patients. Some of the most frequently reported adverse events of grade 3 or higher were diarrhea (in 13% of the patients), pneumonia (in 7%), and dyspnea (in 3%)[8]. Combining idelalisib with other agents resulted in greater episodes of grade 3 or higher events including death. In addition to autoimmune toxicity multiple episodes of severe sepsis were reported with increasing opportunistic infections suggesting possible immune deficiency.[11–13] A recent safety analysis of 3 Phase III studies in subjects with previously untreated CLL (bendamustine /rituximab ± idelalisib) and previously treated indolent B-cell NHL (rituximab ± idelalisib and bendamustine/rituximab ± idelalisib) were recently halted because of an excess of deaths and serious adverse events among patients treated in the idelalisib-containing groups (combined mortality rate, 49/664 [7.4%] vs 14/402 [3.5%])

TGR-1202 (umbralisib) is a PI3K inhibitor with an improved safety profile. In an integrated analysis of two Phase I studies, 165 patients with non-Hodgkin's lymphoma, including CLL, were treated with TGR-1202. Adverse events such as nausea, diarrhea, fatigue, headache, vomiting and cough were the most commonly reported events, the majority of which were Grade 1 and 2. The only Grade ≥3 adverse event in more than 10% of patients was neutropenia (18%). Discontinuation due to an adverse event with TGR-1202 was reported 8% of patients.

The purpose of this study is to evaluate the safety and efficacy of TGR-1202 in previously treated non-follicular indolent non-Hodgkin's lymphoma patients.

2 OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To evaluate the overall response rate (CR + PR + VGPR + MR) and duration of response for TGR-1202 in patients with relapsed or refractory non-follicular indolent non-Hodgkin's lymphoma.

SECONDARY OBJECTIVES

- To determine the progression free survival of TGR-1202 in patients with relapsed or refractory non-follicular indolent non-Hodgkin's lymphoma.
- To evaluate time to treatment failure with TGR-1202.
- To evaluate the safety profile of TGR-1202

[redacted]

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 revised response criteria for malignant lymphoma (Cheson et al, 2014 and Owen et al 2013).

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 (and VGPR, MR for patients with WM) rates.

Duration of response (DOR)

DOR is defined as the interval from the first documentation of CR or PR or VGPR or MR 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. Histologically confirmed diagnosis of B-cell non-follicular indolent non-Hodgkin's lymphoma meeting following requirements.
    a. World Health Organization 2008 classification criteria warranting therapy as per investigator discretion for histologies limited to splenic marginal zone lymphoma (SMZL), nodal marginal zone Lymphoma (NMZL), or extra-nodal marginal zone lymphoma (ENMZL), and lymphoplasmacytic lymphoma.
    b. Presence of $CD20^{+}$ lymphoplasmacytic lymphoma involving the bone marrow, positive serum immunofixation for monoclonal IgM and atleast one criteria for initiation of treatment as per Consensus panel of International Workshops on Waldenstrom's macroglobulinemia.
2. Relapsed or refractory after at least one prior treatment regimen, with no limit on prior therapies.
3. At least 1 measurable disease lesion >1.5 cm in at least one diameter by CT/CT-PET or magnetic resonance imaging (MRI) in an area of no prior radiation therapy, or in an area that was previously irradiated that has documented progression.
    a. Exceptions include for Waldenstrom's macroglobulinemia patients without nodal involvement.
4. Waldenstrom's macroglobulinemia patients must have measurable quantitative IgM monoclonal protein greater than normal value.
5. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) $\geq$ 1,000 / platelet count $\geq$ 50,000.
    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)
6. ECOG performance status ≤ 2
7. Male or female ≥ 18 years of age
8. Ability to swallow and retain oral medication
9. 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.
10. 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 cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1/Day 1.

   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. Refractory to idelalisib, duvelisib, or any drug that specifically inhibits phosphoinositide-3-kinase (PI3K).
3. Prior autologous stem cell transplant within 6 months. Prior allogeneic hematologic stem cell transplant is excluded.
4. 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.
5. Known histological transformation to an aggressive lymphoma
6. Known Central Nervous System (CNS) lymphoma; patients with symptoms of CNS disease must have a negative CT scan and negative diagnostic lumbar puncture.
7. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infection of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion.
8. 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. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization
   c. QTc Interval >470
   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
9. 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.
10. Women who are pregnant or lactating.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This study is designed as a Phase 2 trial to evaluate the efficacy and safety of TGR-1202 (umbralisib) monotherapy in previously treated non-follicular indolent non-Hodgkin's lymphoma. Patients are required to have non-follicular indolent non-Hodgkin's lymphoma that is relapsed or refractory following at least one prior standard therapy regimen.

