Official Title:	**A Phase 3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL)**
NCT Number:	NCT02301156
Document Date:	Protocol Version 2.5: 31 July 2017

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Local Protocol #: Protocol UTX-IB-301

TITLE:

A Phase 3, Randomized, Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL).

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

IND Number: **Ublituximab:** 114,779

Study Chair: Study Chair
[redacted], MD
[redacted]
Tel: [redacted] (Office)

Medical Monitor: [redacted], MD
Tel: (212) 554-4484

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

Version: 1.0	**Date:** 9 September 2014
Version: 1.1	**Date:** 30 September 2014
Version: 2.0	**Date:** 8 October 2016
Version: 2.1	**Date:** 21 October 2016
Version: 2.2	**Date:** 27 January 2017
Version: 2.5	**Date:** 31 July 2017

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol UTX-IB-301 for issuance.

Protocol Title:	**A Phase 3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL)**
Protocol Number:	UTX-IB-301
Study Drugs:	Ublituximab (TG-1101) + Ibrutinib Versus Ibrutinib
IND Number:	114,779
Date FINAL:	31 July 2017

MEDICAL MONITOR, TG Therapeutics, Inc.

[redacted] MD — [redacted] — 10/20/17
Print Name — Date

STUDY CHAIR, [redacted]

[redacted] MD — [redacted] — 10/20/17
Print Name — Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted] — DocuSigned by: [redacted] — 10/21/2017
Print Name — Signature — Date

[redacted] MS, MSF — [redacted] — 23 Oct 2017
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 Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL).**
Protocol Number:	UTX-IB-301
Study Drug:	Ublituximab (TG-1101) + Ibrutinib Versus Ibrutinib
IND Number:	**Ublituximab** 114,779
Date FINAL:	31 July 2017

I have read the attached protocol and agree that it contains all the necessary details for performing UTX-IB-301.

I will provide copies of the protocol and of the ublituximab Investigators' Brochure, which was given to me by TG Therapeutics (Sponsor), to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding ublituximab and Ibrutinib, 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 8 October 2016) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- Sponsor and Study Coordination address updated;
- [redacted]
- Further clarification was provided for inclusion criteria #1b, central FISH analysis can be performed on study UTX-IB-301 or on a separate TGTX-LAB-001 screening protocol;
- 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 phrasing of response assessment intervals has been revised for clarity from "after cycles 2, 4, and 6 then at weeks 8, 16, 24, 36, 48 and every 12 weeks thereafter," to "after the completion of cycles 2, 4, 6 then after the completion of every 3 cycles thereafter" and it was further clarified that patients being followed for PFS off treatment should have evaluations done every 3 months;
- MRD will be evaluated in all patients achieving a PR or CR following the Cycle 6 response assessment as opposed to previously only in patients achieving a CR;
- Schedule of assessments and treatment schedule (Section 7) was updated, including
    - Revised wording for Tumor Evaluation (as listed above);
- Ublituximab packaging has been updated from "one 15 mL vial containing 10 mg/mL solution of ublituximab" to "six 15 mL vials containing 10 mg/mL solution of ublituximab or one 15 mL vial containing 10 mg/mL solution of ublituximab (for replacement if needed)";
- Sections 9.1.1 and 9.2.2 have been updated to include the latest CAEPRS information;
- Clarification was provided in Section 10.3.1 to better describe appropriate selection of target lesions; and
- Appendix D has changed from "Inhibitors of CYP3A" to "Hepatitis B Serologic Test Results". "Inhibitors of CYP3A" is now Appendix E.

Version 2.1 (Dated 21 October 2016) of this Protocol is the second amendment to this clinical trial and contains the following modification:

- The Intent-to-Treat population has been updated to now include all patients who received at least one dose of study medication, instead of all randomized patients. All ORR and safety analysis will now be based on the ITT population

Version 2.2 (Dated 27 January 2017) of this Protocol is the third amendment to this clinical trial and contains the following modification:

- The primary analysis population has been updated

Version 2.5 (Dated 31 July 2017) of this Protocol is the fourth amendment to this clinical trial and contains the following modifications:

- Sections 8.2.1.3.1 and 9.1 were updated to include information regarding the new concentration and vial size of ublituximab
- Sections 9.1 and 9.2 have been updated to include the latest CAEPRS information for ublituximab, ibrutinib, and the combination of ublituximab and ibrutinib.
- Section 10.3.1 has been updated to remove the following statement: "At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be

considered. Because nodal target lesions that have one or both diameters >0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2 (i.e., if all lymph nodes measure < 1.0 cm^2)."

