Official Title: A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 (Umbralisib) Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)

NCT Number: NCT02612311

Document Date: Protocol Version 6: 20-April-2020

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Local Protocol #: Protocol UTX-TGR-304

TITLE: A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 (Umbralisib) Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)

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

IND Number:

Ublituximab	**TGR-1202 (umbralisib)**
114,779	116,762

EudraCT Number: **2015-005758-36**

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

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

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

Version: 1.0	**Date:** 14 Sept 2015
Version: 2.0	**Date:** 10 June 2016
Version: 3.0	**Date:** 10 April 2017
Version: 3.1	**Date:** 18 June 2017
Version: 4.0	**Date**: 04 October 2017
Version: 4.1	**Date:** 20 December 2017
Version: 5.0	**Date:** 13 February 2019
Version: 6.0	**Date:** 15 March 2020

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol UTX-TGR-304 for issuance.

Protocol Title:	**A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 (Umbralisib) Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)**
Protocol Number:	UTX-TGR-304
Study Drugs:	Arm A: Ublituximab + TGR-1202 Arm B: Obinutuzumab + Chlorambucil Arm C: Ublituximab Arm D: TGR-1202
IND Number:	**Ublituximab** 114,779 **TGR-1202 (umbralisib)** 116,762
Date FINAL:	15 March 2020

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted] [redacted] [redacted]

Print Name | Signature | Date

STUDY CHAIR, Barts Cancer Institute

[redacted] MD, PhD [redacted] [redacted]

Print Name | Signature | Date

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

Print Name | Signature | Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	**A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 (Umbralisib) Compared to Obinutuzumab in Combination with Chlorambucil in Patients with Chronic Lymphocytic Leukemia (CLL)**	
Protocol Number:	UTX-TGR-304	
IND Number:	**Ublituximab** 114,779	**TGR-1202 (umbralisib)** 116,762
Date FINAL:	15 March 2020	

I have read the attached protocol and agree that it contains all the necessary details for performing UTX-TGR-304.

I will provide copies of the protocol and of the ublituximab and TGR-1202 Investigator's Brochures, which were given to me by TG Therapeutics (Sponsor), to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding obinutuzumab, chlorambucil, ublituximab, and TGR-1202, 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 10 June 2016) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- Sponsor and study coordination address updated;
- The exclusion criteria as been amended to now allow enrollment of subjects with prior chlorambucil treatment provided they are not refractory to chlorambucil;
- Exclusion criteria #8 has been added to exclude subjects with prior live virus vaccines;
- The phrasing of response assessment intervals has been revised for clarity from "prior to cycles 4, 7, 10, and 13 at Weeks 12, 24, 36, 48, and every 3 cycles after," to "after the completion of cycles 3, 6, 9, 12, 15, 18 and every 3 cycles thereafter" and it was further clarified that subjects being followed for PFS off treatment should have evaluations done every 12 weeks;
- Schedule of assessments and treatment schedule (Section 5) was updated, including:
    - Revised wording for Tumor Evaluation (as listed above)
    - Updated Urine Pregnancy Test, Sparse PK Sampling, Immunogenicity Sampling;
- Further clarification was provided for exclusion criteria #3, now requiring evaluation for the presence of HBV, HCV or CMV by DNA (PCR) if HBc antibody, HCV antibody or CMV are positive during serum virology;
- The pre-infusion medications for obinutuzumab administration was updated in a new table in section 6.2.1 which has been added to reflect the most recently available prescribing information;
- Subjects randomized to Treatment Arms A and D (which include TGR-1202) are now required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy within 7 days prior to randomization (Section 6.2.4), whereas this was previously at investigator discretion;
- The shelf life of ublituximab has been increased to 36 months from 24 months when stored between +2˚C / +8˚C to reflect newly available stability data on ublituximab drug product;
- Sections 7.3.1, 7.4.1, and 7.5.1 were updated to include the most recent adverse event information related to ublituximab and TGR-1202 corresponding to the latest Investigator Brochures;
- Clarification was provided in Section 8.3.1 to better describe appropriate selection of target lesions; and
- Appendix B – Contraceptive Guidelines and Pregnancy has been updated to require women physiologically capable of becoming pregnant to use highly effective contraception and all males physiologically capable of conceiving offspring must use a condom during the study and for 4 months after the last treatment dose if randomized to treatment Arms A, C, or D, or for 18 months after the last treatment dose if randomized to Arm B (obinutuzumab).

Version 3.0 (Dated 10 April 2017) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- Language was inserted to support the planned interim analysis for contribution amongst the first 200 subjects and facilitate the discontinuation of Arms C and D should the interim analysis indicate these arms are to be discontinued;
- Overall Survival (OS) has been added to the efficacy endpoints;
- Inclusion criteria #2 has been updated to include units (per microliter) in regards to absolute neutrophil count and platelet count;

- MRD will now be evaluated in all subjects achieving a PR or CR following the Cycle 6 response assessment as opposed to previously only in subjects achieving a CR;
- Inclusion Criteria # 7 was updated to reflect the appropriate contraception time period per Appendix B as well as for post chlorambucil therapy;
- Exclusion Criteria # 8 was updated to include "4 weeks prior to" for the live virus administration;
- The frequency of CT scans for efficacy evaluation after 36 months was lessened and is now required at least every 6 cycles. Language was changed to state as follows: "After 36 months, subjects should be evaluated for response by CT and/or MRI every 6 cycles unless clinically indicated sooner" and "Subjects being followed for PFS off treatment should have scans done approximately every 3 months prior to 36 months and approximately every 6 months after 36 months, unless clinically indicated sooner";
- As all countries are not participating in the Companion Trial (UTX-TGR-204), language was added to state "select countries only" in respect to the Companion Trial participation;
- MRD sampling window was changed from a +/- 7 day window to +/- 14 day window;
- Informed consent was removed from Section 5 table as is not a 21 day screening procedure;
- Screening period was changed from 21 to 28 days;
- TGR-1202 dose delay/modification section was updated for non-hematologic toxicity specific for diarrhea;
- Ublituximab dose delay/modification section was updated for management of anaphylaxis;
- Section 6.2.4 was updated to eliminate the "within 7 days" requirement for starting PCP and antivirals. It was changed to "…prior to Day 1 of Cycle 1";
- Language was added in Section 6.2.3.1 to allow investigator discretion on infusion rate flow as follows: "If at any time during ublituximab treatment, an infusion related reaction is observed, the treating investigator may reduce the infusion flow rate at their discretion."
- The ublituximab risk profile (Section 7.3.1.3) was updated based on the most recently available safety information since the last study amendment;
- Exclusion Criteria were updated with the addition of Exclusion Criteria # 9, which now excludes subjects with: "History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration";
- General grammatical and administrative updates throughout have been incorporated.

Version 3.1 (Dated 18 June 2017) of this Protocol is the third amendment to this clinical trial and contains the following modifications:

- Section 6.2.3.3.1 and Section 7.3 were both updated to include information regarding a new vial size for ublituximab;
- Inclusion criteria 1d – added the micro symbol "μ" as was left off in error.

Version 4.0 (Dated 4 October 2017) of this Protocol is the fourth amendment to this clinical trial and contains the following modifications:

- Section 4 was updated to reflect the closing of Arms C and D pursuant to the pre-specified interim analysis to establish contribution, conducted by the DSMB in May 2017;
- Section 5.1.4 was updated to clarify that an additional post-baseline sparse PK sample could be collected from subjects;

- Sections 6.3.2 and 6.3.3 were updated to provide the latest guidance for dose delay and modifications for ublituximab, TGR-1202, chlorambucil, and obinutuzumab;
- Sections 7.3.1, 7.4.1, and 7.5.1 were updated to include the most recent adverse event information related to the ublituximab and umbralisib Investigator Brochures;
- Sections 5.0 (Treatment Schedule) and 8.0 were updated to change the window for scans from +/- 7 days to +/- 14 days;
- Updates were made throughout to include the generic name of TGR-1202: umbralisib; and
- Minor administrative updates and typographical errors were corrected throughout.

Version 4.1 (Dated 20 December 2017) of this Protocol is a correction to this clinical trial and contains the following modifications:

- Sections 6.3 and 7.3: Acknowledgement of the Adverse Event "Anaphylaxis" was mistakenly removed from Version 4.0 and has been re-inserted into the respected sections.

Version 5.0 (Dated 13 February 2019) of this Protocol is the sixth amendment to this clinical trial and contains the following modifications:

- Minor administrative and editorial changes.
- Updated response assessment guidelines to state: "During the study period, Response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner.
- Section 4.4. Added reasons for discontinuing a subject from the study to go along with reasons for discontinuing a subject from study treatment.
- Section 5.0, Study Assessments and Treatment Schedule
  - Updated response assessments
  - Added CMV surveillance for all subjects on Arms A and D every 3 months through 30 days from last dose of study drug (EOT Visit)
  - Clarified End of Treatment (EOT) and End of Study (EOS) assessments and schedule. Added Table 3.
- Section 5.1.1. CMV surveillance added for all subjects on Arms A and D every 3 months through 30 days from last dose of study drug (EOT Visit)
- Section 6.2.3 modified:
  - Recommendations for antihypertensives prior to Ublituximab infusion. Window for holding antihypertensive is changed. Consider holding antihypertensives 12-24 hours prior to infusion from previously stated 24 hours.
  - Premedication timing clarified. Ublituximab should be started approximately 30 minutes after the conclusion of premedication infusions and should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). If pre-medication is given orally, administer oral pre-mediation approximately 45-60 minutes prior to the beginning of the ublituximab infusion. If subject has a negative reaction to a premedication the investigatory may consider decreasing its dose, using a different drug, or discontinue if not tolerated. Additionally, if subject has other health conditions that are adversely impacted by a premedication the investigator may consider decreasing its dose, switching premedication to a different drug, or discontinue if medically appropriate.

- Section 6.2.4 was updated to remove Bactrim as a recommended anti-PCP prophylaxis, and additional instructions were given to switch to an alternate prophylaxis therapy, reduce dose, or discontinue prophylaxis at investigator discretion.
- Section 6.3 was updated to remove the requirement to discontinue subjects from investigational product if held more than 28 days. Treatment re-initiation after a treatment delay of greater than 2 cycles is at investigator discretion.
- Section 6.3.3 Table 5
  - Respiratory/Infection section for Umbralisib clarified: *For sinopulmonary infections clearly not related to immune-mediated pneumonitis, TGR-1202 may be continued at investigator's discretion. 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 at start of therapy.
  - Added dose delays/modification and treatment instructions for Umbralisib related to liver injury
- Section 7.3.1 Comprehensive Adverse Events and Potential Risks (CAEPRS) for Ublituximab to align with Ublituximab Investigator Brochure Version: 6.0 dated 20JUL2018.
- Section 7.4.1 Comprehensive Adverse Events and Potential Risks (CAEPRS) for Umbralisib to align with Umbralisib Investigator Brochure Version: 6.0 dated 20JUL2018.
- Language in protocol modified to utilize the term subject replacing patient.
- Clarification throughout protocol confirming subjects will remain in follow up for PFS until progressive disease is confirmed by Independent Review Committee (IRC) through our central radiology vendor.
- Overall Response Rate (ORR) analysis language has been included in Section 9.1.

Version 6.0 (Dated 15 March 2020) of this Protocol is the seventh amendment to this clinical trial and contains the following modifications:

- Response categories of CRi (complete response with incomplete marrow recovery) and nPR (nodular PR) were added throughout;
- Terminology of tumor status and tumor assessment were changed to disease assessment throughout;
- Updates to the statistical analysis plan were integrated throughout, including:
  - The interim analysis for purposes of futility at 75% of target events was converted to an interim analysis of efficacy consistent with updates to the Statistical Analysis Plan (SAP);
  - MRD negativity rate was modified to remove reference to "MRD positivity at baseline" since no baseline MRD samples are to be obtained in the study. MRD was clarified as being assessed amongst responders only.
  - Clarification was made to specify that the primary and secondary efficacy analyses would occur in the ITT population.
  - The timing of the ORR analysis was clarified to be following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis;
- Section 10.9.3 was updated to fix an error in the required reporting of deaths due to disease progression on study which should NOT be reported as an adverse event.
- Minor administrative and editorial changes were incorporated.

STUDY SYNOPSIS

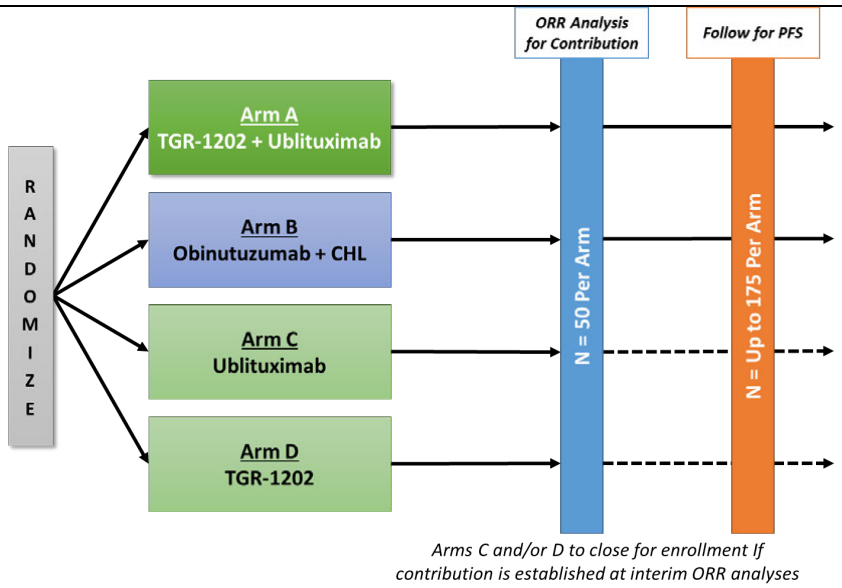
Protocol no.	UTX-TGR-304
Study Title	A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with TGR-1202 (Umbralisib) Compared to Obinutuzumab in Combination with Chlorambucil in Subjects with Chronic Lymphocytic Leukemia (CLL)
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Sites & Enrollment	• This study will be carried out in up to 200 centers in the United States and select ex-US sites • Enrollment is expected to take approximately 24 months
Study Rationale	The purpose of this study is to demonstrate the superiority of ublituximab in combination with TGR-1202 in the treatment of subjects with chronic lymphocytic leukemia (CLL) in terms of improved progression-free survival (PFS) compared to treatment with obinutuzumab in combination with chlorambucil. The combination of ublituximab and TGR-1202 will also be compared to ublituximab alone and TGR-1202 alone to demonstrate the contribution of each agent in the combination in accordance with the FDA guidance on the approval of two novel agents. Despite an array of available therapies, CLL remains an incurable disease. Furthermore, the presence of certain cytogenetic abnormalities and high-risk mutational features predicts for a reduced response to treatment, and as a result, a shorter period of progression-free survival. As such, there is a pressing need for innovative, targeted therapies for the treatment of subjects with CLL. Ublituximab (also known as TG-1101) is a glycoengineered monoclonal antibody that binds to the trans-membrane antigen CD20 found on B-lymphocytes. The binding of ublituximab induces an immune response that results in the lysis of B cells. Umbralisib (also known as TGR-1202) is a highly-specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated in various hematologic malignancies. TGR-1202 is currently in a Phase I dose escalation trial and has been administered safely at daily doses up through 1200 mg QD. Given the non-overlapping mechanisms of action of each of these agents, the combination of ublituximab and TGR-1202 was explored in a Phase I/Ib study in subjects with previously treated hematologic malignancies (Lunning ASH 2015). The combination regimen was well tolerated with ublituximab administered at doses up to 900 mg per infusion, and TGR-1202 administered at doses up through 800 mg QD. Clinical activity was noted in a variety of hematologic malignancies, with responses reported in subjects with a broad range of non-Hodgkin's lymphomas and CLL.