Enrollment

Following Screening, qualified patients will be administered TGR-1202 monotherapy at 800 mg QD.

During the study period, all patients will be evaluated for response by CT, PET-CT and/or MRI every 3 cycles. For patients with WM without nodal involvement, response will be assessed by quantitative monoclonal IgM protein every 3 cycles. The best clinical response as well as disease progression will be determined by local investigator. Patients will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed should continue to be followed for progression every 6 months or per standard of care.

An independent DSMB will be established to advise the Sponsor on safety and ethical issues of the study. Once the database has been locked, the independent DSMB will review the primary and secondary efficacy analyses and safety data.

4.2 REGISTRATION

Patients who are eligible and who have signed an informed consent will be enrolled in the trial with TGR-1202 monotherapy.

4.3 STUDY SITES

Up to 5 centers in the United States may be asked to participate in this study.

4.4 DISCONTINUATION FROM STUDY TREATMENT

Patients may 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) will continue to be followed for progression.

After discontinuation from protocol treatment, patients should be followed for AEs for 30 calendar days after their last dose of either study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigators must record his or her reasoning for this decision in the 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

5.1 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Cycle = 28 days	Screen	Cycle 1[1]			Cycles 2-6[2]					> Cycle 6[3]	End of Study	Follow-up
					C2	C3	C4	C5	C6	Every 3 Months		Every 3 Months
Procedure\Days	-28-0	D1	D8	D15	Day 1					Day 1		Day 1
Medical History	X											
ECOG Performance Status	X	X			X	X	X	X	X	X	X	
Physical Examination[4]	X	X			X	X	X	X	X	X	X	
Vital Signs (pulse, BP, temp, weight)	X	X	X	X	X	X	X	X	X	X	X	
BM Aspirate/Biopsy[5]	X											
12-lead EKG	X											
Tumor Evaluation[6]	X	Every 3 cycles										
Serology: HCV, HBV, CMV[7]	X											
Hematology[8]	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	
PT/INR	X	As clinically warranted										
Serum Pregnancy Test[9]	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
AE Evaluation[10]	X	X	X	X	X	X	X	X	X	X	X	
LTFU[11]												X
[redacted]												
TGR-1202		Administered orally daily with food										

[1] Treatment Administration +/- 1 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have - 1 day window

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

[3] Treatment Administration +/- 7 day window. Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have a - 7 day window for all cycles after cycle 6.

[4] To include assessment of B-symptoms

[5] Unilateral bone marrow aspirate and/or biopsy should be completed within 90 days prior to Day 1 of Cycle 1 as clinically indicated per standard of care. In addition, a post-baseline bone marrow biopsy should be completed to confirm potential CR by radiological assessment.

[6] Scans should be completed within 30 days prior to Day 1 of Cycle 1. All tumor evaluations have a +/- 7 day window. Radiology assessment should include FDG-PET and/or a contrast enhanced CT scan of chest, abdomen, and pelvis. If iodinated contrast is contraindicated, a non-contrast chest CT coupled with a gadolinium-enhanced MRI of the abdomen/pelvis is an acceptable substitute. For Waldenstrom's macroglobulinemia evaluation should include immunofixation and serum electrophoresis. For patients with WM without nodal involvement, response will be assessed by quantitative monoclonal IgM protein every 3 cycles

[7] Serum virology to include HBsAg, HBc antibody, HCV and CMV. If HBc antibody is positive, subjects must be evaluated for the presence of HBV DNA (PCR)

[8] Must be obtained once a week for 3 weeks in cycle 1.

[9] For women of child bearing potential completed within 3 days prior to Day 1 of Cycle 1

[10] If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of study visit, continue to monitor and record up through 30 days after study drug discontinuation.

[11] Assessment of progression-free survival (for patients off study for reasons other than disease progression) approximately every 6 months or per standard of care by investigator.