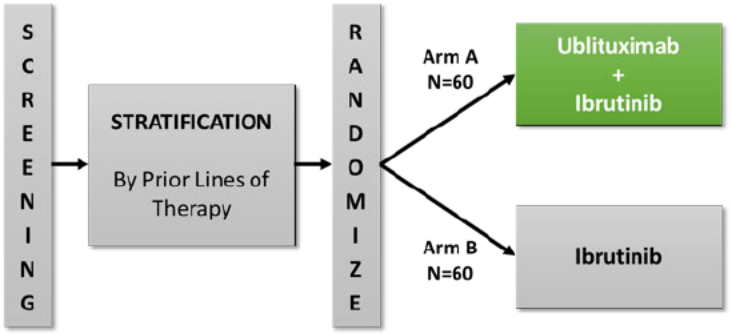
Protocol no.	UTX-IB-301
Study Title	A Phase 3 Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination with Ibrutinib Compared to Ibrutinib Alone, in Patients with Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL)
Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Sites & Enrollment	Up to 200 study sites may participate in this study. Enrollment is expected to take approximately 18 - 24 months
Study Rationale	With the advent of novel targeted therapies, the paradigm of treatment for patients with Chronic Lymphocytic Leukemia (CLL) is rapidly evolving away from chemotherapy based regimens, which while active, result in considerable toxicity to patients. Novel non-chemotherapy based therapies have demonstrated greater clinical benefit than current standard of care regimens with the added benefit of significantly greater tolerability. Despite the introduction of these novel targeted agents, CLL remains an incurable disease. Furthermore, the presence of certain cytogenetic abnormalities is associated with 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 patients with relapsed/refractory CLL, especially in those patients with cytogenetic abnormalities. 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. Ibrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK), an enzyme found in the B-Cell Receptor pathway which has been found to regulate B-cell proliferation and survival. Ibrutinib is currently approved for the treatment of patients with relapsed or refractory Chronic Lymphocytic Leukemia. Both ibrutinib and ublituximab have displayed single agent activity in patients with relapsed or refractory CLL (Byrd et al, 2013, Deng et al, 2014), acting with separate, non-overlapping mechanisms of action. An ongoing Phase II with Safety Run-in evaluating the combination of ublituximab and ibrutinib (NCT02013128) has demonstrated an acceptable safety profile with clinical activity beyond that observed to date with each agent alone. As reported at the 2014 European Hematology Association meeting (EHA) by Sharman, et. al., the combination of ublituximab plus ibrutinib achieved a 90% ORR with all patients achieving at least 35% reduction in tumor volume. These data support the potential for clinical efficacy that can address nodal and peripheral blood activity in patients with an unmet medical need.

Study Objectives	PRIMARY OBJECTIVE • To evaluate the effect of the addition of ublituximab to ibrutinib on antitumor activity, as measured by the overall response rate (ORR = CR + PR) in patients with previously treated CLL with documented high-risk cytogenetics. SECONDARY OBJECTIVES • To evaluate the effect of the addition of ublituximab to ibrutinib on complete response (CR) rate. • To evaluate the effect of the addition of ublituximab to ibrutinib on the rate of patients achieving minimum residual disease (MRD) negativity. • To evaluate the effect of the addition of ublituximab to ibrutinib on progression-free survival (PFS), duration of response (DOR) and time to response (TTR). • To describe the safety profile observed with the addition of ublituximab to ibrutinib. [redacted]
Inclusion Criteria	Participants must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Diagnosis of B-cell CLL, with diagnosis established according to IWCLL criteria [Hallek 2008] and documented within medical records. Patients must have: a. Received at least 2 cycles of one prior standard treatment regimen (*NOTE: Prior anti-CD20 antibody or cytotoxic drugs, including investigational or commercially available therapies, may have been administered as single agents or as components of combination therapies*) b. High-risk cytogenetics confirmed by FISH analysis (presence of at least one of the following: 17p deletion, 11q deletion and/or P53 gene mutation). Central FISH analysis can be performed on UTX-IB-301 study or the TGTX-LAB-001 screening protocol. 2. CLL that warrants treatment consistent with accepted IWCLL criteria for initiation of therapy. Any 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/L), 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. 3. Adequate organ system function, defined as follows: a. Absolute neutrophil count (ANC) ≥ 750 / platelet count ≥ 40,000 *(patients with bone marrow infiltration due to CLL are eligible if their ANC is ≥ 500)* 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) 4. 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) 5. ECOG performance status ≤ 2 6. Male or female ≥ 18 years of age 7. Ability to swallow and retain oral medication 8. Female patients who are not of child-bearing potential (see Appendix B-Contraceptive Guidelines and Pregnancy), and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1, Day 1. Female patients of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception throughout the study period and for 30 days after the last dose of either study drug. 9. Willingness and ability to comply with study and follow-up procedures, [redacted] and give written informed consent.