	Recently the novel anti-CD20 monoclonal antibody, obinutuzumab, was approved in combination with chlorambucil for subjects with previously untreated CLL, displaying a significant advantage in progression-free survival (PFS) over chlorambucil alone. While novel targeted agents recently approved for subjects with CLL are offering greater efficacy and tolerability than current standard of care chemotherapy-based regimens, CLL remains an incurable disease. In this study, the efficacy and safety of the combination of ublituximab and TGR-1202 will be compared to the combination of obinutuzumab and chlorambucil in a 4-arm design, with a third and fourth arm assessing the effect of ublituximab monotherapy and TGR-1202 monotherapy to accurately characterize the contribution of each agent in the combination regimen. Following screening, eligible subjects will be initially randomized in a 1:1:1:1 ratio to one of four treatment arms: ublituximab in combination with TGR-1202 (Arm A), obinutuzumab in combination with chlorambucil (Arm B), ublituximab alone (Arm C), or TGR-1202 alone (Arm D). An interim analysis of ORR is planned on the first 50 subjects enrolled into each arm to assess the contribution of each single agent in the ublituximab + TGR-1202 combination regimen. Approximately 175 subjects will be enrolled in total into each of Arms A and B for the PFS analysis, and up to 175 subjects may be enrolled into each of Arms C and D unless contribution is established at the interim ORR analysis, in which case enrollment into Arms C or D may be terminated after consultation with the FDA.
Study Objectives	PRIMARY OBJECTIVES • To establish that the combination of ublituximab + TGR-1202 is superior to the combination of obinutuzumab + chlorambucil as measured by Progression-Free Survival (PFS) in subjects with CLL KEY SECONDARY OBJECTIVES • To establish that the combination of ublituximab + TGR-1202 provides clinical benefit over both ublituximab alone and TGR-1202 alone • To evaluate and compare the combination of ublituximab + TGR-1202 to the combination of obinutuzumab + chlorambucil with respect to overall response rate in subjects with CLL OTHER SECONDARY OBJECTIVES • To assess safety, tolerability and other efficacy outcomes. • To determine the pharmacokinetics and any potential drug-drug interactions of ublituximab and TGR-1202 in combination.
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1. B-cell CLL (treatment naïve or previously treated) that warrants treatment consistent with accepted IWCLL criteria (Hallek 2008) for initiation of therapy. Any one of the following conditions constitute CLL that warrants treatment:

	a. Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or b. Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or c. Massive (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/μL), or e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or f. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection: i. Unintentional weight loss of ≥10% within the previous 6 months, or ii. Significant fatigue (≥ Grade 2), or iii. Fevers >100.5°F or 38.0°C for ≥2 weeks, or iv. Night sweats for >1 month. 2. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) ≥ 1,000/mm³ (μL) / platelet count ≥ 50,000/mm³ (μL). 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 formula). 3. Presence of measurable lymphadenopathy, defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter (LD) and ≥ 1.0 cm in the longest perpendicular diameter (LPD) as assessed by computed tomography (CT) or magnetic resonance imaging (MRI). 4. ECOG performance status ≤ 2. 5. Male or female ≥ 18 years of age. 6. Ability to swallow and retain oral medication. 7. Female subjects who are not of child-bearing potential (see Appendix B-Contraceptive Guidelines and Pregnancy), and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female subjects of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of ublituximab or TGR-1202, or 18 months after the last dose of obinutuzumab or at least 4 weeks after the last dose of chlorambucil. 8. Willingness and ability to comply with trial and follow-up procedures and give written informed consent.
Exclusion Criteria	1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor

	embolization) or any investigational drug within 21 days of Cycle 1/Day 1 (contact sponsor for < 21- day washout period requests). a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted. 2. Autologous hematologic stem cell transplant within 3 months of study entry. Prior Allogeneic hematologic stem cell transplant is excluded. 3. Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by PCR - See Appendix D. 4. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation). 5. Prior exposure to idelalisib (CAL-101), duvelisib (IPI-145), ACP-319, or any drug that specifically inhibits phosphoinositide-3-kinase (PI3K). 6. Subjects who have received prior therapy with obinutuzumab. Subjects who are refractory to prior chlorambucil (defined as disease progression while receiving or within 6 months of completion of a chlorambucil based regimen). 7. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required for subjects on TGR-1202 arms. 8. Live virus vaccines within 4 weeks prior to or during obinutuzumab or ublituximab therapy. 9. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration. 10. 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 – NYHA Classifications]) b. Myocardial infarction within 6 months of randomization c. QTcF >470 msec d. Angina not well-controlled by medication e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of randomization. 11. 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. 12. Women who are pregnant or lactating.

Efficacy Endpoints	**Progression-free survival (PFS)** PFS is defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression based on standard criteria (Hallek et al. 2008) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis. **Overall response rate (ORR)** ORR is defined as sum of CR, CRi, PR, and nPR rates. **Complete Response (CR) Rate** CR rate is defined as the proportion of subjects who achieve a CR or CRi. **Minimal Residual Disease (MRD) Negativity Rate** MRD negativity rate is defined as the proportion of subjects who are MRD negative. **Duration of response (DOR)** DOR is defined as the interval from the first documentation of CR, CRi, PR, or nPR to the earlier of the first documentation of definitive disease progression or death from any cause. **Overall Survival (OS)** OS is defined as the interval from randomization to death from any cause.
Safety Endpoints	All Adverse Events (AE's) will be reported and evaluated using National Cancer Institute's Common Terminology Criteria (CTCAE) v4.0.
DSMB	An independent Data Safety Monitoring Board (DSMB) has been established to advise the Sponsor on safety and provide benefit/risk oversight of the study as described in the DSMB Charter.
Independent Response Review	For the efficacy objectives of the study, an Independent Review Committee (IRC) will provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation and confirmation of changes in disease status.
Study Design	This study is designed as a Phase 3, randomized, four-arm trial to evaluate the efficacy and safety of ublituximab in combination with TGR-1202 compared to that of obinutuzumab in combination with chlorambucil (CHL), and to ublituximab alone and to TGR-1202 alone in subjects with CLL. While the primary objective of the study is to demonstrate the superiority of Arm A (Ublituximab + TGR-1202) over Arm B (Obinutuzumab + Chlorambucil) as measured by progression-free survival (PFS) and overall response rate (ORR), an interim analysis of ORR among the first 50 subjects enrolled into each arm is planned to assess the contribution of each single agent in the ublituximab + TGR-1202 combination regimen. **Study Schema**



Enrollment

Following Screening, qualified subjects will be randomized in a 1:1:1:1 ratio to one of the four arms:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202

Approximately 175 subjects will be enrolled into each of Arms A and B for the PFS analysis, and up to 175 subjects may be enrolled into each of Arms C and D unless contribution is established at the interim ORR analysis among the first 50 subjects enrolled into each arm, in which case enrollment into Arms C or D may be terminated early.

If contribution is established at the planned interim analysis and Arms C and D close for enrollment, qualified subjects will be randomized in a 1:1 ratio to one of two arms:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil

Contribution was established at the interim analysis and as of May 2017 Arms C and D are closed for enrollment.

Stratification:

Randomization will be stratified according to 17p deletion status (presence vs. absence) and treatment status (treatment naïve vs. previously treated). For purposes of stratification, subjects will be considered "previously treated" only

	if they have previously received at least 2 cycles of one or more prior treatment regimens. During the study period, response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner. Date of progression, initiation of new treatment, and/or death should be entered in the eCRF. The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC). Subjects will remain on study treatment until the occurrence of definitive disease progression confirmed by central radiology, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression until confirmed by central radiology. During the study, subjects from Treatment Arms B, C, and D with disease progression confirmed by the independent review committee (IRC), may be enrolled into a Companion Study immediately (select participating countries only). At the end of the study, non-progressed subjects from all treatment arms may also be enrolled to the above-mentioned Companion Study. In the Companion Study, subjects from Treatment Arms B, C, and D may start treatment with ublituximab + TGR-1202 as described in this protocol, while subjects entering the Companion Study from Treatment Arm A may continue their treatment per specified by this protocol. An independent DSMB will advise the Sponsor on safety and provide benefit/risk oversight of the study as described in the DSMB Charter. Once the database has been locked, the independent DSMB will review the primary and secondary efficacy analyses and safety data. The study will include a non-binding interim analysis for ORR at 50 subjects per arm (contribution), and 2 planned interim analyses for PFS, one at 50% information time (approximately 140 events) solely for purposes of assessing futility, and one at the later to occur of: i) 75% information time (210 events), and ii) sufficient follow-up for all enrolled subjects to be defined in the UTX-TGR-304 Statistical Analysis Plan. The interim analyses will be performed by the designees of the independent DSMB. The study will end either at the second interim PFS analysis or at the final PFS analysis after approximately 280 PFS events are observed.
Dosing Regimen & Treatment Study Visits	***ARM A: Ublituximab + TGR-1202*** **Cycle 1:** **Ublituximab** | **TGR-1202** **Day 1** | **Day 2** | **Day 8 & 15** | **Daily**

150 mg	750 mg	900 mg	800 mg

Cycles 2 through 6:

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

After Cycle 6:

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

ARM B: Obinutuzumab + Chlorambucil

Cycle 1:

Obinutuzumab			Chlorambucil
Day 1	**Day 2**	**Day 8 & 15**	**Day 1 & 15**
100 mg	900 mg	1000 mg	0.5 mg/kg

Cycles 2 through 6:

Obinutuzumab	Chlorambucil
Day 1	**Day 1 & 15**
1000 mg	0.5 mg/kg

After Cycle 6:

No Further Treatment

ARM C: Ublituximab (if applicable)

Cycle 1:

- 150 mg Ublituximab on Day 1
- 750 mg Ublituximab on Day 2
- 900 mg Ublituximab on Days 8 & 15

Cycles 2 through 6:

- 900 mg Ublituximab on Day 1

After Cycle 6:

- 900 mg Ublituximab on Day 1, every 3 cycles (i.e. Cycle 9, 12, 15, etc.)

ARM D: TGR-1202 (if applicable)

Cycle 1, and Onward:

- 800 mg TGR-1202 once daily until removal from study

Study Drugs	Ublituximab is a recombinant chimeric monoclonal antibody against the CD20 antigen, available as either a 10 mg/mL or 25 mg/mL concentrate for solution for infusion, supplied by TG Therapeutics, Inc.

	TGR-1202 (umbralisib) is a highly specific and orally available PI3K delta (δ) inhibitor available in 200 mg tablets, supplied by TG Therapeutics, Inc. Obinutuzumab is a humanized monoclonal antibody against the CD20 antigen, available as a 25 mg/mL concentrate for solution for infusion in 40 mL vials. Chlorambucil is an oral alkylating agent that is available in 2mg tablets.
Statistical Considerations	The primary efficacy variables will be PFS and the key secondary efficacy variable will be ORR. An overall p-value of 0.01 will be used to establish contribution of the two individual components (Treatment Arms C and D) in the combination regimen (Treatment Arm A) based on ORR in an interim analysis to be conducted when approximately 50 subjects in each arm have provided ORR assessment, as well as to establish superiority of treatment A over treatment B based on ORR. The remaining overall p-value of 0.04 will be used to establish superiority of Treatment A over Treatment B based on PFS. Should contribution in the combination regimen fail to be established at the interim ORR analysis, both single agent arms (Treatment Arms C and D) will continue to enroll subjects and be followed for PFS. All interim analyses will be conducted by an independent data safety monitoring board (DSMB). *Overall Response Rate:* One interim analysis based on ORR will be performed when approximately 50 subjects each in Arms A, B, C and D have provided disease assessments to determine ORR status. Should contribution be established at the interim ORR analysis, enrollment into Arms C and D will be terminated, however, enrollment into Arms A and B will continue until 175 subjects have been enrolled into each arm. Furthermore, an ORR analysis of Arms A and B will be conducted following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis. If enrollment to Arm C or Arm D cannot be terminated at the ORR interim analysis, enrollment to these arms will continue until they reach the target sample size of up to 175 in each arm. *Progression Free Survival:* Two interim analyses based on PFS will be performed. The first interim analysis will be performed at approximately 50% information time and will be solely for evaluating futility. The second interim PFS analysis will be conducted at the later to occur of: i) 75% information time (210 events), and ii) sufficient follow-up for all enrolled subjects to be defined in the UTX-TGR-304 Statistical Analysis Plan. If contribution was unable to be established by ORR at the interim analysis, both single agent arms C and D will be evaluated for PFS. PFS will be analyzed using a stratified log-rank test preserving an overall two-sided 0.04 level of significance. For each treatment arm, the median duration of PFS and the proportion of subjects alive and progression-free at 6, 12, and 18 months will be estimated using the Kaplan-Meier method. For each estimate, a 95% confidence interval will be reported.