[redacted]

5.2 LABORATORY ASSESSMENTS

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

5.2.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include:

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

2. Serum β-HCG test.
3. Coagulation lab tests to include, PT and INR.
4. Serum Virology to include HBsAG, HBc antibody, HCV antibody, and CMV
5. Baseline bone marrow aspirate/biopsy to be completed 90 days prior to Day 1 of Cycle 1 as clinically indicated per standard of care. In addition, in patients with bone marrow involvement at baseline, a post-baseline bone marrow biopsy should be completed to confirm potential CR by radiological assessment.

5.2.2 CENTRAL LABORATORY ASSESSMENTS

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

[redacted]

6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

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

TGR-1202
Cycle 1+:

TGR-1202(umbralisib)
800 mg taken orally daily with food
*TGR-1202 to continue until disease progression, unacceptable toxicity or withdrawal from the study for other reasons.

6.2 AGENT ADMINISTRATION

TGR-1202 will be self-administered orally on an outpatient basis.

6.2.1 GUIDELINES FOR ADMINISTRATION OF TGR-1202(UMBRALISIB)

- *Method of Administration:* TGR-1202 will be administered orally once daily with food
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* Patients are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy within 7 days prior to Cycle 1/Day 1.
    - *Anti-viral Prophylaxis*: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
    - *PCP Prophylaxis:* Bactrim DS 1 tablet 3x per week or Dapsone 100 mg daily or equivalent.

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

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

TGR-1202 will be self-administered (by the patient). Tablets should be taken at approximately the same time each day with food (within 30 minutes of a meal). Patients should be instructed to swallow the tablets as a whole and should not chew or crush them.

If a dose of TGR-1202 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 TGR-1202(UMBRALISIB)

Before dispensing, the site pharmacist or his/her representative must check that the TGR-1202 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 TGR-1202 must be recorded within the eCRF, patient's medical records, and/or in the drug accountability records. For the purpose of drug accountability and dosing subjects should record any missed doses of TGR-1202 on a drug diary. Any error in drug administration should be recorded (e.g., missed dose) in the eCRF.

The Pharmacist or his/her representative should record the date dispensed and patient's number and initials, as well as complete the accountability record in the electronic drug accountability system with information concerning the dispensation of TGR-1202.

6.2.2 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that patient has:

- No intolerable toxicities related to study drug.
    - Treatment may be delayed to recover from toxicity for a maximum of one cycle.
- No clinical or radiographic evidence of disease progression.
- Not withdrawn from the study for other reasons.

6.3 DOSING DELAYS AND MODIFICATIONS

Patients should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) grading scale. Dose delay and/or modification guidance is for adverse events considered at least possibly related to the study drug. If cytopenias are deemed related to the underlying disease rather than study drug, dose modifications are not required, or are per investigator discretion.

A maximum one cycle delay of treatment (28 days) for recovery from toxicity is allowed to recover from hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If greater than a one cycle delay is necessary, then the patient should discontinue treatment and continue to be followed for progression. If a patient withdraws consent or has documented progression, an end of study visit should be completed.

6.3.1 DOSE DELAY/MODIFICATION RECOMMENDATIONS: TGR-1202

Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. A maximum 28 day (1 cycle) delay for recovery from toxicity is allowed to allow recovery of hematologic toxicities to ≤Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If greater than a 28- day delay is necessary, then the patient should discontinue treatment and continue to be followed for progression. If the patient withdraws consent or has documented progression, an end of study visit should be completed.

TABLE 1: TGR-1202(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 TGR-1202 until Grade ≤3 and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider supportive care. If delay is > 28 days discontinue study drug. 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 TGR-1202 until Grade ≤3; thereafter, resume at full dose. Consider supportive care intervention as warranted. If delay is > 28 days, discontinue TGR-1202. If recurrence after rechallenge, resume at next lower dose level at discretion of the investigator.
Pulmonary & Related Infections*	
Grade 1 & 2	Withhold TGR-1202 as warranted, provide supportive care and hold until complete resolution. Resume TGR-1202 at one dose lower. If recurrence after re-challenge, discontinue TGR-1202.
Grade ≥ 3	Discontinue TGR-1202 and intervene as warranted.
***While pneumonitis has been minimal with TGR-1202, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required.**	
All Other Non-Hematological Adverse Events	
Grade ≤ 2	Maintain current dose level.
Grade ≥ 3	Withhold TGR-1202 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. **NOTE**: If persistent grade 2 diarrhea, despite supportive care, delay TGR-1202 until ≤ grade 1. If recurrence after re-challenge, resume at full dose or next lower dose level at discretion of the investigator.
Diarrhea Grade ≥ 3	Withhold TGR-1202 until Grade ≤2. Resume at full dose or next lower dose level as per discretion of investigator. If recurrence after rechallenge, resume at next lower dose level at discretion of the investigator.
Colitis (all Grades)	Hold TGR-1202. Treat with supportive care and after resolution of colitis, resume TGR-1202 at next lower dose level.