Exclusion Criteria	1. Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of randomization (contact sponsor for < 21 day washout period requests) a. Corticosteroid therapy started at least 7 days prior to study entry (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted. 2. 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 patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by DNA (PCR) - See Appendix D. 4. Known histological transformation from CLL to an Aggressive lymphoma (i.e. Richter's transformation) 5. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion. 6. Patients requiring treatment with moderate or strong CYP3A inhibitors/inducers. 7. 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. 8. 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. 9. Patients in which ibrutinib therapy is medically contraindicated. 10. Women who are pregnant or lactating. 11. Current participation in another therapeutic clinical study. 12. Previous therapy with ibrutinib, CC-292, or any drug that specifically inhibits Bruton's tyrosine kinase (BTK).

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. **Duration of Response (DOR)** Defined as the interval from the first documentation of CR or PR to the first documentation of disease progression or death from any cause. **Complete Response (CR) Rate** CR rate is defined as the proportion of patients who achieve a CR. **Minimal Residual Disease (MRD) Negativity Rate** MRD negativity rate is defined as the proportion of patients who are MRD negative, excluding any patients who remain on study treatment at the time of the analysis and have a Cycle 1/Day 1 start date less than 6 months from the time of the analyses. For the sake of clarity, the MRD negative analysis will exclude those patients that are too early to evaluate because MRD negativity is only tested for patients on study ≥ 6 months. Patients who drop off study for any reason prior to their 6 month visit will be included in the analysis. **Time to response (TTR)** TTR is defined as the interval from randomization to the first documentation of CR or PR
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) will be established to advise the Sponsor on safety and ethical issues of the study.
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 tumor status.
[redacted]	[redacted]

	[redacted]
Study Design	The study is designed as a fixed-dose, randomized, two-arm, Phase 3 study to evaluate the efficacy and safety of the addition of ublituximab to ibrutinib in patients with previously treated chronic lymphocytic leukemia who have at least one high-risk cytogenetic abnormality (17p deletion, 11q deletion, and/or P53 gene mutation). The study will evaluate the effect of the addition of ublituximab to ibrutinib on overall response rate (ORR = CR + PR) in all study patients who are evaluable for efficacy assessment. **Study Schema**  Following screening, patients meeting the inclusion/exclusion criteria will be randomized in a 1:1 ratio to either Arm A or Arm B. Randomization will be stratified according to prior lines of therapy (1 prior line vs. ≥2 or more prior lines). During the study period, patients will be evaluated for response by CT and/or MRI after the completion of cycles 2, 4, and 6 then after the completion of every 3 cycles thereafter if under treatment or every 3 months if in follow up. Clinical response for the efficacy objectives of this study will be determined by an Independent Review Committee (IRC). Patients should remain on study treatment until the occurrence of definitive disease progression (as confirmed by the IRC), unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression. The study will continue until all planned study patients (approximately 120) have been enrolled. Upon first assessment scan, or confirmation scan, if necessary, of the last planned study patient and site submission of all required efficacy and safety data, the independent Data and Safety Monitoring Board (DSMB) will review the primary and secondary efficacy analyses and safety data.

Ublituximab Premedication

ARM A Study Patients Only:
Pre-medicate approximately 30 minutes prior to each ublituximab dose with an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (e.g. dexamethasone 10-20 mg or equivalent). Use of corticosteroids as a premedication after cycle 6 is at the discretion of the investigator. Use of oral acetaminophen 650 mg (or equivalent) may be used in patients who have a history of or experience fever or pyrexia, or as clinically warranted.