	More details of efficacy analyses can be found in Section 9, Statistical Considerations Section. Sample Size: An approximate total number of 280 events between Treatments A and B will be required to provide 80% power to detect a treatment superiority of Treatment Arm A over Treatment Arm B at an overall two-sided significance level 0.04. In the sample size calculation, it was assumed that the median PFS was 25 months for Treatment B and 35.5 months for Treatment A and that the subjects would be accrued within 24 months and followed for at least 48 months. **Safety Analyses:** Treatment-emergent AEs through 30 days after last dose of study treatment will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™), System Organ Class and preferred term. The incidences and percentages of subjects experiencing each AE preferred term will be summarized with descriptive statistics. More details of safety analyses can be found in Section 10, Safety Reporting and Analysis Section.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Definitions of Terms	
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BM	Bone Marrow
BTK	Bruton's Tyrosine Kinase
Ca	Calcium
CBC	Complete Blood Cell Count
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
Cl	Clearance
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
Cmax	Maximum Concentration
CR	Complete Response
CRi	Complete Response with incomplete marrow recovery
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebro-Vascular Accident
D, d	Day
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRG	Data Review Group
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Fc	Fragment crystallizable (region)
FCR	Fludarabine, Cyclophosphamide, Rituximab
FISH	Fluorescence in-situ hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
ITT	Intent-to-treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LD	Longest Diameter
LDH	Lactate dehydrogenase

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

1 INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

In the US, an estimated 15,720 new cases of Chronic Lymphocytic Leukemia (CLL) will be reported in 2014 with deaths totaling 4,600 due to the disease according to American Cancer Society estimates (American Cancer Society, 2014). CLL affects mainly older adults, accounts for one third of all diagnosed cases of leukemia and is characterized by the accumulation of clonal mature B lymphocytes in the blood, bone marrow, and secondary lymphoid tissues (Lin K, 2002). CLL is a heterogeneous disease, with several higher risk cytogenetic abnormalities which are generally more difficult to treat, including 17p deletion, P53 gene mutation, and 11q deletion (Hallek M, 2008) (Lin K, 2002). Subjects with 17p deletion show higher resistance to conventional chemotherapies as well as shorter duration of survival than non 17p deletion subjects. Subjects with 11q deletion have been associated with marked lymphadenopathy (Hallek M, 2008). Subjects with P53 gene mutations are associated with an adverse clinical outcome (Lin 2002).

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

1.2 UBLITUXIMAB

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

1.2.1 PRE-CLINICAL EVALUATIONS OF UBLITUXIMAB

1.2.1.1 IN VITRO ACTIVITY

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

1.2.1.2 IN VIVO ACTIVITY

The antitumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models. Single agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in the FL xenograft at a dose of 100mg/kg, and a superior tumor growth delay (21 days) compared to rituximab. Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels (4).

1.2.1.3 TOXICOLOGY

In single-dose and repeat dose toxicology studies performed under GLP, ublituximab displayed a safety profile similar to what might be expected for anti-CD20 monoclonal antibodies. Single administration of up to 100 mg/kg ublituximab in cynomolgus monkeys was well tolerated, with no local irritation with intravenous administration. Genotoxicity studies (Ames test) showed that ublituximab was not mutagenic. Monkeys that received a single injection of 0.3 mg/kg of ublituximab developed an anti-ublituximab response, whereas anti-ublituximab antibodies were not detected in the animals which received 10 or 100 mg/kg (see Ublituximab Investigator Brochure).

1.2.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB - CLL

Ublituximab has been studied in a variety of subject populations, both as a single agent, and in combination with other agents, with over 100 subjects having received ublituximab therapy to date across all studies. Two Single-Agent Phase I/Ib trials have been conducted with ublituximab treating both NHL and CLL subjects, with a total of 41 subjects with relapsed or refractory CLL having been treated with single-agent ublituximab (TG-1101). Further, following demonstration of safety and tolerability in these early single agent studies, Phase I and II combination studies were undertaken with a variety of agents. Given the number of subjects who have received ublituximab in early-phase trials, the safety and side effect profile of the agent is well characterized. Summaries of the single-agent experience are provided below as well as data with use of ublituximab in combination with ibrutinib.

In a two part, first-in human dose escalation study (protocol CD20-0703), subjects with relapsed or refractory CLL received one weekly infusion of single agent ublituximab for 4 doses in a 3+3 dose escalation design through 5 sequential dose levels. Part II of the study was a dose-confirmation component which used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg)

– the clinical summary will focus on the Part II part of the study as the dose is more relevant to the clinical application used in current clinical studies. In Part II, 12 subjects were enrolled at 9 centers in France and followed for 12 months. Demographic data for the 12 subjects enrolled in the study were as follows. The median age was 69.5 years [62–77]; median time from diagnosis to inclusion was 10.4 years [4.0–23.6] and median prior therapies was 3 [1–8]. Seven subjects (58%) received at least one prior rituximab-containing regimen. The median lymphocyte bone marrow infiltration was 85% [40–94].

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

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

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

Of the 8 CLL subjects enrolled, 4 had infusion related reactions that were manageable with infusion interruptions only and all subjects received all schedule doses. Other observed adverse events which were considered at least possibly related to study drug included neutropenia Grade 1/2 (n=1) and Grade 3/4 (n=3), as well as thrombocytopenia Grade 1/2 (n=1) and Grade 3/4 (n=1). Six subjects were evaluable for efficacy as of data cutoff for ASCO 2014, with 4 out of 6 subjects achieving a partial response. Rapid and profound circulating lymphocyte depletion (> 50% reduction) was noted with median time to peripheral response of 1 day (O'Connor OA, 2014).

1.2.2.1 PHARMACOKINETICS

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

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

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

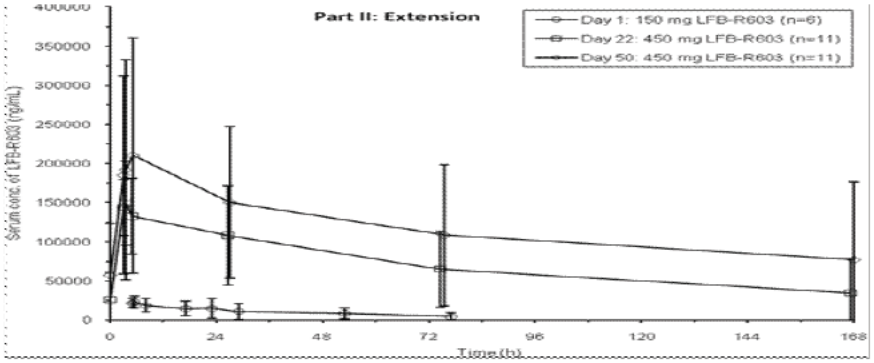


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150 MG), THE 4TH (450 MG) AND THE 8TH (450 MG) INFUSION OF UBLITUXIMAB

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

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

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

1.3 TGR-1202 (UMBRALISIB)

TGR-1202 is a highly specific and orally available phosphoinositide-3-kinase (PI3K) delta (δ) inhibitor with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma isoforms. The PI3Ks are a family of enzymes involved in various cellular functions, including cell

proliferation and survival, cell differentiation, intracellular trafficking and immunity. The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated in various hematologic malignancies. TGR-1202 has demonstrated safety and efficacy in an ongoing Phase I clinical trial in subjects with a wide variety of relapsed or refractory hematologic malignancies.

1.3.1 PRE-CLINICAL DEVELOPMENT OF TGR-1202

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

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

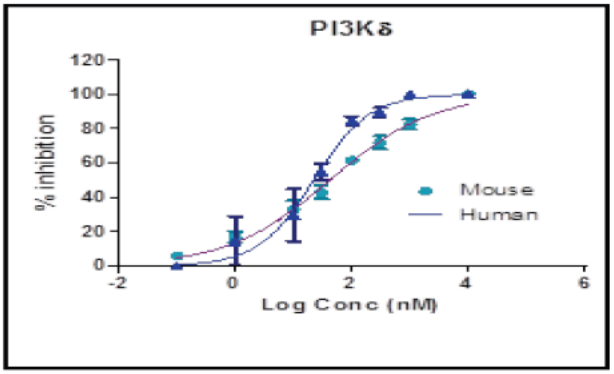


FIGURE 2: TGR-1202 POTENCY AGAINST HUMAN AND MOUSE PI3K ISOFORMS

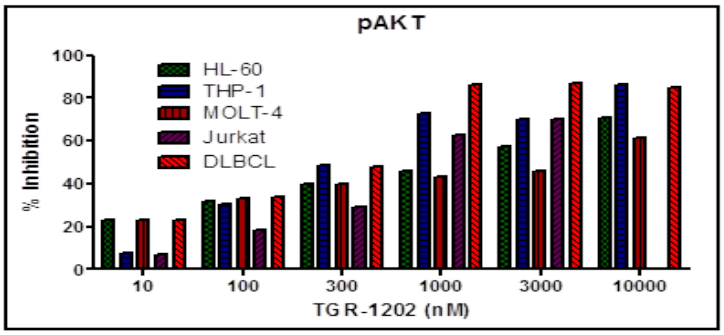
PI3K isoforms (Human)	IC_{50} (nM)
α	>10,000
β	1,116
γ	1,065
δ	22.23

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.

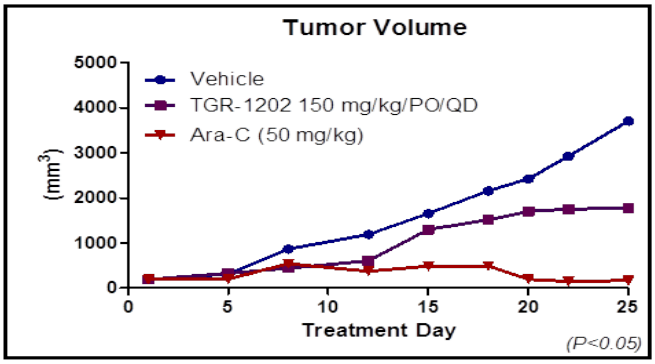
FIGURE 3: REDUCTION OF PAKT BY TGR-1202 IN CELL LINES BY WESTERN BLOTTING



1.3.1.1 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 4: TGR-1202 IN VIVO EFFICACY



1.3.1.2 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.

1.3.2 CLINICAL DEVELOPMENT OF TGR-1202

1.3.2.1 SINGLE-AGENT IN SUBJECTS WITH RELAPSED OR REFRACTORY HEMATOLOGIC MALIGNANCIES

TGR-1202 is under evaluation in an ongoing single-agent Phase I dose-escalation study in subjects with relapsed and refractory hematologic malignancies (Burris et al, ASH 2014). As of the latest cutoff date for this study of December 1, 2014, 55 subjects were enrolled and eligible for safety evaluation, with 43 subjects evaluable for efficacy. The median age was 62 years (range 22-82), 73% male and 18/55 enrolled subjects had a diagnosis of CLL. Among all subjects the median number of prior therapies was 3, with 80% receiving prior rituximab-based chemotherapy. Other histological diagnoses included; FL (n=15), HL (n=9), DLBCL (n=7), MCL (n=2), MZL (n=2), HCL and WM (n=1 each). The majority of subjects had an ECOG of 1 and 51% received 3 or more prior therapies.

Subjects 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 1.3.2.2 Healthy Subject Pharmacokinetic Studies below). This micronized formulation was introduced into dose escalation at 200 mg QD and dosed as high as 1200 mg QD, with no maximum tolerated dose (MTD) reached. Intra-subject dose escalation rules have allowed subjects 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 ref), 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 subjects. Of the 14 evaluable CLL subjects treated at or above this therapeutic threshold, 93% 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 subjects 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 subjects. The Grade 3 rash resolved upon suspension of TGR-1202 and concomitant medications and did not recur upon re-challenging the subject at 800 mg QD. See Section 7.4.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for a complete overview of the TGR-1202 side effect profile.

Dosing of TGR-1202 initially occurred in the fasting state, but was transitioned mid-study to fed state dosing, with subjects instructed to take TGR-1202 with food. All dosing of TGR-1202 is now conducted using the micronized formulation and in the fed state.

Overall, TGR-1202 was well tolerated and displayed promising signs of clinical activity at the higher dosing cohorts. No drug-related transaminase elevations or events of colitis have been reported to date. No MTD has been reached and dose escalation continues.

1.3.2.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

In parallel with the Phase 1 single-arm, dose-escalation study in subjects with relapsed or refractory hematologic malignancies; two healthy subjects, crossover, bioequivalence pharmacokinetics studies have been completed. The first pharmacokinetic study was a Phase 1 drug-food interaction study

with a single 200 mg oral dose of TGR-1202 in healthy volunteers followed by a second single dose Phase 1 pharmacokinetic study evaluating the absorption, distribution, metabolism and excretion characteristics of two different oral formulations of 200 mg TGR-1202 (original formulation vs. micronized formulation) in healthy volunteers.

1.3.2.2.1 TGR-1202-PK101: FOOD EFFECT

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

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

Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Fasting	Fed		
$AUC_{0\text{-}t}$ (ng·hr/mL)	6029.87	9692.02	160.73	140.25 – 184.21
$AUC_{0\text{-}inf}$ (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 ($AUC_{0\text{-}t}$) and total extent ($AUC_{0\text{-}inf}$) 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 $AUC_{0\text{-}inf}$.