STUDY DRUG DOSE REDUCTION RECOMMENDATIONS

Study Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction
TGR-1202	800 mg	600 mg	400 mg

A maximum of two dose level reductions are allowed for TGR-1202.

If a patient requires a dose reduction of TGR-1202 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 TGR-1202, 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 TGR-1202

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 patient is identified, a shipment of pre-determined quantity of TGR-1202 will be shipped to the clinical study site.

Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms for TGR-1202. If any abnormality on the supplied bottles (TGR-1202) is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

6.5 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 patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

During the study period, all patients will be evaluated for response by CT, PET-CT and/or MRI every 3 cycles. For patients with WM without nodal involvement, response will be assessed by quantitative monoclonal IgM protein every 3 cycles. The best clinical response as well as disease progression will be determined by local investigator. Patients will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression approximately every 6 months or per standard of care.

7 STUDY MEDICATIONS OVERVIEW AND SAFETY

7.1 TGR-1202(UMBRALISIB)

Chemical *Name:*	Umbralisib
Other Name:	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:	TGR-1202: 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:	TGR-1202 is provided in HDPE bottles each containing 30 tablets and a silica gel canister as a desiccant.
Availability:	TGR-1202 is available from TG Therapeutics.

7.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in patients treated with single agent TGR-1202 and were considered at least possibly related to study medication. See the TGR-1202 investigator brochure for a complete list of all adverse events reported regardless of causality.

7.1.1.1 COMMON (>20%)

- **Gastrointestinal Disorders:** Diarrhea, Nausea
- **General Disorders and Administration Site Conditions:** Fatigue

7.1.1.2 LESS COMMON (≥10% - ≤ 20%)

- **Blood and Lymphatic System Disorders:** Neutropenia
- **Gastrointestinal Disorders:** Vomiting
- **Metabolism and Nutrition Disorders:** Decreased Appetite
- **Skin and Subcutaneous Tissue Disorders:** Rash

7.1.1.3 UNCOMMON (≥1 - <10%)

- **Blood and Lymphatic System Disorders:** Anemia, Febrile neutropenia, Leukocytosis, Thrombocytopenia
- **Eye Disorders**: Vision Blurred

- **Gastrointestinal Disorders:** Abdominal distension, Abdominal pain, Constipation, Dry mouth, Dyspepsia, Colitis
- **General Disorders and Administration Site Conditions:** Asthenia, Chills, Oedema peripheral, Pyrexia
- **Infections and infestations** Oral candidiasis, Pneumonia, Upper respiratory tract infection
- **Investigations:** Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Lymphocyte count increased, Weight decreased
- **Metabolism and Nutrition Disorders:** Dehydration, Hyperglycemia, Hypokalemia, Hypophosphatemia,
- **Musculoskeletal and Connection Tissue Disorders:** Arthralgia, Muscle spasms, Pain in extremity
- **Nervous System Disorders:** Dizziness, Dysgeusia, Headache, Neuropathy peripheral, Tremor
- **Psychiatric Disorders:** Insomnia
- **Respiratory, Thoracic and Mediastinal Disorders:** Cough
- **Skin and Subcutaneous Tissue Disorders:** Alopecia, Night sweats, Pruritus