For all patients at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

Dosing Regimen & Treatment Study Visits

Cycle 1:

Arm A				*Arm B*
Ublituximab			**Ibrutinib**	**Ibrutinib**
Day 1	Day 2	Day 8 & 15	Daily	Daily
Up to 150mg	750 mg	900 mg	420 mg	420 mg

Cycles 2 through 6:

Arm A		*Arm B*
Ublituximab	**Ibrutinib**	**Ibrutinib**
Day 1 Cycles 2, 3, 4, 5, 6	Daily	Daily
900 mg	420 mg	420 mg

Beyond Cycle 6:

Arm A		*Arm B*
Ublituximab	**Ibrutinib**	**Ibrutinib**
every 3 months thereafter	Daily	Daily
900 mg	420 mg	420 mg

Study Drugs

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

Ibrutinib (Imbruvica®) is a small molecule inhibitor of BTK, available in 140 mg capsules supplied by Pharmacyclics, Inc. / Janssen, Inc.

Statistical Considerations

Sample Size:

Analysis Populations:
The intent-to-treat (ITT) population will include all randomized patients. The "Treated Population" will include all randomized patients who received at least one dose of study medication. The primary efficacy analysis will be

	performed on the ITT and Treated Population. The secondary efficacy analysis and safety analysis will be performed on the Treated Population according to the actual treatment regimen received. **Efficacy Analyses:** Demographic (e.g., gender, age, race, ethnicity) and baseline characteristics (e.g., performance status, height, weight, and prior therapy) will be summarized with descriptive statistics. For each part of the study, ORR, as determined by the IRC, will be compared between treatment groups by a Cochran-Mantel-Haenzel test with adjustment for the randomization stratification factors. The CR and MRD negativity rates will be compared between treatment groups using the same methodology as in the analysis of ORR. **Safety Analyses:** Treatment-emergent AEs through 30 days after last dose of study treatment will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™), Version 13.1 (or higher), System Organ Class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. The severity of AEs will also be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0 (or higher) grade and by causality (relationship to study treatment). Grade 3 and 4 AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will also be summarized by preferred term. Laboratory results will be classified according to NCI-CTCAE, Version 4.0 (or higher). Laboratory results not corresponding to an NCI-CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics. Vital signs and physical examination results will be summarized with descriptive statistics.

2 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
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
eCRF	Electronic Case Report Form
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
LPD	Longest Perpendicular Diameter
LTFU	Long-Term Follow Up

Abbreviations and Definitions of Terms	
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
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
ULN	Upper limit of normal
UTX	Ublituximab
V	Visit
Vd	Volume of distribution
WHO	World Health Organization

3 INTRODUCTION

3.1 CLL

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). Patients with 17p deletion show higher resistance to conventional chemotherapies as well as shorter duration of survival than non 17p deletion patients. Patients with 11q deletion have been associated with marked lymphadenopathy (Hallek M, 2008). Patients with P53 gene mutations are associated with an adverse clinical outcome (Lin 2002).

Chemotherapy regimens in combination with monoclonal antibody therapy comprise the current standard of care for patients with CLL, with novel targeted agents now entering the market. Frontline therapy for patients 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 patient, 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 patients 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 patients will progress and eventually die from their disease. Furthermore, patients 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 patients with relapsed/refractory CLL, especially those with cytogenetic abnormalities.

3.2 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).

3.2.1 PRE-CLINICAL EVALUATIONS OF UBLITUXIMAB

3.2.1.1 IN VITRO ACTIVITY

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

3.2.1.2 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).

3.2.1.3 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).

3.2.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB - CLL

Ublituximab has been studied in a variety of patient populations, both as a single agent, and in combination with other agents, with over 100 patients 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 patients, with a total of 41 patients 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 patients 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), patients 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 patients were enrolled at 9 centers

in France and followed for 12 months. Demographic data for the 12 patients 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 patients (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 patients, including 33% of patients 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 patients: 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 (Cazin B, 2013).