1.3.2.2.2 TGR-1202-PK102: FORMULATION EFFECT

Study TGR-1202-PK 102 was a two-period, randomized, two-way cross over, relative bioavailability and 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:

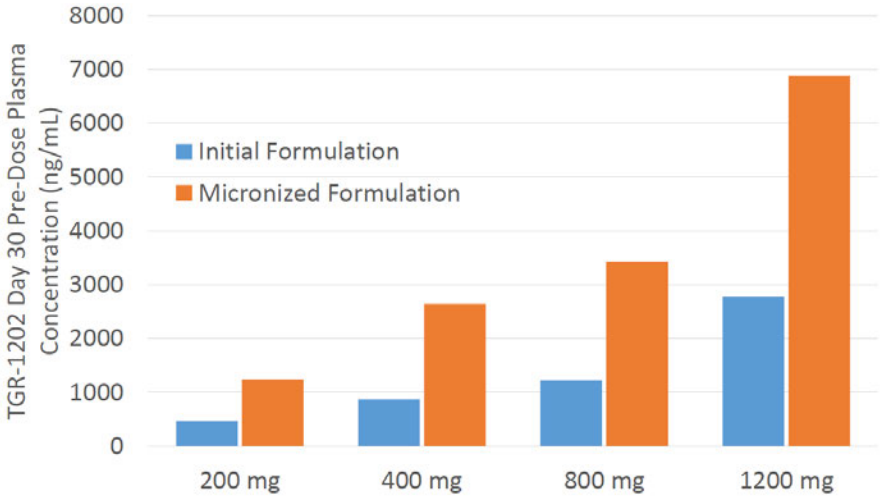
Parameters	Geometric LS Means		% Geometric Mean Ratio	Confidence Interval
	Original Formulation	Micronized Formulation		
$AUC_{0\text{-}t}$ (ng·hr/mL)	5906.11	9439.82	159.83	149.43 – 170.95

$AUC_{0\text{-}inf}$ (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 ($AUC_{0\text{-}t}$) and total extent ($AUC_{0\text{-}inf}$) 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 subjects 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 subjects administered equivalent doses of either the initial formulation in the fasting state or the micronized formulation in the fed state:



1.4 UBLITUXIMAB IN COMBINATION WITH TGR-1202

The combination of ublituximab and TGR-1202 is currently under evaluation in an ongoing Phase I/Ib study in subjects with relapsed or refractory NHL and CLL (Lunning et al., ASH 2014). In this study, ublituximab is being dosed on Days 1, 8, and 15 of Cycle 1 & 2, and on Day 1 of Cycles 4, 6, 9 and 12. After Cycle 12, no further ublituximab is administered and TGR-1202 is continued until removal from study.

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

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

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

Among the 27 subjects evaluable for safety, Infusion Related Reaction (IRR) was the most prevalent adverse event (52%), followed by neutropenia (41%), nausea (37%), diarrhea (33%), fatigue (30%), and insomnia (30%). Adverse events were observed to be similar across dosing cohorts, and only one subject had their dose of TGR-1202 reduced (Gr. 1 diarrhea). IRR and neutropenia were managed through dose delays, with 1 CLL subject having a neutropenia related dose delay which met the criteria for a DLT, necessitating enrollment of additional CLL subjects into Cohort 1. One subject was removed from study without progressive disease due to an event of itching which was deemed possibly related to TGR-1202.

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

Responses are as follows:

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

Overall, the preliminary data suggests the combination of ublituximab and TGR-1202 is well tolerated and active in subjects with relapsed or refractory hematologic malignancies, including those with CLL (both high and low risk).

2 OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To establish that the combination of ublituximab + TGR-1202 is superior to the combination of obinutuzumab + chlorambucil as measured by duration of Progression-Free Survival (PFS) in subjects with CLL

KEY SECONDARY OBJECTIVES

- To evaluate and compare the combination of ublituximab + TGR-1202 to the combination of obinutuzumab + chlorambucil with respect to overall response rate in subjects with CLL
- To establish that the combination of ublituximab + TGR-1202 provides clinical benefit over both ublituximab alone and TGR-1202 alone

OTHER SECONDARY OBJECTIVES

- To assess safety, tolerability and other efficacy outcomes.
- [redacted]

2.2 EFFICACY ENDPOINTS

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

Definitive disease progression based on standard criteria (Hallek et al. 2008) and occurring for any reason (i.e., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis.

Overall response rate (ORR)
ORR is defined as sum of CR and PR rates.

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

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

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

Overall Survival (OS)
OS is defined as the interval from randomization to death from any cause.

3 ELIGIBILITY CRITERIA

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

3.1 INCLUSION CRITERIA

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

1. B-cell CLL that warrants treatment consistent with accepted IWCLL criteria (Hallek 2008) for initiation of therapy. Any one of the following conditions constitute CLL that warrants treatment:
    a. Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
    b. Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or
    c. Massive (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
    d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/μL), or
    e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
    f. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
        i. Unintentional weight loss of ≥10% within the previous 6 months, or
        ii. Significant fatigue (≥ Grade 2), or
        iii. Fevers >100.5°F or 38.0°C for ≥2 weeks, or
        iv. Night sweats for >1 month.
2. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 (μL) / platelet count $\geq$ 50,000/mm^3 (μL).
    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 formula.)
3. Presence of measurable lymphadenopathy, defined as the presence of $\geq$ 1 nodal lesion that measures $\geq$ 2.0 cm in the longest diameter (LD) and $\geq$ 1.0 cm in the longest perpendicular diameter (LPD) as assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
4. ECOG performance status ≤ 2.
5. Male or female ≥ 18 years of age.
6. Ability to swallow and retain oral medication.
7. Female subjects who are not of child-bearing potential (see Appendix B- Contraceptive Guidelines and Pregnancy), and female subjects of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female subjects of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 months after the last dose of

ublituximab or TGR-1202, or 18 months after the last dose of obinutuzumab or 4 weeks after the last dose of chlorambucil.

8. Willingness and ability to comply with trial and follow-up procedures, and give written informed consent.

3.2 EXCLUSION CRITERIA

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

1. Subjects receiving cancer therapy (i.e., chemotherapy, radiation , immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of Cycle 1/Day 1 (contact sponsor for < 21-day washout period requests)
    a. Corticosteroid therapy started at least 7 days prior to Cycle 1/Day 1 (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
2. Autologous hematologic stem cell transplant within 3 months of study entry. Prior Allogeneic hematologic stem cell transplant is excluded.
3. Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV IgM is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by DNA (PCR). - See Appendix D.
4. Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation).
5. Prior exposure to idelalisib (CAL-101), duvelisib (IPI-145), ACP-319, or any drug that specifically inhibits phosphoinositide-3-kinase (PI3K)
6. Subjects who have received prior therapy with obinutuzumab. Subjects who are refractory to prior chlorambucil (defined as disease progression while receiving or within 6 months of completion of a chlorambucil based regimen)
7. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Subjects may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. Use of anti-pneumocystis and antiviral prophylaxis is required for subjects on TGR-1202 arms.
8. Live virus vaccines within 4 weeks prior to or during obinutuzumab or ublituximab therapy.
9. History of anaphylaxis (excluding infusion related reactions) in association with previous anti-CD20 administration.
10. 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 – NYHA Classifications])
    b. Myocardial infarction within 6 months of randomization
    c. QTcF >470 msec
    d. Angina not well-controlled by medication
    e. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac/vascular stenting within 6 months of randomization.
11. 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.

12. Women who are pregnant or lactating.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This study is designed as a Phase 3, randomized, four-arm trial to evaluate the efficacy and safety of ublituximab in combination with TGR-1202 compared to that of obinutuzumab in combination with chlorambucil (CHL), and to ublituximab alone and to TGR-1202 alone in subjects with CLL. While the primary objective of the study is to demonstrate the superiority of Arm A (Ublituximab + TGR-1202) over Arm B (Obinutuzumab + Chlorambucil) as measured by progression-free survival (PFS) and overall response rate (ORR), an interim analysis of ORR among the first 50 subjects enrolled into each arm is planned to assess the contribution of each single agent in the ublituximab + TGR-1202 combination regimen.

During the study, subjects from Treatment Arms B, C, and D with disease progression confirmed by the independent review committee (IRC), may be enrolled into a Companion Study (select participating countries only) immediately. At the end of the study, non-progressed subjects from all treatment arms may also be enrolled to the above mentioned Companion Study. In the Companion Study, subjects from Treatment Arms B, C, and D may start treatment with ublituximab + TGR-1202 as described in this protocol, while subjects entering the Companion Study from Treatment Arm A may continue their treatment per specified by this protocol. These subjects enrolled to the open Companion Study will receive ublituximab in combination with TGR-1202 (at the same dose as the Treatment Arm A in this current study) until they show disease progression, are unable to continue treatment for any reason such as lack of tolerability, or until the treatment is commercially available.

Enrollment

Following Screening, qualified subjects will be randomized in a 1:1:1:1 ratio to one of the four arms:

- Arm A: Ublituximab + TGR-1202 (umbralisib)
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202 (umbralisib)

Approximately 175 subjects will be enrolled into each of Arms A and B for the PFS analysis, and up to 175 subjects may be enrolled into each of Arms C and D unless contribution is established at the interim ORR analysis among the first 50 subjects enrolled into each arm, in which case enrollment into Arms C or D will be terminated early.

If contribution is established at the planned interim analysis and Arms C and D close for enrollment, qualified subjects will be randomized in a 1:1 ratio to one of two arms:

- Arm A: Ublituximab + TGR-1202 (umbralisib)
- Arm B: Obinutuzumab + Chlorambucil

Contribution was established at the interim analysis and as of May 2017 Arms C and D are closed for enrollment.

Stratification:

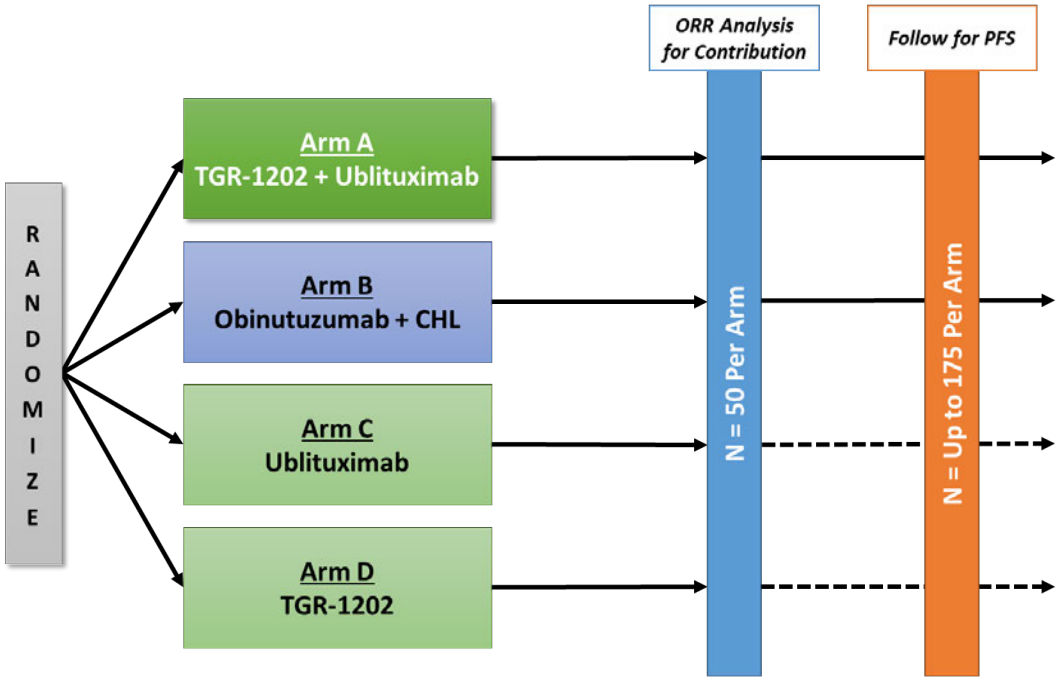
Randomization will be stratified according to 17p deletion status (presence vs. absence) and treatment status (treatment naïve vs. previously treated). For purposes of stratification, subjects will be considered "previously treated" only if they have previously received at least 2 cycles of one or more prior treatment regimens.

During the study period, response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner. Date of progression, beginning of new treatment, and/or death should be entered in the eCRF.

The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC). Subjects will remain on study treatment until the occurrence of definitive disease progression confirmed by central radiology, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression is confirmed by central radiology review.

An independent DSMB has been established to advise the Sponsor on safety and provide benefit/risk oversight of the study as described in the DSMB Charter Once the database has been locked, the independent DSMB will review the primary and secondary efficacy analyses and safety data.

Study Schema



Arms C and/or D to close for enrollment If contribution is established at interim ORR analyses

4.2 REGISTRATION AND RANDOMIZATION/BLINDING

Subjects who are eligible and who have signed an informed consent will be randomized in a 1:1:1:1 ratio to one of four treatment arms: ublituximab in combination with TGR-1202 (Arm A), obinutuzumab in combination with chlorambucil (Arm B), ublituximab alone (Arm C), or TGR-1202 alone (Arm D). Randomization will be stratified according to 17p deletion status (presence vs. absence) and treatment status (treatment naïve vs. previously treated). For purposes of stratification, subjects will be considered "previously treated" only if they have previously received at least 2 cycles of one or more prior treatment regimens.

Investigators will use an interactive web response system (IWRS) to assign subjects to one of four treatment arms as follows:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil
- Arm C: Ublituximab
- Arm D: TGR-1202

If contribution is established at the planned interim analysis and Arms C and D close for enrollment, qualified subjects will be randomized in a 1:1 ratio to one of two arms:

- Arm A: Ublituximab + TGR-1202
- Arm B: Obinutuzumab + Chlorambucil

Contribution was established at the interim analysis and as of May 2017 Arms C and D are closed for enrollment.

Subjects must begin study treatment within 7 days of randomization. Please see the Study Manual for additional information on randomization. Of note, randomization to treatment must occur within the 28-day screening period.

Upon entering subject information into the IWRS, investigators will receive an enrollment approval and a unique subject identifier that will include the randomization assignment. This confirmation must be received by the site prior to dispensing study drug to the participant. Further details about the subject registration process using the IWRS system will be outlined in the Study Manual.

As this is an open-label study, to protect data integrity, the following procedures will be implemented to ensure all clinical and statistical decisions are made in a treatment blinded manner. The Sponsor, except for Clinical Operations personnel monitoring the study and the Medical Monitor, will be blinded to treatment assignment and specific dosing data within the four individual treatment arms. In addition, unblinded Clinical Operations personnel will not be involved in any discussions regarding the analysis of data after enrollment of the first subject into the trial or any protocol amendment, except those related to safety.