7.1.1.4 EVENTS REPORTED IN LESS THAN 1% OF SUBJECTS

- **Blood and Lymphatic System Disorders**: Leukopenia, Hyperbilirubinemia, Bacteremia
- **Ear and Labyrinth Disorders**: Tinnitus
- **Eye Disorders**: Visual Impairment, Visual acuity reduced
- **Gastrointestinal Disorders**: Eructation, Flatulence, Gastrooesophageal Reflux Disease, Abdominal Pain Upper, Mouth Ulceration, Anal Hemorrhage, Hypoaesthesia Oral, Paraesthesia Oral, Pancreatitis
- **General Disorders and Administration Site Conditions**: Malaise, Mucosal Inflammation,
- **Hepatobiliary Disorders**: Hypocalcemia
- **Infections and Infestations**: Candida infection, Fungal skin infection, Lung infection, Sinusitis
- **Investigations**: International Normalized Ratio Increase, Blood lactate dehydrogenase increase, Blood phosphorus increased, Blood sodium increased, Blood uric acid increased, White blood cell count decreased
- **Injury, Poisoning and Procedural Complications**: Contusion
- **Metabolism and Nutrition Disorders**: Hyperlipidemia, Hypertriglyceridemia, Hyponatremia
- **Musculoskeletal and Connective Tissue Disorders**: Muscular Weakness, Myalgia, Pain in Jaw
- **Nervous System Disorders**: Somnolence, Peripheral Sensory Neuropathy, Memory Impairment
- **Psychiatric Disorders**: Anxiety, Libido Decrease, Delirium, Parasomnia
- **Reproductive System and Breast Disorders**: Erectile Dysfunction
- **Respiratory, Thoracic and Mediastinal Disorders**: Dyspnea, Epistaxis, Hypoxia, Influenza, Respiratory Failure
- **Skin and Subcutaneous Tissue Disorders**: Dermatitis, Dermatitis Acneiform,
- **Vascular Disorders**: Hot Flush

8 MEASUREMENT OF EFFECT

During the study period, all patients will be evaluated for response by CT, PET-CT and/or MRI every 3 cycles. All baseline assessments to characterize disease will be performed within 30 days of Cycle 1 Day 1, prior to initiation of therapy. During the treatment period, all efficacy assessments have a +/- 7 day window. The determination of response and progression will be based on the Response Criteria for non-Hodgkin's lymphoma, Lugano Classification (Cheson et al., 2014) and IWWM-6 (Owen et al 2013) consensus for respective disease histology. The best clinical response as well as disease progression will be determined by the independent central radiology group (ICRG). The findings of the ICRG will be considered primary for analyses of ORR, PFS, and other tumor control endpoints. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression approximately every 6 months or per standard of care.

8.1 METHOD OF ASSESSMENT

CT scan is the preferred method for radiographic tumor assessment. CT with iodinated IV contrast is preferred. If iodinated contrast is contraindicated, a non-contrast chest CT coupled with a gadolinium-enhanced MRI of the abdomen/pelvis is an acceptable substitute. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in patients for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, or tumor markers will not be considered for response assessment. PET-CT may also be used if per standard of care by investigator.

Bone marrow assessment should be used to assess response to therapy if the patient was deemed to have disease in the bone marrow prior to initiation of protocol therapy, per standard of care and at the discretion of the investigator.

For radiographic evaluations, the same method of assessment and the same technique (e.g., scan type, patient 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 patient is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless medically contraindicated.

8.2 RESPONSE REVIEW

All responses will be made by local investigator assessment.

8.3 ANTITUMOR EFFECT

Assessment of lymphoma response (CR, PR, VGPR or MR) and disease progression will be evaluated as outlined in the schedule of events, according to the Response Criteria for non-Hodgkin's lymphoma, Lugano Classification (Cheson et al., 2014) and IWWM-6 consensus (Owen et al 2013) for respective disease histology. Overall response rate, CR, PR, VGPR, MR, SD, PFS and DOR will be calculated as detailed below.

8.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Evaluable for objective response. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

8.4.1 COMPLETE RESPONSE

Complete response (CR) is defined as the complete disappearance of all evidence of disease and disease-related symptoms. The spleen and/or liver, if considered enlarged before therapy, on the basis of physical exam or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. Bone marrow infiltrate cleared on repeat biopsy, if indeterminate by morphology, immunohistochemistry should be negative (Cheson et al., 2014 Lugano Classification).

Previously involved nodes that were 1.1 to 1.5 cm in the long axis and more than 1.0 cm on their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment (Cheson et al., 2014 Lugano Classification).