Clinical response was based on the criteria established by the National Cancer Institute (NCI)-Working Group updated in 2008 (Hallek M, 2008). All patients but one received the planned 8 infusions without any dose reduction--one patient was prematurely withdrawn due to a concomitant secondary leukemia unrelated to ublituximab therapy. Response was evaluated at month 4 for the 11 evaluable patients, with an initial response rate of 64% (7/11) with a confirmed response at month 6 in 5/11 patients (45%) patients (all PRs). Four of the 11 patients 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 patients with B-cell lymphoma who were relapsed or refractory to a prior rituximab containing regimen, which included 8 patients 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 patients enrolled into the dose-escalation component, and expansion cohorts were subsequently undertaken at 600, 900, and 1200 mg. Patients 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 patients enrolled, 4 had infusion related reactions that were manageable with infusion interruptions only and all patients 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 patients were evaluable for efficacy as of data cutoff for ASCO 2014, with 4 out of 6 patients 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).

3.2.2.1 PHARMACOKINETICS

After infusion of ublituximab (previously known as LFB-R603) at 150 mg dose followed by seven weekly injection infusions at 450 mg, results suggested non-linear pharmacokinetics with respect to dose (450 mg vs. 150 mg) and time (week 4 vs. week 8); and more than proportional increase of Cmax and AUC∞ due to a clearance decrease. The volume of distribution at steady state was small (~5 L), approximately equal to blood volume. These non-linear pharmacokinetics may be explained

by binding of ublituximab to its target, with a large component of target-mediated elimination after the first dose that is decreased after subsequent infusions due to a reduction in the available target. However, limited data for each dose level cohort and considerable variability in baseline patient characteristics, particularly in terms of tumor burden, make firm conclusions difficult.

The linear mean serum concentration-times profile after the first, the fourth and the eight 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 EIGTH INFUSION OF UBLITUXIMAB

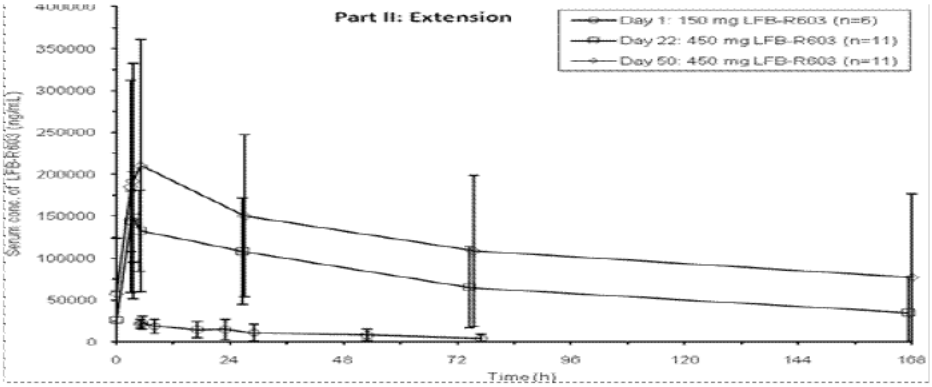


TABLE 1: PHARMACOKINETIC RESULTS AFTER THE 1ST (150MG), THE 4TH (450 MG) AND THE 8TH (450MG) INFUSION OF UBLITUXIMAB

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

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

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

3.3 IBRUTINIB

Ibrutinib is a selective and irreversible inhibitor of Bruton's Tyrosine Kinase (BTK), an enzyme found in the B-Cell Receptor pathway which has been found to regulate B-cell proliferation and survival. Ibrutinib has demonstrated single-agent activity in a number of B-cell malignancies including CLL/SLL, MCL, DLBCL, and WM. Ibrutinib is currently approved for the treatment of patients with relapsed or refractory MCL and the treatment of patients with relapsed or refractory CLL, and is manufactured and supplied by Janssen and Pharmacyclics, Inc. For more information on the safety and efficacy profile of ibrutinib, refer to the ibrutinib label available at www.imbruvica.com.

3.4 UBLITUXIMAB IN COMBINATION WITH IBRUTINIB

Both ublituximab and ibrutinib target, deplete, and inhibit the proliferation of B-lymphocytes through separate and non-overlapping mechanisms of action. Ongoing Phase 3 studies are evaluating therapeutic regimens consisting of other, non-glycoengineered or ADCC optimized, anti-CD20 antibodies in combination with ibrutinib or other kinase inhibitors targeting related pathways, with early signs of tolerability and promising clinical activity.