4.3 STUDY SITES

Up to 200 centers in the United States and select ex-US sites may be asked to participate in this study. Enrollment is expected to be completed approximately 24 months after the first subject is randomized.

4.4 DISCONTINUATION FROM STUDY TREATMENT

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

- Disease progression confirmed by central radiology
- Intolerable toxicity related to study drug
- Subject requests to withdraw consent or discontinue treatment
- Pregnancy
- Initiation of therapeutic intervention not permitted by the protocol
- Investigator discretion
- Discontinuation of the study by the Sponsor

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

- Disease progression confirmed by central radiology
- Subject requests to withdraw consent
- Initiation of therapeutic intervention not permitted by the protocol
- Discontinuation of the study by the Sponsor

Subjects who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression until PD is confirmed by central radiology or until a new treatment regimen has begun.

Subjects who discontinue all study treatment but remain on study for disease progression assessment, will have an End of Treatment visit (EOT) and will continue to be followed for adverse events (treatment-related AEs and disease-related AEs), disease progression and other protocol required procedures (see Section 5, Table 3 for EOT and follow up assessment schedule). All new treatment-related AEs occurring within 30 calendar days from treatment discontinuation must be reported and followed until resolution, unless, in the opinion of the investigator, these events are not likely to improve because of the underlying disease. In this case the investigators must record the reason for not conducting the 30-day safety evaluation in the subject's medical records and as a comment on the electronic Case Report Form (eCRF).

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

Subjects who discontinue from the study will have an End of Study visit (EOS - see Section 5, Table 3).

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Table 2 below lists all required assessments that should be performed at each study visit. Table 3 provides more specific follow-up assessments for subjects on Arm B after Cycle 6, as well as for subjects who permanently discontinue study treatment but remain on study, and for subjects who initiate non-study treatment, have confirmed disease progression or withdraw consent from participating in the study.

Table 2: STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Cycle = 28 days	Screen*	Cycle 1[1]				Cycles 2-6[2]						All Arms, Cycles 9, 12, 15, 18 and q 3 cycles thereafter[3]	EOS
						C2		C3	C4	C5	C6		
Procedure\Days	-28-1	D1	D2[4]	D8	D15	D1	D15	Day 1				Day 1	
Medical history	X												
Rai Staging	X												
ECOG Performance Status	X	X				X		X	X	X	X	X	X
Physical examination	X	X				X		X	X	X	X	X	X
Vital signs (pulse, BP, temp)	X	X	X	X	X	X	X	X	X	X	X	X	X
BM aspirate/biopsy[5]	X												
12-lead EKG	X												
Disease evaluation[6]	X	Every 3 cycles for the first 24 cycles. After Cycle 24, every 6 cycles unless clinically indicated sooner. Subjects off treatment but on study should have response assessments approximately every 6 months unless clinically indicated sooner.											
Serology: HCV, HBV, CMV[7]	X												
CMV Screening								X[8]			X[8]	X[8]	
MRD[9]						For subjects in PR or CR beginning at the Cycle 6 response assessment							
Hematology[10]	X	X	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												
Serum Pregnancy Test[11]	X												
Urine Pregnancy Test[15]						X		X	X	X	X	X	
β_2-microglobulin	X												
CLL Mutation Panel[12]	X												
[redacted]													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation[14]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Samling[16]		X			X			X			X	X (Cycle 12 only)	
Treatment Schedules													
ARM A: Ublituximab Dose		X	X	X	X	X		X	X	X	X	q 3 mos after cycle 6	
ARM A: TGR-1202 Dose		Days 1 – 28 (Daily)											
ARM B: Obinutuzumab Dose		X	X	X	X	X		X	X	X	X		
ARM B: Chlorambucil Dose		X			X	X	X	Day 1 & 15					
ARM C: Ublituximab Dose		X	X	X	X	X		X	X	X	X	q 3 mos after cycle 6	
ARM D: TGR-1202 Dose		Days 1 – 28 (Daily)											
***Randomize Day -7 to 1**													

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

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

[4] Cycle 1 Day 2, and Cycle 2 Day 15 visits only required for subjects randomized into Arms A, B, & C.

[5] Unilateral bone marrow aspirate and/or biopsy performed at investigator discretion in subjects for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility. 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 Cycle 1 Day 1. All tumor evaluations post baseline assessments have a +/- 14 day window. Radiology assessment should include CT or MRI imaging of neck, chest, abdomen, and pelvis. All CT and/or MRI scans **must** be submitted for central review – see Central Radiology Manual.

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

[8] Q3 months CMV screening by PCR for all subjects on Arm A and Arm D. CMV surveillance will discontinue 30 days after last dose of umbralisib.

[9] Peripheral Blood sample draw (See study manual for all central lab instructions. +/- 14 day window for MRD sample). For subjects MRD negative by peripheral blood, a bone marrow sample should be completed to confirm MRD negativity. If subject is unable to complete or refuses, another peripheral blood sample should be collected to assess the MRD negativity at least 12 weeks later. MRD should continue to be evaluated at response assessment intervals until MRD negative while in PR/CR

[10] Must be obtained prior to ublituximab or obinutuzumab administration if on day of infusion.

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

[12] For del(13q), del(11q), del(17p), and (12)trisomy, t(11:14), and IgHV mutation status

[redacted]

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

[15] For women of child-bearing potential only

[16] For Arms A and C only. See Section 5.1.5 (see Lab Manual for detailed description of the procedures for immunogenicity sampling, processing and shipping)

TABLE 3: FOLLOW-UP EOT AND EOS ASSESSMENT SCHEDULE

Procedures	Arm B Follow Up Post Cycle 6	Discontinued Study Treatment without PD (All Treatment Arms)	Initiated Non-Study Treatment, Confirmed PD by Central Radiology or Withdrew Consent from Study
ECOG Performance Status	x	X[2]	
Physical Exam	x	X[2]	
Vital Signs	x	X[2]	
Hematology	x	X[2]	
Chemistry	x	X[2]	
Con Meds	x[3]	X[3]	
AE Evaluation	x	X[2]	
Disease Evaluations[1]	x[1]	x[1]	
End Of Treatment (EOT) eCRF Page	x	X	x
Post Treatment Visits	x	X[2]	
End Of Study (EOS) Visit[4]			x
Long Term Follow Up Visits[5]			x

[1] Response assessment should be performed approximately every 6 months unless clinically indicated sooner. All response assessments must be submitted for central radiology review.
[2] Approximately every 3 months until disease progression that has been confirmed by central radiology review.
[3] Con meds assessment at treatment discontinuation only.
[4] EOS visit should be documented in EDC once subject has PD, starts non-study therapy, or withdraws consent from study.
[5] Long Term Follow up for Overall Survival should be entered approximately every 6 months. Enter date of disease progression and/or death occurred in eCRF

5.1 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.

5.1.1 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

Hematologic and Serum Chemistry windows as follows:

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

2. Serum β-HCG test.

3. Coagulation lab tests to include PT and INR.
4. Beta2-microglobulin
5. Serum Virology to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM. If HBc antibody, HCV antibody or CMV IgG and/or IgM are positive the subject must be evaluated for the presence of active HBV, HCV or CMV by PCR - See Appendix D. **CMV surveillance every 3 months for all subjects on Arm A and Arm D. CMV surveillance will discontinue 30 days after last dose of umbralisib.**
6. Baseline bone marrow aspirate/biopsy (if applicable)
7. Fluorescence in situ hybridization (FISH) of peripheral blood for 13q deletion, 11q deletion, 17p deletion, trisomy 12, t(11:14); DNA sequencing for IgHV mutation status**.**

5.1.2 CENTRAL LABORATORY ASSESSMENTS

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

1. Minimal Residual Disease (MRD) assessment for subjects in PR or CR beginning at Cycle 6 response assessment.

[redacted]

[redacted]

6 TREATMENT PLAN

6.1 TREATMENT SUMMARY

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

Treatment Schema Overview

ARM A: Ublituximab + TGR-1202

Cycle 1:

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

Cycles 2 through 6:

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

After Cycle 6:

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

ARM B: Obinutuzumab + Chlorambucil

Cycle 1:

Obinutuzumab			Chlorambucil
Day 1	**Day 2**	**Day 8 & 15**	**Day 1 & 15**
100 mg	900 mg	1000 mg	0.5 mg/kg

Cycles 2 through 6:

Obinutuzumab	Chlorambucil
Day 1	**Day 1 & 15**
1000 mg	0.5 mg/kg

After Cycle 6:

No Further Treatment

ARM C: Ublituximab (if applicable)

Cycle 1:

- 150 mg Ublituximab on Day 1
- 750 mg Ublituximab on Day 2
- 900 mg Ublituximab on Days 8 & 15

Cycles 2 through 6:

- 900 mg Ublituximab on Day 1

After Cycle 6:

- 900 mg Ublituximab on Day 1, every 3 cycles (i.e. Cycle 9, 12, 15, etc.)

ARM D: TGR-1202 (if applicable)
Cycle 1, and Onward:

- 800 mg TGR-1202 once daily until removal from study

6.2 AGENT ADMINISTRATION

Ublituximab and obinutuzumab treatment will be administered as an IV infusion while TGR-1202 and chlorambucil will be self-administered orally, all on an outpatient basis.

6.2.1 GUIDELINES FOR ADMINISTRATION OF OBINUTUZUMAB & CHLORAMBUCIL

Guidelines for administration of obinutuzumab and chlorambucil are per the FDA approved prescribing information. Please refer to www.gazyva.com (U.S. only) or www.gazyvaro.com (ex-U.S. sites) for the most up to date information.

- *Method of Administration:* Obinutuzumab will be administered as an IV infusion and chlorambucil will be administered orally, each in accordance with prescribing information
- *Potential Drug Interactions*: There are no known drug-interactions with obinutuzumab or chlorambucil
- *Pre-medications:* Pre-medicate before each dose of obinutuzumab according to the following table:

Day of Treatment Cycle	Subjects requiring premedication	Premedication	Administration
Cycle 1: Day 1, Day 2	All subjects	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[1]	Completed at least 1 hour prior to GAZYVA infusion.
		650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion
		anti-histamine (e.g., 50 mg diphenhydramine)	
All subsequent infusions	All subjects	650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
	Subjects with an IRR (Grade 1-2) with the previous infusion	650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	
	Subjects with a Grade 3 IRR with the previous infusion OR with a lymphocyte count > 25 x 10^9 /L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[1]	Completed at least 1 hour prior to GAZYVA infusion
		650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	

[1] Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.

- Subjects with high tumor burden and/or high circulating absolute lymphocyte counts (greater than 25 x 10^9/L) should be pre-medicated with anti-hyperuricemics (e.g., allopurinol) beginning 12–24 hours prior to start of therapy. Ensure adequate hydration for prophylaxis of tumor lysis syndrome. Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for subjects with CLL during treatment and for up to 12 months following treatment as per investigator discretion. See prescribing information for more information.

6.2.1.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE -OBINUTUZUMAB

General Concomitant Medication and Supportive Care Guidelines

Obinutuzumab can cause severe and life-threatening infusion reactions. Two thirds of subjects experienced a reaction to the first 1000 mg infused of obinutuzumab. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Pre-medicate subjects with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed. Closely monitor subjects during the entire infusion. Infusion reactions within 24 hours of receiving obinutuzumab have occurred.

For subjects with any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction: Stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.

For subjects with Grade 1, 2, or 3 infusion reactions: Interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.

For subjects with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable. For subjects at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested.

Please refer to the FDA approved prescribing information and www.gazyva.com (U.S. sites) or www.gazyvaro.com (ex-U.S. sites) for the most up to date information including warnings and precautions, adverse reactions, and boxed warnings.

6.2.1.2 DISPENSING OF OBINUTUZUMAB

Before use, the obinutuzumab vials should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

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

The Pharmacist or his/her representative should record the date dispensed and subject's number and initials, as well as complete the accountability forms with information concerning the dispensation of obinutuzumab. Preparation should be done by the Pharmacist or his/her representative according to instructions for sterile dilution.

6.2.1.2.1 DILUTION OF OBINUTUZUMAB

Prepare the solution for infusion, using aseptic technique, as follows:

- Inspect visually for any particulate matter and discoloration prior to administration.
- Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%).
- Preparation of solution for infusion on day 1 (100 mg) and day 2 (900 mg) of Cycle 1:
    - Withdraw 40 mL of GAZYVA solution from the vial.
    - Dilute 4 mL (100 mg) of GAZYVA into a 100 mL 0.9% sodium chloride infusion bag for immediate administration.
    - Dilute the remaining 36 mL (900 mg) into a 250 mL 0.9% sodium chloride infusion bag at the same time for use on day 2 and store at 2°C to 8°C (36°F to 46°F) for up to 24 hours. After allowing the diluted bag to come to room temperature, use immediately.
    - Clearly label each infusion bag.
- Preparation of solution for infusion on day 8 and 15 of Cycle 1 and day 1 Cycles 2–6:
    - Withdraw 40 mL of GAZYVA solution from the vial.
    - Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag.
- Mix diluted solution by gentle inversion. Do not shake or freeze.
- For microbiological stability, the diluted GAZYVA infusion solution should be used immediately. Dilute under appropriate aseptic conditions. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use.
- The product can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.

The intravenous solution should be prepared and dispensed by the clinical research center pharmacist and should be infused by a qualified nurse with experience in monitoring the administration of chemotherapeutic agents.

6.2.2 GUIDELINES FOR ADMINISTRATION OF CHLORAMBUCIL

- *Method of Administration:* Chlorambucil will be administered orally Days 1 & 15 of Cycles 1 - 6
- *Potential Drug Interactions*: There are no known drug-interactions with obinutuzumab in combination with chlorambucil. See chlorambucil prescribing information more information.
- *Pre-medications:* None

Chlorambucil will be self-administered (by the subject). Subjects should be instructed to swallow the tablets as a whole and should not chew or crush them.

If a dose of chlorambucil is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should be taken the next day. If vomiting occurs, no attempt should be made to replace the vomited dose.