For Waldenstrom's macroglobulinemia patients, complete response is defined as disappearance of serum monoclonal IgM protein by immunofixation with a normal serum IgM level. The spleen and/or liver, if considered enlarged before therapy, on the basis of physical exam or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to WM should disappear. Bone marrow infiltrate cleared on repeat biopsy, if indeterminate by morphology, immunohistochemistry should be negative. (Owen et al 2013)

8.4.2 VERY GOOD PARTIAL RESPONSE

A response criteria exclusive for Waldenstrom's macroglobulinemia patients, Very Good Partial Response (VGPR) is defined as reduction of Monoclonal IgM protein greater than 90 % from baseline. The spleen and/or liver, if considered enlarged before therapy, on the basis of physical exam or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to WM should disappear. (Owen et al 2013)

8.4.3 PARTIAL RESPONSE

Partial response (PR) is defined as the regression of measurable disease and no new sites of disease. Regression is defined as greater than or equal to 50% decrease in the sum of the products of the diameters (SPD) of the index lesions, coupled with no unequivocal increase in size of other lymph nodes, liver or spleen. No new sites of disease should be observed. If bone marrow was involved prior to therapy and a clinical CR was achieved but no bone marrow assessment is completed after treatment, then these patients are considered partial responders (Cheson et al., 2014 Lugano Classification).

For Waldenstrom's macroglobulinemia patients, partial response is defined as reduction of Monoclonal IgM protein between 50-90 % from baseline with regression of measurable disease. Regression is defined as greater than or equal to 50% decrease in the sum of the products of the

diameters (SPD) of the index lesions, coupled with no unequivocal increase in size of other lymph nodes, liver or spleen. No new sites of disease should be observed. (Owen et al 2013)

8.4.4 MINOR RESPONSE

A response criteria exclusive for Waldenstrom's macroglobulinemia patients, Minor Response (MR) is defined as presence of detectable Monoclonal IgM protein with reduction of monoclonal IgM protein greater than 25 % but less than 50 % from baseline. No new sites of disease should be observed. (Owen et al 2013)

8.4.5 STABLE DISEASE

Stable disease is defined as the failure to attain CR/PR but does not fulfill the criteria for progressive disease. For those with disease evaluated by CT only, there must be no unequivocal change in the size of the previous lesions on the post-treatment CT scan (Cheson et al., 2014 Lugano Classification)

For Waldenstrom's macroglobulinemia patients, stable disease is defined as presence of detectable Monoclonal IgM protein with less than 25% reduction and less than 25% increase in serum IgM level from baseline. No unequivocal increase in size of other lymph nodes, liver or spleen. No new sites of disease should be observed. (Owen et al 2013)

8.4.6 RELAPSED DISEASE OR PROGRESSION OF DISEASE

Any of the following conditions will constitute relapsed or progressive disease:

Appearance of any new lesion more than 1.5 cm in any axis, even if other lesions are decreasing in size will be considered relapsed or progressive disease. Increase in FDG uptake in a previously unaffected site should be confirmed with other modalities, a therapeutic decision should not be made solely on the basis of PET without histologic confirmation (Cheson et al., 2014 Lugano Classification).

There is at least a 50% increase from nadir in one of the following:

- The SPD of index lesions,
- The greatest transverse diameter (GTD) of any individual previously involved node, or
- The GTD of any previously involved node provided that the GTD of that node is now ≥ 1.5 cm. (Cheson et al., 2014 Lugano Classification).

For Waldenstrom's macroglobulinemia patients, progressive disease is defined as more than 25% increase in serum IgM level from lowest nadir and/or progression in clinical features attributable the disease. (Owen et al 2013)

8.5 DEFINITIONS OF DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least two dimensions with conventional techniques (CT, PET/CT, MRI, x-ray) and meet one of the following criteria: nodal lesion with a long axis > 1.5 cm regardless of short axis, nodal lesion with

long and short axes ≥ 1.0 cm, or extra-nodal lesions with long and short axes ≥ 1.0 cm with spiral CT scan. All tumor measurements should be recorded in centimeters.

Non-measurable disease (evaluable disease): All other lesions (or sites of disease) including small lesions, (< 1.0 cm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, and cystic lesions are all non-measurable.