Consequently, a Phase II study was undertaken to establish the safety and preliminary efficacy of the combination of ublituximab and ibrutinib in patients with relapsed or refractory CLL and MCL. Ublituximab was dosed at 600 and 900 mg in patients with CLL and at 900 mg in patients with MCL, with infusions on Days 1, 8, and 15 of Cycle 1, and on Day 1 of Cycles 2 through 6, with ibrutinib administered daily. As of the data cutoff for the European Hematology Association 2014 meeting, 28 patients were evaluable for safety, with 10 patients evaluable for efficacy.

The combination regimen was well tolerated with infusion related reaction being the most common adverse event reported (29%), followed by diarrhea (21%), rash (21%), and fatigue (18%).

Responses among the 10 evaluable patients are below:

Type	Pts (n)	CR n (%)	PR n (%)	nPR n (%)	SD n (%)	PD n (%)	ORR n (%)
CLL	7	-	6 (86)	-	1 (14)	-	6 (86)
MCL	3	1 (33)	2 (67)	-	-	-	3 (100)
Total	10	1 (10)	8 (80)	-	-	-	9 (90)

The addition of ublituximab appears to abrogate the ibrutinib related lymphocytosis, with a median 79% decrease in ALC from baseline among patients by Cycle 4, with 3/5 CLL patients for whom data was available showing a normalization of ALC (<4000/uL).

4 OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVE

- To evaluate the effect of the addition of ublituximab to ibrutinib on antitumor activity, as measured by the overall response rate (ORR = CR + PR) in patients with previously treated CLL with high-risk cytogenetics.

SECONDARY OBJECTIVES

- To evaluate the effect of the addition of ublituximab to ibrutinib on complete response (CR) rate.
- To evaluate the effect of the addition of ublituximab to ibrutinib on the rate of patients achieving minimum residual disease (MRD) negativity.
- To evaluate the effect of the addition of ublituximab to ibrutinib on progression-free survival (PFS), duration of response (DOR), and time to response (TTR).
- To describe the safety profile observed with the addition of ublituximab to ibrutinib.

[redacted]

4.1 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.

Duration of Response (DOR)
Defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression or death from any cause.

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

Minimal Residual Disease (MRD) Negativity Rate
MRD negativity rate is defined as the proportion of patients who are MRD negative, excluding any patients who remain on study treatment at the time of the analysis and have a Cycle 1/Day 1 start date less than 6 months from the time of the analyses. For the sake of clarity, the MRD negative analysis will exclude those patients that are too early to evaluate because MRD negativity is only tested for patients on study ≥ 6 months. Patients who drop off study for any reason prior to their 6-month visit will be included in the analysis.

Time to Response (TTR)
TTR is defined as the interval from randomization to the first documentation of CR or PR

5 ELIGIBILITY CRITERIA

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

5.1 INCLUSION CRITERIA

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

1. Diagnosis of B-cell CLL, with diagnosis established according to IWCLL criteria [Hallek 2008] and documented within medical records. Patients must have:
    a. Received at least 2 cycles of one prior standard treatment regimen (*NOTE: Prior anti-CD20 antibody or cytotoxic drugs, including investigational or commercially available therapies, may have been administered as single agents or as components of combination therapies*)
    b. High-risk cytogenetics confirmed by FISH analysis (presence of at least one of the following: 17p deletion, 11q deletion and/or P53 gene mutation). Central FISH analysis can be performed on UTX-IB-301 study or the TGTX-LAB-001 screening protocol.
2. CLL that warrants treatment consistent with accepted IWCLL criteria for initiation of therapy. Any 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/L), 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.
3. Adequate organ system function, defined as follows:
    a. Absolute neutrophil count (ANC) $\geq$ 750 / platelet count $\geq$ 40,000
    (patients with bone marrow infiltration due to CLL are eligible if their ANC is $\geq$ 500)
    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)

4. 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)
5. ECOG performance status ≤ 2
6. Male or female ≥ 18 years of age
7. Ability to swallow and retain oral medication.
8. Female patients not of child-bearing potential (see Appendix B- Contraceptive Guidelines and Pregnancy), and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior Cycle 1, Day 1. Female patients of child-bearing potential, and male partners must consent to use a medically acceptable method of contraception during the study period and for 30 days after the last dose of either study drug.
9. Willingness and ability to comply with study and follow-up procedures, [redacted] and give written informed consent.