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

6.2.3 GUIDELINES FOR ADMINISTRATION OF UBLITUXIMAB

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line.
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* Ublituximab should be started approximately 30 minutes after the conclusion of the last pre-medication infusion and should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). If pre-medication is given orally, administer pre-medication approximately 45-60 minutes prior to the beginning of the ublituximab infusion. If the subject has a negative reaction to a pre-medication, the investigator may consider decreasing its dose, using a different drug or discontinue if not tolerated. Additionally, if a subject has other health conditions that are adversely impacted by a pre-medication, the investigator may consider decreasing its dose, switching premedication to a different drug or discontinue if clinically appropriate.
  - Use of oral acetaminophen 650 mg (or equivalent) should be restricted to subjects who experience fever or pyrexia after week 1 dose, or as clinically warranted.
- *Hypersensitivity and Infusion Reaction Precautions*: Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions.
- *Subject Care Implications*:
  - Ublituximab should not be administered as an IV push or bolus.
  - Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if does not conform to the specifications. Immediately inform the Monitor/Sponsor with any product quality concerns or questions.
  - It is recommended that ublituximab be administered immediately after dilution.
  - No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
  - Concurrent glucocorticoid therapy if started at least 7 days prior to study entry (≤ 10 mg per day of prednisone or equivalent) is allowed as clinically warranted.
  - Since infusion-related hypotension may occur, **consider holding antihypertensive medications 12-24 hours prior to and throughout infusion of ublituximab.**
  - For subjects at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

6.2.3.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE - UBLITUXIMAB

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

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) in which treatment should be interrupted. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

1st or 2nd Infusion Interruption:

- Hold infusion and closely monitored subject, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the Investigator and provided the subject is stable, the infusion may be resumed at no more than half the previous rate.
- If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate at the treatment cycle dose (see Section 6.2.3.2.

3rd Infusion Interruption (same day):

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

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

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

6.2.3.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

Cycle 1 Day 1 & 2 infusion over 4 hours

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

Cycle 1 Day 8 & 15 infusions over 3 hours

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

Cycle 2 and remaining infusions over 90 minutes

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

6.2.3.3 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or his/her representative must check that the ublituximab is in accordance with the product specifications and the validity is within the re-test date. The exact dose and the date and time of administration of ublituximab must be recorded within the eCRF, subject's medical records, and/or in the drug accountability records.

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

6.2.3.3.1 DILUTIONS OF UBLITUXIMAB

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

[redacted]

Dilutions for Cycle 1 Day 1 & Day 2

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

Dilutions for ≥Cycle 1 Day 8 Infusions

Dose of ublituximab for infusion	[redacted]
900 mg	

[redacted]

Dilutions for Cycle 1 Day 1 & Day 2

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

Dilutions for ≥Cycle 1 Day 8 Infusions

Dose of ublituximab for infusion	[redacted]
900 mg	

6.2.4 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:* For subjects randomized to Treatment Arms A and D which include TGR-1202, subjects are required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PJP) and antiviral therapy prior to Cycle 1, Day 1. Choice and dose of PJP and anti-viral prophylaxis therapy is at the investigator discretion. Recommended prophylactic agents are provided below:
  - Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent
  - PJP Prophylaxis: Dapsone 100 mg daily or equivalent.

    If anti-viral or anti-bacterial prophylaxis is not tolerated, the investigator may consider an alternate dose and/or dosing regimen, using a different prophylactic agent as well as discontinuing prophylaxis. Final choice of PJP and anti-viral prophylaxis therapy is per investigator discretion.

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

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

If a dose of TGR-1202 is missed, it should be taken as soon as possible on the same day. If it is missed for a period greater than 12 hours, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

6.2.4.1 DISPENSING OF TGR-1202

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, subject's medical records, and/or in the drug accountability records. For the purpose of drug accountability and dosing, subjects should record any missed doses of 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 subject'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.

6.2.5 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that subject has:

- No drug-related toxicity that warrants permanent study treatment discontinuation.
- No radiographic evidence of disease progression that is confirmed by central radiology review.
- Not withdrawn consent from the study for other reasons.

6.3 DOSING DELAYS AND MODIFICATIONS

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

If greater than 2 cycle delay is necessary for recovery of toxicities to levels outlined in Sections 6.3.1, 6.3.2 and 6.3.3, re-initiation of treatment is at the discretion of the investigator. Contact TG Therapeutics prior to re-initiating treatment with any questions. If a subject discontinues treatment due to toxicity, then the subject should continue to be followed for progression as described for end of treatment (EOT) assessments (Section 5, Table 3). If a subject withdraws consent from the study, begins a non-study treatment or has documented progression by central radiology, an end of study (EOS) visit should be completed (Section 5, Table 3).

6.3.1 DOSE DELAY/MODIFICATIONS: OBINUTUZUMAB AND/OR CHLORAMBUCIL

No reduction in the dose of obinutuzumab is permitted. Chlorambucil dose reductions are described below. A dose delay is permitted for chlorambucil or obinutuzumab to allow recovery of hematologic toxicities to ≤ Grade 2 or non-hematologic toxicities to Grade 1 or baseline level. If chlorambucil is discontinued, obinutuzumab may continue at the discretion of the investigator.

If obinutuzumab is discontinued, the subject is withdrawn from study treatment. If a subject discontinues treatment due to toxicity or has completed 6 cycles of treatment with obinutuzumab (and chlorambucil, if applicable), and the subject does not have disease progression that is confirmed by central radiology review, then the subject should continue to be followed for progression as described for end of treatment (EOT) assessments (Section 5, Table 3). If a subject withdraws consent from the study, begins a non-study treatment or has documented progression by central radiology, an end of study (EOS) visit should be completed (Section 5, Table 3). If a Grade 3 or 4 cytopenia prevents treatment on day 15 of any cycle, the day 15 chlorambucil dose will be skipped. Obinutuzumab + Chlorambucil administration on day 1 of the following cycle will be given if the cytopenia has resolved to ≤ Grade 2. If the cytopenia persists, obinutuzumab + chlorambucil administration will be delayed until the cytopenia has improved to ≤ Grade 2.

If a subject experiences Grade 3 or 4 cytopenia, the guidelines for dose delay (chlorambucil and obinutuzumab) and dose reduction recommendations (chlorambucil only) are outlined the table below:

NCI-CTCAE Grade	Chlorambucil	Obinutuzumab
Grade 3 or 4 cytopenia	Delay dosing for a maximum of one cycle Administer G-CSF for neutropenia or platelets or red blood cells as required. First episode: If improvement to ≤ Grade 2*, decrease chlorambucil dose to 75% of initial dose for subsequent cycles Second episode: If improvement to ≤ Grade 2*, decrease chlorambucil dose to 50% of initial dose for subsequent cycles Third episode: Discontinue chlorambucil	Delay dose for a maximum of one cycle If improvement to ≤ Grade 2*, administer full dose If chlorambucil is discontinued obinutuzumab may continue at the investigator discretion.
Grade 1 or 2 cytopenia	No dose reduction or delay	No dose reduction or delay

*or baseline

Obinutuzumab can cause severe, including fatal, infusion reactions. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue obinutuzumab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.

To ensure reference to the most up to date information, please see www.gazyva.com (U.S. sites) or www.gazyvaro.com (ex-U.S. sites).

6.3.2 DOSE DELAY: UBLITUXIMAB

No reduction in the dose of ublituximab is permitted. Please refer to Section 6.2.3.1 and 6.2.3.2 for detailed information on infusion rate guidance for infusion related reactions related to ublituximab.

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenia or Grade ≥ 1 non-hematologic toxicities. A delay of treatment is permitted for both study drugs (individually or together) for recovery of toxicities to levels outlined in Sections 6.3.2 and 6.3.3. If a delay greater than 2 cycles is necessary for either drug, re-initiation of treatment is at the discretion of the investigator. Contact TG Therapeutics prior to re-initiating treatment with any questions. If a subject discontinues treatment due to toxicity, then the subject should continue to be followed for progression according to EOT assessments (Section 5, Table 3). If the subject withdraws consent, begins a new treatment, or has documented progression, an end of study (EOS) visit should be completed.

If a subject in Arm A discontinues only one study drug (either ublituximab or TGR-1202), the subject may continue treatment with the other study drug per the protocol.

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

TABLE 4: DOSE DELAY GUIDELINES: UBLITUXIMAB

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 3 neutropenia	Maintain current dose. Consider supportive care as warranted.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Delay ublituximab until Grade ≤ 3 and/or neutropenic fever or infection is resolved; consider growth-factor support as warranted; thereafter, resume at full dose. .
Thrombocytopenia	

Grade ≤3 thrombocytopenia	Maintain current dose level and provide supportive care as clinically warranted.
Grade 4 thrombocytopenia	Delay ublituximab until Grade ≤ 3; consider intervention with supportive care as warranted; thereafter resume at full dose.
Non-Hematological Adverse Events	
Grade ≤2	Maintain current dose level
Grade ≥3	Withhold ublituximab until Grade ≤ 2 at the discretion of the investigator; consider supportive care intervention as warranted. Resume at full dose or if delay >

6.3.3 DOSE DELAY/MODIFICATIONS: TGR-1202

Supportive care should be considered for any subject who experiences Grade ≥ 2 cytopenia, or Grade ≥ 1 non-hematologic toxicities. A delay for recovery from toxicity is allowed for all study drugs (ublituximab and/or TGR-1202: individually or together) to allow recovery of toxicities to levels outlined in Sections 6.3.2 and 6.3.3. If a delay greater than 2-cycles is necessary for either study drug, re-initiation of treatment is at the discretion of the investigator. Contact TG Therapeutics prior to re-initiating treatment with any questions. If a subject discontinues treatment due to toxicity, then the subject should continue to be followed for progression – See Table 3 in Section 5. If a subject withdraws consent, begins a non-protocol treatment, or has documented progression, an end of study visit should be completed (Section 5, Table 3).

If a subject in Arm A discontinues one study drug, the subject may continue treatment with the other study drug per the protocol.

TABLE 5: TGR-1202 DOSE DELAY AND/OR MODIFICATIONS GUIDANCE

NCI-CTCAE Grade	Dose Delay and/or Modification
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.
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.
***For sinopulmonary infections clearly not related to immune-mediated pneumonitis, TGR-1202 may be continued at investigator's discretion. 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-viral prophylaxis is required at start of therapy.**	

Liver Injury (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Grade 1	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Monitor Labs every 1-2 weeks
Grade 2	• Maintain current dose • Assess Concomitant Medications and Risk Factors* • Begin supportive care (40-60 mg prednisone orally per day or equivalent) ** • Monitor labs at least weekly until Grade 1 • Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off. o If liver injury recurs to Grade 2 once off steroids, re-initiate steroids with 10 mg per week taper until off. o Consider withholding umbralisib. If delay is greater than 2 cycles notify TG Therapeutics prior to re-initiation.
Grade ≥3	• Hold Umbralisib. If delay is greater than 2 cycles notify TG Therapeutics prior to re-initiation. • Assess Concomitant Medications and Risk Factors* • Begin/continue supportive care (40-60 mg prednisone orally per day or equivalent) ** • Monitor labs at least weekly until Grade 1 • Once resolved to Grade ≤1, taper prednisone by 10 mg per week until off • Resume -1 dose level when Grade ≤1
* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc. **Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc. Important: Before initiating steroids, check for viral hepatitis or CMV infection.	
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.
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 > 2 cycles notify TG Therapeutics prior to re-initiation. 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 > 2 cycles notify TG Therapeutics prior to re-initiation. If recurrence after rechallenge, resume at next lower dose level at discretion of the investigator.

TABLE 6: STUDY DRUG DOSE LEVELS

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

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

If a subject 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 OBINUTUZUMAB AND CHLORAMBUCIL

6.4.1 OBINUTUZUMAB AND CHLORAMBUCIL

The obinutuzumab and chlorambucil to be used in this study should be obtained from available commercial source. Costs for obinutuzumab and chlorambucil should be submitted for insurance reimbursement. However, if such costs are not covered by the medical insurance for the subject, please see Study Manual for further instructions.

6.5 ORDERING UBLITUXIMAB AND 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 subject is identified, a shipment of pre-determined quantity of ublituximab and 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 both ublituximab and TGR-1202. If any abnormality on the supplied boxes (ublituximab) or 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.

6.6 DURATION OF THERAPY

During the study period, response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner. Date of progression, beginning of new treatment, and/or death should be entered in the eCRF.

The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC). Subjects will remain on study treatment until the occurrence of definitive disease progression confirmed by central radiology, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Subjects who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression confirmed by central radiology.

For subjects in Arms B, C and D with definite disease progression (as confirmed by the IRC), a single-arm companion study will be available in select participating countries only. In this companion study, compliant subjects who are tolerating primary study therapy are eligible to receive ublituximab in combination with TGR-1202, at the dose used in Arm A.

7 STUDY MEDICATION OVERVIEW AND SAFETY

7.1 OBINUTUZUMAB

Chemical Name:	obinutuzumab
Other Names:	Gazyva®, Gazyvaro®
Classification:	Humanized monoclonal antibody
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Glycoengineered humanized monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells.
How Supplied:	Supplied in 1000-mg (40-mL) single-use vials.
Storage:	Obinutuzumab vials are stable at 2°C–8°C (36°F–46°F). Vials should be protected from direct sunlight and should not be frozen or shaken.
Stability:	Diluted obinutuzumab solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and are known to be stable for an additional 48 hours at room temperature.
Route of Administration:	Intravenous
Availability:	Obinutuzumab is commercially available from Genentech/Roche.

7.2 CHLORAMBUCIL

Chemical Name:	chlorambucil
Other Names:	Leukeran®
Classification:	alkylating agent of the nitrogen mustard type
Mode of Action:	interferes with DNA replication and induces cellular apoptosis
How Supplied:	Supplied as brown, film-coated tablets, containing 2 mg chlorambucil
Storage:	Refer to chlorambucil prescribing information
Route of Administration:	Oral
Availability:	Chlorambucil is available commercially.