Index lesions: All measurable lesions up to a maximum of 6 nodal and extra-nodal lesions total, representative of all involved organs, should be identified as **index lesions** and recorded and measured at baseline. For patients with splenic marginal zone lymphoma without lymphadenopathy, the spleen size should be used as an index lesion. Index lesions should be selected on the basis of their size (clearly measurable in two perpendicular dimensions) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A baseline sum of product of the diameters (SPD) for all index lesions will be calculated and reported as the baseline SPD. The baseline SPD will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-index lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 6 index lesions should be identified as **non-index lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.6 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria as per the NHL established criteria used in this study (See Appendix A).

8.6.1 DURATION OF RESPONSE

Duration of response is defined as the time from documentation of a response to treatment to the first documentation of tumor progression or death due to any cause, whichever comes first. Duration of the response will be summarized using n (sample size), mean, standard deviation, median, minimum, and maximum for the responders.

Duration of stable disease:

Stable disease is measured from the start of the treatment (Cycle 1/Day1) until the criteria for progression are met.

Progression-Free Survival:

Progression free survival (PFS) is defined as the time from Cycle 1/Day1 to the first documentation of tumor progression or death due to any cause, whichever comes first. This variable will be analyzed via Kaplan-Meier methodology. The median PFS will be estimated.

9 STATISTICAL CONSIDERATIONS

The sections of the Statistical Considerations describe the statistical methods to be used to analyze the efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

9.1 SAMPLE SIZE AND POWER

[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.

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

In general, safety and efficacy data will be presented by histology type and overall.

9.3 ANALYSIS POPULATIONS

The safety population will include all enrolled patients who have received at least one dose of study treatment. The safety analyses will be based on this safety population.

The modified Intent-to-Treat (mITT) population will consist of all safety patient who have provided at least some post baseline efficacy assessments. The efficacy analyses will be based on this mITT population.

9.4 PATIENT DISPOSITION

Patient disposition summaries will be presented by histology type and overall and will include the number of patients enrolled and the number and percentage of enrolled patients in the mITT and safety populations. The summaries will also include the reasons for permanent discontinuation of study treatment and study.

9.5 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

9.6 MEDICAL HISTORY

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

9.7 EXTENT OF EXPOSURE

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

9.8 EFFICACY ANALYSES

Each patient will be assigned to one of the following categories: 1) complete response, 2) partial response, 3) very good partial response, 4) minor response, 5) stable disease, 6) progressive disease, 7) early death from malignant disease, 8) early death from toxicity, 9) early death because of other cause, or 10) 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 an independent central radiology group (ICRG) which will be blinded to treatment arm assignment. Definitive disease progression will be based on standard criteria (Cheson, B 2014 Lugano Classification; Appendix A –Criteria for Response Assessment and Owen et al 2013 Appendix B).

9.9 MISSING VALUE HANDLING PROCEDURES

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

9.10 STATISTICAL ANALYSES

9.10.1 PRIMARY EFFICACY VARIABLE

The primary efficacy outcome is Overall Response Rate (ORR). The ORR is defined as percent of patients who achieve CR or PR for MZL histology type patients and is defined as percent of patients

who achieve CR, VGPR, PR or MR for WM histology type patients. The estimated response rates as well as the two-sided 95% confidence interval of the response rate will be presented.

9.10.2 EFFICACY VARIABLE

The secondary efficacy variable will include:

- Complete Response (CR) rate;
- Progression free survival (PFS);
- Duration of response (DOR);
- Time to Treatment Failure (TTF).

These variables will be analyzed as appropriate.

9.11 MULTIPLE COMPARISON PROCEDURES

The study is a single treatment arm study. No formal claims will be made.

9.12 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 patient's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

9.13 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 TGR-1202(umbralisib) Investigator Brochure. Please refer to prescribing information for a listing of expected AEs.

9.14 DEFINITIONS OF ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient 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.

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

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

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

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

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

At each level of summarization, a patient 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.

9.16 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.

9.16.1 RECORDING OF ADVERSE EVENTS

All adverse events of any patient 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 – TGR-1202). 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 study drug treatment spanning from Cycle 1/Day 1 until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded on the eCRF.

9.16.2 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 patient 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. Patients 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. Patient incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

9.16.3 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization. Patients should be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific. 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 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.