5.2 EXCLUSION CRITERIA

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

1. Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any investigational drug within 21 days of randomization (contact sponsor for < 21- day washout period requests)
    a. Corticosteroid therapy started at least 7 days prior to study entry (prednisone ≤10 mg daily or equivalent) is allowed as clinically warranted. Topical or inhaled corticosteroids are permitted.
2. 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 patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV is positive, the subject must be evaluated for the presence of HBV, HCV, or CMV by DNA (PCR) - See Appendix D.
4. Known histological transformation from CLL to an Aggressive lymphoma (i.e. Richter's transformation)
5. Evidence of ongoing systemic bacterial, fungal or viral infection, except localized fungal infections of skin or nails. NOTE: Patients may be receiving prophylactic antiviral or antibacterial therapies at investigator discretion.
6. Patients requiring treatment with moderate or strong CYP3A inhibitors/inducers.
7. 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.

8. 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.
9. Patients in which ibrutinib therapy is medically contraindicated.
10. Women who are pregnant or lactating.
11. Current participation in another therapeutic clinical study.
12. Previous therapy with ibrutinib, CC-292, or any drug that specifically inhibits Bruton's tyrosine kinase (BTK).

6 STUDY DESIGN

6.1 OVERVIEW OF STUDY DESIGN

This study is a fixed-dose, randomized, two-arm Phase 3 trial to assess the efficacy and safety of ublituximab in combination with ibrutinib compared to ibrutinib alone in patients with CLL who have received at least one prior standard treatment regimen and who have at least one high-risk cytogenetic abnormality (17p deletion, 11q deletion, and/or P53 gene mutation).

Following screening, patients meeting the inclusion/exclusion criteria will be randomized in a 1:1 ratio, to either:

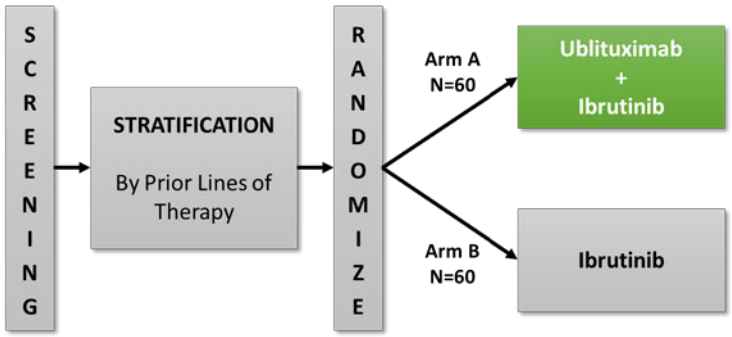
- Arm A: Ublituximab + ibrutinib; or
- Arm B: Ibrutinib

Randomized patients will be stratified according to prior lines of therapy (1 prior vs 2 or more prior lines of therapy).

All study patients will be evaluated for response after cycles 2, 4, and 6, then every 3 cycles thereafter if patient is on active treatment, or approximately every 3 months thereafter if patient is in follow up. The best clinical response as well as disease progression will be determined by an Independent Review Committee (IRC).

Patients will continue treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue study treatment for reasons other than disease progression will continue to be followed for progression and/or survival approximately every 3 months.

Upon first assessment scan, or confirmation scan (if necessary), of the last randomized patient, and site submission of all required efficacy and safety data, the independent DSMB will review the primary and secondary efficacy analyses, and safety data.



6.2 REGISTRATION AND RANDOMIZATION

The patient must sign consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and

discomforts. Patients who have signed informed consent and who are eligible will be randomized in a 1:1 ratio to Arm A (ublituximab plus ibrutinib) or Arm B (ibrutinib alone).

Investigators will use an interactive web response system (IWRS) which will assign patients to either treatment Arm A (ublituximab plus ibrutinib) or treatment Arm B (ibrutinib alone).

Patients should begin study treatment within 4 days of randomization. In case of administrative or other delays, every attempt should be made to initiate study drug as soon as possible but no more than 7 days from randomization. Please see the IWRS Manual for additional information on randomization.

Upon entering patient information into the IWRS, investigators will receive an enrollment approval and a unique patient 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 patient registration process using the IWRS system will be outlined in the IWRS Manual.

6.3 STUDY SITES

Up to 200 study sites may be asked to participate in this study. Enrollment is expected to be completed approximately 18-24 months after the first patient is randomized.