7.2.1 ADVERSE EVENTS

Please see obinutuzumab and chlorambucil full prescribing information for detailed information. Common adverse reactions (≥25%) in clinical trials of CLL for obinutuzumab in combination with chlorambucil were infusion reactions and neutropenia. Warnings and Precautions for obinutuzumab include; infusion reactions, tumor lysis syndrome, neutropenia, thrombocytopenia, infections, anemia, pyrexia, cough, nausea, diarrhea, and cytopenias. Fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus reactivation and Progressive Multifocal Leukoencephalopathy (PML) can occur in subjects receiving obinutuzumab. Additionally, do not administer live virus vaccines prior to or during obinutuzumab therapy.

7.3 UBLITUXIMAB

Chemical Name:	ublituximab
Other Names:	TG-1101
Classification:	Recombinant chimeric anti-CD20 monoclonal antibody
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.
How Supplied:	Concentration of 10 mg/mL in 15 mL (150 mg) or 25 mg/mL in 6 mL (150 mg) single-use glass vials.
Storage:	Ublituximab must be stored in a secured limited-access refrigerated area at a temperature ranging from 2°C - 8°C. Ublituximab must not be frozen.
Stability:	Once a vial of ublituximab has been opened and/or diluted it must be used immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions it is stable for 8 hours at 25°C. Ublituximab has a shelf-life of 36 months if stored between 2°C - 8°C, based on stability data.
Route of Administration:	Intravenous
Packaging:	Ublituximab is packed in kits. Each kit contains: • Six vials containing 150 mg solution of ublituximab each or • One vial containing 150 mg solution of ublituximab (for replacement if needed)

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

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

Availability: Ublituximab is available from TG Therapeutics.

7.3.1 UBLITUXIMAB - COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in subjects treated with single agent ublituximab and were considered at least possibly related to the study medication. The preliminary safety data as of May 01, 2018 is provided for a total of 117 subjects exposed to single agent ublituximab with a maximum follow up of 2+ years. See the latest ublituximab Investigator's Brochure for updated safety information a complete list of all adverse events reported regardless of causality.

7.3.1.1 VERY COMMON (≥ 10%)

Blood and Lymphatic System Disorders: neutropenia, thrombocytopenia

General Disorders and Administration Site Conditions: pyrexia

Injury, Poisoning and Procedural Complications: infusion related reaction

Nervous System Disorders: headache

7.3.1.2 COMMON (≥ 2% - < 10%)

Blood and Lymphatic System Disorders: anemia, pancytopenia

Gastrointestinal Disorders: diarrhea, abdominal pain, nausea, oral pruritus

General Disorders and Administration Site Conditions: fatigue, asthenia, chills, oedema peripheral, pain

Hepatobiliary Disorders: cytolytic hepatitis

Infections and Infestations: herpes zoster

Investigations: aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased

Musculoskeletal and Connective Tissue Disorders: muscular weakness

Nervous System Disorders: dysgeusia

Respiratory, Thoracic and Mediastinal Disorders: throat irritation, throat tightness

Skin and Subcutaneous Tissue Disorders: pruritus, hyperhidrosis

Vascular Disorders: hypertension

7.4 TGR-1202 (UMBRALISIB)

Classification:	Phosphatidylinositol-3-Kinase (PI3K) Delta Inhibitor
Formulation:	See Investigator Brochure
Mode of Action:	Irreversibly inhibits activity of the Class I Delta isoform of PI3K
How Supplied:	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.

7.4.1 TGR-1202 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

The following adverse events were observed in subjects treated with single agent umbralisib and were considered at least possibly related to the study medication. The preliminary safety data as of May 01, 2018 is provided for a total of 136 subjects exposed to single agent umbralisib with a maximum follow up of 5+ years. See the latest umbralisib Investigator's Brochure for updated safety information a complete list of all adverse events reported regardless of causality.

7.4.1.1 VERY COMMON (≥10%)

Blood and Lymphatic System Disorders: neutropenia

Gastrointestinal Disorders: nausea, diarrhoea, vomiting

General Disorders and Administration Site Conditions: fatigue

7.4.1.2 COMMON (≥ 2% - < 10%)

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

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: vision blurred

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

General Disorders and Administration Site Conditions: pyrexia, oedema peripheral

Infections and Infestations: pneumonia, oral candidiasis

Injury, Poisoning and Procedural Complications: contusion

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

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

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

Nervous System Disorders: dizziness, headache, dysgeusia, tremor

Psychiatric Disorders: insomnia

Respiratory, Thoracic and Mediastinal Disorders: cough

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

7.4.2 UBLITUXIMAB + TGR-1202 – COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPRS)

The following adverse events were observed in subjects treated with the combination of ublituximab + umbralisib and were considered at least possibly related to one or both of the study medications. The preliminary safety data as of May 01, 2018 is provided for a total of 75 subjects exposed to ublituximab + umbralisib with a maximum follow up of 3+ years. See the latest ublituximab and umbralisib Investigator's Brochures for updated safety information a complete list of all adverse events reported regardless of causality.

7.4.2.1 VERY COMMON (≥ 10%)

Blood and Lymphatic System Disorders: anemia, neutropenia

Gastrointestinal Disorders: diarrhea, nausea, vomiting

General Disorders and Administration Site Conditions: fatigue

Injury, Poisoning and Procedural Complications: infusion related reaction

Metabolism and Nutrition Disorders: decreased appetite

7.4.2.2 COMMON (≥ 1% - < 10%)

Blood and Lymphatic System Disorders: thrombocytopenia

Cardiac Disorders: cardiac failure congestive

Ear and Labyrinth Disorders: ear congestion, ear discomfort

Eye Disorders: conjunctival pallor, conjunctivitis, corneal oedema, vision blurred

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastrooesophageal reflux disease, haematochezia, salivary hypersecretion, stomatitis

General Disorders and Administration Site Conditions: asthenia, chills, face oedema, infusion site pain, local swelling, odedema peripheral, pyrexia, systemic inflammatory response syndrome

Hepatobiliary Disorders: hyperbilirubinaemia

Immune System Disorders: hypogammaglobulinaemia

Infections and Infestations: bronchitis, cellulitis, clostridium difficile colitis, enterocolitis infectious, oral candidiasis, oral herpes, otitis media, pneumonia, pneumonia streptococcal, rhinovirus infection, sepsis, sepsis syndrome, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection

Injury, Poisoning and Procedural Complications: wound

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, computerised tomogram thorax abnormal, immunoglobulins decreased, weight decreased

Metabolism and Nutrition Disorders: dehydration, failure to thrive, hyperglycaemia, hyperuricaemia, hypokalaemia, hypophosphataemia

Musculoskeletal and Connective Tissue Disorders: joint swelling, muscle spasms, muscular weakness, myalgia, pain in extremity

Nervous System Disorders: dizziness, dysgeusia, headache, lethargy, sinus headache, somnolence

Psychiatric Disorders: agitation, anxiety

Renal and Urinary Disorders: micturition urgency, renal failure, renal failure acute

Reproductive System and Breast Disorders: scrotal cyst, semen discolouration

Respiratory, Thoracic and Mediastinal Disorders: choking, cough, dysphonia, dyspnea, epistaxis, hypoxia, oropharyngeal pain, pneumonitis, productive cough, sinus congestion

Skin and Subcutaneous Tissue Disorders: alopecia, cold sweat, dermatitis acneiform, dermatitis bullous, dry skin, ecchymosis, pruritus, rash, maculo-papular, rosacea, urticaria

Vascular Disorders: hypertension

8 MEASUREMENT OF EFFECT

During the study period, response assessments should be obtained every 3 cycles for the first 24 cycles. After Cycle 24, evaluate for response approximately every 6 cycles unless clinically indicated sooner. Subjects followed for PFS off treatment should have response assessments done approximately every 6 months unless clinically indicated sooner. Date of progression, beginning of new treatment, and/or death should be entered in the eCRF. After baseline assessment, all efficacy assessments have a +/- 14-day window. The determination of response and progression will be based on IWCLL criteria (Hallek M, 2008). Radiographic and clinical disease assessments will be subject to independent confirmation by the Independent Review Committee (IRC). The findings of the IRC will be considered primary for analyses of ORR, PFS, and other efficacy endpoints.

CT scan is the preferred method of tumor assessment, but MRI may be used at the investigator's discretion. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the study. Please see study manual for detailed instructions for disease assessment, and submission of scans for independent review.

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

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

8.1 METHOD OF ASSESSMENT

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

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

All relevant clinical and radiographic information required to make each disease assessment must be made available for source verification and for submission to the IRC.

8.2 RESPONSE REVIEW

An Independent Review Committee (IRC) will provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in disease status. The subject should continue study treatment pending confirmation of progression status.

The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of the IRC's processes and reading methods will be described in an independent review charter developed by the contracted imaging facility in conjunction with the Sponsor.

8.3 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

8.3.1 TARGET LESIONS

At baseline, up to 6 lymph nodes should be selected as target lesions that will be used to quantify the status of the disease during study treatment. Ideally, the target lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as target lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

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

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

A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD will be considered progressive disease.

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

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

8.3.2 SPLEEN AND LIVER

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

By imaging, the spleen will be considered enlarged if it is >12 cm in LVD, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (e.g., if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

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

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the spleen in its LVD or decrease to ≤ 12 cm by imaging is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% from nadir (minimum increase of 2 cm) is required for declaration of splenic progression. By imaging, the liver will be considered enlarged if it is >18 cm in LVD.

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

8.3.3 NON-TARGET LESIONS

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

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

8.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

Responses will be categorized by the IRC as CR, CRi, nPR, PR, SD, or PD. In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

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

disease progression the smallest measurements recorded since treatment started). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

8.5 COMPLETE RESPONSE

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

- No evidence of new disease
- ALC in peripheral blood of <4 x 10^9/L
- Regression of all target nodal masses to normal size ≤1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-target disease and disappearance of all detectable non-nodal, non-target disease
- Morphologically negative bone marrow defined as <30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood counts meeting all of the following criteria:
  - ANC >1.5 x 10^9/L without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count ≥100 x 10^9/L without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

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

8.6 PARTIAL RESPONSE

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

- No evidence of new disease
- A change in disease status meeting ≥2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: 1) only lymphadenopathy is present at baseline; 2) only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:
  - In a subject with baseline lymphocytosis (ALC ≥4 x 10^9/L), a decrease in peripheral blood ALC by ≥50% from baseline or a decrease to <4 x 10^9/L
  - A decrease by ≥50% from the baseline in the SPD of the target nodal lesions
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 8.3.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 8.3.2
  - A decrease by ≥50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- No target, splenic, liver, or non-target disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting 1 of the following criteria:
  - ANC >1.5 x 10^9/L or >50% increase over baseline without need for exogenous growth factors (e.g., G-CSF)

- Platelet count ≥100 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors
- Hemoglobin ≥110 g/L (11.0 g/dL) or ≥50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (e.g., erythropoietin)

8.7 STABLE DISEASE

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

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

8.8 DEFINITIVE DISEASE PROGRESSION

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

- Evidence of any new disease:
  - A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD
  - New or recurrent splenomegaly, with a minimum LVD of 14 cm
  - New or recurrent hepatomegaly, with a minimum LVD of 20 cm
  - Unequivocal reappearance of an extra-nodal lesion that had resolved
  - A new unequivocal extra-nodal lesion of any size
  - *New non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL).

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

- Evidence of worsening of target lesions, spleen or liver, or non-target disease:
  - Increase from the nadir by ≥50% from the nadir in the SPD of target lesions
  - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
  - Splenic progression, defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
  - Hepatic progression, defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)
  - Unequivocal increase in the size of non-target disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)
  - Transformation to a more aggressive histology (e.g., Richter's syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).

- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells
  - The current platelet count is <100 x 10^9/L and there has been a decrease by >50% from the highest on-study platelet count

- The current hemoglobin is <110 g/L (11.0 g/dL) and there has been a decrease by >20 g/L (2 g/dL) from the highest on-study hemoglobin

If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression; in such subjects, both CLL-related and non-CLL-related causes for the constitutional symptoms should be considered.

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

8.9 NON-EVALUABLE

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

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

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

8.10 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of TGR-1202, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) may occur. The onset of isolated lymphocytosis usually occurs during the first few weeks of TGR-1202 therapy and usually resolves within three to four months. Subjects with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (i.e., disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy.

9 STATISTICAL CONSIDERATIONS

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.

9.3 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population will consist of all randomized subjects, regardless of administration of study treatment (ublituximab, TGR-1202, obinutuzumab + chlorambucil or ublituximab + TGR-1202). Analyses of this population will assign subjects the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications. Subjects who received treatment in the group that is different from what they have been randomized to, will be noted in the Clinical Study Report. The ITT population is the primary analysis population for efficacy analyses.

The safety population will include all randomized subjects who received at least one dose of study treatment (ublituximab, TGR-1202, obinutuzumab + chlorambucil, or ublituximab + TGR-1202). Subjects who are included in a treatment group that is different from what they have been randomized to will be noted.

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

9.4 SUBJECTS DISPOSITION

Subject disposition summaries will be presented by treatment arm and will include the number of subjects enrolled, randomized, and the number and percentage of randomized subjects in the ITT and safety populations. The summaries will also include the reasons for permanent discontinuation of study treatment and study. Disposition by investigational sites will also be presented.

9.5 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

9.6 MEDICAL HISTORY

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

9.7 EXTENT OF EXPOSURE

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

9.8 EFFICACY ANALYSES

Each subject will be assigned to one of the following categories: 1) complete response (CR or CRi), 2) partial response (PR or nPR), 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

Many of the efficacy measures will be based on disease assessments. The best clinical response as well as disease progression will be determined by an independent review committee (IRC) which will be blinded to treatment arm assignment. Definitive disease progression will be based on standard criteria (Hallek et al. 2008, Appendix A – CLL Response Definition) occurring for any reason

(e.g., increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis.

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 duration of progression-free survival (PFS).

9.10.1.1 PROGRESSION-FREE SURVIVAL

Duration of PFS is defined as the number of days between randomization and the date of progression (as confirmed by the IRC) or death due to any cause. The duration of PFS for subjects who progress and then subsequently die will be the number of days between randomization and the date of progression is first observed.