9.17 SERIOUS ADVERSE EVENTS

9.17.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

The definitions of serious adverse events (SAEs) are given below. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that:

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient 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 IWG Cheson et al. 2014, should not be reported as a serious adverse event.

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

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

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units

- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

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

9.17.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

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

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

To report an SAE, see the appropriate form.

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

NHL progression or death due to NHL 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 NHL progression (i.e. by a means other than lack of effect). Unrelated events of NHL 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).

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

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate SAE form. The detailed SAE reporting process will be provided to the sites in the Safety Monitoring Plan.

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

9.18 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).

9.19 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.

9.20 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the patient'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.

9.20.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between patient 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 patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF for each recurrence.

9.20.2 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.

9.20.3 DEATHS

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of the patient's NHL for up to 30 days post the last dose of study drug will be recorded on the appropriate study eCRF and reported on the Adverse Event page of the eCRF, i.e. are exempted from expedited reporting. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sponsor.

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

9.20.4 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 9.17.1.

9.20.5 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.

9.20.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

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

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in **Error! Reference source not found.**) 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 patient 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 patient must not receive any study drug(s), and must be discontinued from the study.

If an investigator suspects that a patient may be pregnant after the patient 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 patient must be discontinued from the study, and the investigator must notify the Study Chair or Medical Monitor as soon as possible.

If a patient 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 that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, patients should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary Malignancy

Any secondary 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.

10 CLINICAL DATA COLLECTION AND MONITORING

10.1 SITE MONITORING

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 patient 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 patient confidentiality is maintained.

Site monitoring shall be conducted to ensure the human patient 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.

10.2 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 patient, increase to dosing or exposure, patient 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 patient exposure and/or patient 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 patient
- Increase to dose or patient exposure to drug

- Patient 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 patients, their consent to continue participation in the study should be obtained.

10.3 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.

10.4 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.

11 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).

11.1 IRB APPROVAL

The study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients 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.

11.2 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 TGR-1202 (umbralisib) will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority. Insurance and Indemnity

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

11.3 INFORMED CONSENT

Informed consent is a process by which a patient 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 patient'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 patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

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

11.4 CONFIDENTIALITY

Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients 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 patient's medical records, but the patient 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 patient to revoke his or her authorization.

In the event that a patient 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 patient authorization. For patients 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 patient 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 patient'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 patients on the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF or database. No material bearing a patient's name will be kept on file by the Sponsor. Patients will be informed of their rights within the ICF.

11.5 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.

11.6 FINANCIAL INFORMATION

The finances for this study will be patient 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.

12 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

12.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

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

Documents at a minimum required to begin the 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 Vita 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.

12.2 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 patient'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 patient'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, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

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

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

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

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (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.

12.3 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 patients' status throughout the course of the study.

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

12.4 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.

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

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

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

12.6 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.

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14 APPENDIX A –CRITERIA FOR RESPONSE ASSESSMENT

Revised Response Criteria for Non- Hodgkin's Lymphoma (Cheson et. al. 2014 Lugano Classification)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response		
Lymph nodes and extra-lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extra-nodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra-lymphatic sites of disease
Non- measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response		
Lymph nodes and extra-lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm

		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non- measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease		
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease		
Individual target nodes/nodal masses, Extra-nodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at	PPD Progression: An individual node/lesion must be abnormal with: - LDi > 1.5 cm - Increase by ≥ 50% from PPD nadir.

	interim or end-of-treatment assessment	An increase in LDi or SDi from nadir - 0.5 cm for lesions ≤ 2 cm - 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly.
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (eg, GI

tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

Consensus-based uniform response criteria for WM developed by the IWWM, updated in the sixth IWWM

Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation. Normal serum IgM level. Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline. Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline. No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable.≥50% but<90% reduction in serum IgM level from baseline. Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline. No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline No new signs or symptoms of active disease
Stable disease	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline No progression in extramedullary disease, ie, lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease	≥25% increase in serum IgM level[*] [‡]from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

15 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 patient. 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 patients on the study, the vasectomised male partner should be the sole partner for that patient.
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 the treatment period and for 30 days after study drug discontinuation and should not father a child in this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient 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.

16 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

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