Hypothesis testing for comparison between the treatment arms will be performed using a stratified (by randomization stratification factors) log-rank test via [redacted] For each treatment arm, the median duration of PFS and the proportion of subjects alive and progression-free at 6, 12, and 18 months will be estimated using the Kaplan-Meier method. For each estimate, a 95% confidence interval will be reported.

The primary objective that Treatment A is superior to Treatment B will be tested at an overall two-sided 0.04 level of significance.

Unless earlier established at the interim analysis for ORR, contribution of the individual components will be analyzed according to the testing plan described in the UTX-TGR-304 Statistical Analysis Plan which will be conducted in agreement with the FDA.

9.10.2 SECONDARY EFFICACY OUTCOMES

Other secondary efficacy outcomes include: Overall Response Rate (ORR), CR rate, Minimal Residual Disease (MRD) negativity, Duration of response (DOR), and overall survival (OS).

9.10.2.1 OVERALL RESPONSE RATE

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

Overall Response Rate (ORR) is defined as percent of subjects who achieve CR, CRi, nPR, or PR. The response rate will be analyzed using a Cochran-Mantel-Haenzel (CMH) test stratified by the

randomization factors. The 95% confidence intervals for the response rates as well as for the differences of the response rate will be presented.

The key secondary objective that Treatment A provides additional clinical benefit over treatments C alone and D alone will be tested a two-sided 0.01 level of significance at the interim (when the first 50 subjects enrolled into each arm provided ORR assessment).

Contribution of the individual components based on ORR will be analyzed according to the testing plan described in the UTX-TGR-304 Statistical Analysis Plan which will be conducted in agreement with the FDA.

If contributions of individual components based on ORR is established at the interim ORR analysis, a formal test of ORR between Treatment A will be tested conducted at a two- sided 0.01 level following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis.

9.10.2.2 CR RATE

CR rate is defined as the percent of subjects who achieve a CR or CRi. CR rate will be analyzed using a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. The 95% confidence intervals for the response rates as well as for the differences of the complete response rate will be presented.

9.10.2.3 MINIMAL RESIDUAL DISEASE NEGATIVITY

The MRD negativity rate is defined as the proportion of subjects who achieve MRD negativity post-baseline. MRD is assessed only amongst responders, defined as subjects achieving CR/CRi/PR/nPR. Subjects who do not have an MRD assessment at any post-baseline visits will be considered non-responders and will be included in the denominator when calculating MRD negativity rate. MRD negativity rate will be analyzed in the ITT population using a Cochran-Mantel-Haenzel (CMH) test stratified by the randomization factors. The 95% confidence intervals for the MRD negativity rates as well as for the differences of the MRD negativity rate will be presented.

9.10.2.4 DURATION OF RESPONSE

Duration of response (DOR) defined as the interval from the first documentation of CR, CRi, nPR, or PR to the earlier of the first documentation of definitive disease progression or death from any cause. The Kaplan-Meier estimator for DOR will be presented for patients who achieve an objective response in each treatment arm. The same censoring rules will be applied as for PFS.

9.10.2.5 OVERALL SURVIVAL

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

[redacted]

9.11 MULTIPLE COMPARISON PROCEDURES

The study has the following three pre-specified primary efficacy evaluations:

1. Assessing whether Treatment A is superior to Treatment B based on PFS;
2. Assessing contributions of individual components in Treatment A established based on PFS;
3. Assessing contributions of individual components in Treatment A established based on ORR;

Contributions of individual components of Treatment A will be established if positivity is established for either #2 or #3, above.

To control for the overall Type I error rate at 0.05, an overall two-sided p-value of 0.01 will be used to evaluate #3, at the interim analysis when the first 50 patients in Treatment Arms A, C, and D have provided adequate ORR data (at least one post-baseline disease assessment). If contributions of individual components in Treatment A based on ORR is established at the interim ORR analysis, a formal test of ORR between Treatment A and Treatment B will be conducted at a two-sided 0.01 level following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis. Analysis of CR rate and MRD negativity rate will also be conducted sequentially at the two-sided 0.01 level.

The remaining overall two-sided p-value of 0.04 will be used to evaluate #1 (and to evaluate #2 if #3 is not earlier established to be positive). If #1 is established to be positive and #3 has not been established to be positive at the interim ORR analysis for contribution, the following assessments will be evaluated at the overall two-sided 0.04 significance level to establish #2:

1. Assessing whether treatment A is superior to Treatment C regarding PFS; and
2. Assessing whether treatment A is superior to Treatment D regarding PFS.

[redacted]

To control for the overall Type I error rate, a claim cannot be made unless all proceeding claims, if any, are made. For completeness, all p-values will be presented.

9.12 INTERIM ANALYSES

One interim analysis based on ORR will be performed when approximately 50 subjects each in Arms A, B, C and D have provided disease assessments to determine ORR status. If contributions of individual components in Treatment A based on ORR is established at the interim ORR analysis, a secondary claim that Treatment A is superior over Treatment B based on ORR will be tested at a two-side 0.01 level following a positive interim PFS analysis or, if the interim PFS analysis is negative, following the final PFS analysis. Further, should contribution be established at the interim ORR analysis, enrollment into both Arms C and D will be terminated, however enrollment into Arms A and B will continue until 175 patients have been enrolled into each arm. If contribution was unable to be established by ORR at the interim analysis, both single agent arms C and D will be evaluated for PFS.

One interim analysis based on PFS will be performed solely for purposes of assessing futility at approximately 50% information time (140 events). A second interim PFS analysis will be conducted at the later to occur of i) 75% information time (210 events), and ii) December 10, 2019, to evaluate the superiority hypothesis for Arm A compared to Arm B. At this interim analysis, early study termination will be guided by an O'Brien-Fleming monitoring boundary that is preserving the (one-sided) 0.0005 false positive error rate. At 75% of the events (i.e., 210 PFS events), the corresponding Z-value would be 3.81, with corresponding nominal two-sided p=0.00013. If early termination does not occur, nearly all of the two sided 0.04 false positive error rate allocated to PFS would have been preserved, statistical significance for PFS at the 280 event final analysis would be achieved with Z-value 2.06. The study will end either at the second interim PFS analysis or at the final PFS analysis.

An independent DSMB has been established and will conduct all interim analyses in addition to reviewing clinical data periodically throughout the trial. The DSMB may recommend stopping or modifying the trial for safety.

10 SAFETY REPORTING AND ANALYSIS

10.1 SAFETY ANALYSES

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented by the dose of ublituximab, TGR-1202, obinutuzumab + chlorambucil and/or the combination of ublituximab + TGR-1202 study drug actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

10.2 ADVERSE EVENT CHARACTERISTICS

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

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Expected AEs are defined as those described in the ublituximab Investigator Brochure and the TGR-1202 Investigator Brochure. Please refer to the obinutuzumab as well as chlorambucil prescribing information for a listing of expected AEs.

10.3 DEFINITIONS OF ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

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

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

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

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

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

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

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

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

10.5 ADVERSE EVENTS / SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the relationship of any adverse event to the use of study drugs (whether none, one, or both), based on available information, using the following guidelines:

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

10.5.1 RECORDING OF ADVERSE EVENTS

All adverse events of any subject during the course of the study will be reported on the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to study drug treatment (i.e., whether the event is related or unrelated to study drug administration – either ublituximab, TGR-1202, obinutuzumab + chlorambucil or ublituximab + 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 ublituximab, TGR-1202, obinutuzumab + chlorambucil or ublituximab + TGR-1202 treatment spanning from Cycle 1/Day 1 until 30 calendar days after discontinuation or completion of either protocol-specific treatment (Arm B subjects should complete at end of study (EOS) visit) as defined by the protocol for that subject, are to be recorded on the eCRF.

10.5.2 ABNORMAL LABORATORY VALUES AND VITAL SIGNS

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

Clinical Laboratory Results will be summarized. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized, and graded per NCI CTCAE Version 4.0 when applicable. Subject incidence of abnormal laboratory results will be summarized by treatment group and maximum grade for each abnormal laboratory finding.

10.5.3 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study should be followed until resolution or stabilization. Subjects should be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment (either ublituximab, TGR-1202, obinutuzumab + chlorambucil or ublituximab + TGR-1202). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the eCRF. After

30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

10.6 SERIOUS ADVERSE EVENTS

10.6.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

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

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

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per IWCLL Hallek et al. 2008, should not be reported as a serious adverse event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is suspected to be at least possibly related to study medication(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-subject 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 (including study-specific infusions)
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

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

10.6.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

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

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

To report an SAE, see the appropriate form.

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

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

The investigator must review and sign off on the SAE data on the SAE report. The SAE should be reported to the Sponsor (or Sponsor designee) as outlined in the Safety Monitoring Plan.

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

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

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

10.7 SPONSOR SAE REPORTING REQUIREMENTS

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

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

10.8 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

10.9 DIAGNOSIS VS. SIGNS AND SYMPTOMS

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

10.9.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

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

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

10.9.2 ABNORMAL LABORATORY VALUES

Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require or prolong inpatient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

10.9.3 DEATHS

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

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

10.9.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission of >24 hours or prolongs hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. See section 10.6.1.

10.9.5 PRE-EXISTING MEDICAL CONDITIONS

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

10.9.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

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

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

During the course of the study, all female subjects of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix B- Contraceptive Guidelines and Pregnancy) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

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

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

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

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

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment (either ublituximab, TGR-1202, obinutuzumab + chlorambucil or ublituximab + TGR-1202) that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, subjects should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary/Second Primary Malignancy

Any secondary and/or second primary malignancy event must be reported via the SAE form (in addition to the routine AE reporting mechanisms). Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in the protocol.

11 DATA SAFETY MONITORING BOARD (DSMB)

An independent Data Safety Monitoring Board (DSMB) has be established to advise the Sponsor on safety and provide benefit/risk oversight of the study as described in the DSMB Charter. This independent DSMB will review the study clinical data at regular intervals or as necessary. The DSMB may advise the Sponsor to terminate the study early or modify the protocol to address safety signals that they may identify.

12 CLINICAL DATA COLLECTION AND MONITORING

12.1 SITE MONITORING PLAN

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

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

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

12.2 CURRICULA VITAE AND FINANCIAL DISCLOSURES

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

12.3 DATA OWNERSHIP AND PUBLICATION

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

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

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

13 GCP, 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).

13.1 IRB APPROVAL

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

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

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

13.2 REGULATORY APPROVAL

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

Safety updates for ublituximab and/or TGR-1202 will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

13.3 INSURANCE AND INDEMNITY

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

13.4 INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

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

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

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

13.5 CONFIDENTIALITY

Subject Confidentiality

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

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

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

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

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

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

13.6 INVESTIGATOR AND STAFF INFORMATION

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

13.7 FINANCIAL INFORMATION

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

14 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

14.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

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

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

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

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

14.2 STUDY DOCUMENTATION AND STORAGE

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

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

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

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

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

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

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

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

14.3 AMENDMENTS TO THE PROTOCOL

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

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

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

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

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

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

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

14.4 DATA COLLECTION

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

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

14.5 STUDY MONITORING, AUDITING, AND INSPECTING

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

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

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

14.6 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to the Clinical Monitoring component of this protocol, the Sponsor's Quality Assurance (QA) department shall establish an Auditing Plan document separate from the protocol to establish the criteria by which independent auditing shall be conducted during the conduct of the study to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

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

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

As this is an open-label study, to protect data integrity, the following procedures will be implemented to ensure all clinical and statistical decisions are made in a treatment blinded manner. The Sponsor, except for Clinical Operations personnel monitoring the study and the Medical Monitor, will be blinded to treatment assignment and specific dosing data within the three individual treatment arms. In addition, unblinded Clinical Operations personnel will not be involved in any discussions regarding the analysis of data after enrollment of the first subject into the trial or any protocol amendment, except those related to safety.

14.7 DISCLOSURE AND PUBLICATION POLICY

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

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

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

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

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

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

15 REFERENCES

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

American Cancer Society. (2014). *American Cancer Society.* Retrieved June 5, 2014, from www.cancer.org: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

Cazin B, L. S. (2013). Final results of a multicenter phase Ib single agent study with the novel anti-CD20 monoclonal antibody ublituximab (TG-1101) in patients with relapsed chronic lymphocytic leukemia (CLL). *European Hematology Assocation*, (p. abstractP111). Stockholm.

de Romeuf C, D. C.-T.-B. (2008). Chronic lymphocytic leukaemia cells are effeciently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. *British Journal of Haematology, 6*(140), 635-643.

Esteves IT, D. C. (2011). LFB-R603 (ublituximab), a third-generation monoclonal anti-CD20 antibody, displays additive antitumor activity with antileukemic chemotherpeutic agents in mouse xenograft models. *American Society of Hematology*, abstract 1660.

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

Hallek M, C. B.-C. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Wrokshop on Chronic Lymphocytic Leukemia updating the National Cancer Institue - Wroking Group 1996 Guidelines. *blood, 12*(111), 5446-5456.

Lin K, S. P. (2002). Relationship between p53 dysfunction, CD38 expression and IgVH mutatin in chronic lymphcytic leukemia. *blood*, 1404.

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

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

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

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

16 APPENDIX A – CLL RESPONSE DEFINITION

Assessment of response will follow the guidelines published by Hallek et al. (2008).

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

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

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

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

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

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

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008;111:5446-56.

17 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 a) 4 months after the last treatment dose if randomized to treatment Arms A, C, or D; or b) 18 months after the last treatment dose of obinutuzumab and 4 weeks after the last dose of chlorambucil if randomized to Arm B. The highly effective contraception is defined as either:

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

The following are **unacceptable** forms of contraception for women of childbearing potential:

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

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

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use a condom during treatment, and for a) 4 months after the last treatment dose if randomized to treatment Arms A, C, or D; or b) 18 months after the last treatment dose of obinutuzumab and 4 weeks after the last dose of chlorambucil if randomized to Arm B, and should not father a child in this period.

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to TG Therapeutics Inc. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug and reported by the investigator to TG Therapeutics Inc. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

18 APPENDIX C – NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

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

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

Interpretation of Hepatitis B Serologic Test Results

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

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

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

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

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

CDC

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