6.4 DISCONTINUATION FROM STUDY TREATMENT

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

- Disease progression
- Intolerable toxicity related to study drug
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy
- Inability of the patient to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Non-compliance/lost to follow-up
- Investigator discretion
- Discontinuation of the study by the Sponsor

Patients who discontinue from study treatment (for reasons other than progressive disease) will continue to be followed for progression. **Every attempt to continue to follow the patient for progression should be made.**

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

All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the investigator, it is not likely that these values are to improve because of the underlying disease. In this

case, the investigator must record his or her reasoning for making this decision in the patient's medical records and as a comment on the eCRF.

7 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Table 2 below lists all of the required assessments that should be performed at each study visit.

TABLE 2: STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Cycle = 28 days	Screen *	Cycle 1[1]				Cycles 2-6[2]					After Cycle 6[3]	End of study
						C2	C3	C4	C5	C6	q3 Cycles (C9, 12, etc.)	
Procedure\Days	-21-0	D1	D2[4]	D8	D15	Day 1					Day 1	
Informed consent	X											
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
BM aspirate/biopsy[5]	X											
12-lead EKG	X											
Tumor evaluation[6]	X	After the completion of cycles 2, 4 and 6 then after the completion of every 3 cycles if under treatment or every 3 months if in follow up										
Serology: HCV, HBV, CMV[7]	X											
MRD[8]						For patients in PR or CR at response assessment intervals beginning at the Cycle 6 response assessment						
Hematology[9]	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[8]	X	X		X	X	X	X	X	X	X	X	X
PT/INR	X					X		X				
Serum Pregnancy Test[10]	X											
Urinalysis	X											
Quantitative Immunoglobulin[11]		X			X		X			X		
β_2-microglobulin	X											
FISH Analysis[12]	X											
[redacted]												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation[15]	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Schedule												
Ublituximab Dose		X[16]	X	X	X	X	X	X	X	X	X	

[1] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 3 day window
[2] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 7 day window
[3] Physical Exam, Vital Signs, ECOG PS, Hematology and Serum Chemistry visit days have +/- 14 day window
[4] Day 2 visit only required for patients randomized into Arm A.
[5] Unilateral bone marrow aspirate and/or biopsy performed at investigator discretion in patients 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 for screening should be completed within 30 days prior to Day 1 of Cycle 1. Response tumor evaluations have a +/- 7 day window. Radiology assessment should include CT or MRI imaging of neck, chest, abdomen, and pelvis.
[7] Serum virology to include HBsAg, HBc antibody and CMV. If HBcAg, HBc antibody, HCV or CMV is positive, patients must be evaluated for the presence of DNA/PCR
[8] Peripheral Blood sample draw (See study manual for all central lab instructions. +/- 7 day window for MRD sample). For patients MRD negative by peripheral blood, a bone marrow sample should be completed to confirm MRD negativity.
[9] Must be obtained prior to ublituximab administration if on a day of infusion.
[10] For women of child bearing potential, completed within 3 days prior to Day 1 of Cycle 1
[11] IgA, IgE, IgG, IgM
[12] For del(13q), del(11q), del(17p), and (12)trisomy, IgHV and P53 gene mutation status in peripheral blood. Central FISH analysis can be performed on UTX-IB-301 study or the TGTX-LAB-001 screening protocol.
[redacted]
[15] If clinically significant adverse event or abnormal result is observed that is not resolved by the end-of treatment visit, continue to monitor and record until stabilization or resolution of event
[16] Patients should receive up to 150 mg on Day 1 and 750 mg on Day 2. Collect a hematology panel prior to Day 2/Cycle 1 infusion.

Ibrutinib Dose		**Days 1 – 28 (Daily)**	
***Randomize Days -7 to 0**			

7.1 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 assessments requiring central labs.

7.1.1 LOCAL LABORATORY ASSESSMENTS

1. Hematologic profile and serum chemistry to include:

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

2. Serum β-HCG test.
3. Coagulation lab tests to include, PT, aPTT, and INR.
4. Quantitative immunoglobulin (IgG, IgM, IgA, IgE).
5. Urinalysis - dipstick for pH, protein, glucose, blood, nitrite, leukocytes
6. Beta2-microglobulin
7. Serum Virology to include HBsAG, HBc antibody, HCV antibody, and CMV (PCR to rule out positive Hepatitis or CMV result as warranted)
8. Baseline bone marrow aspirate/biopsy (if applicable)

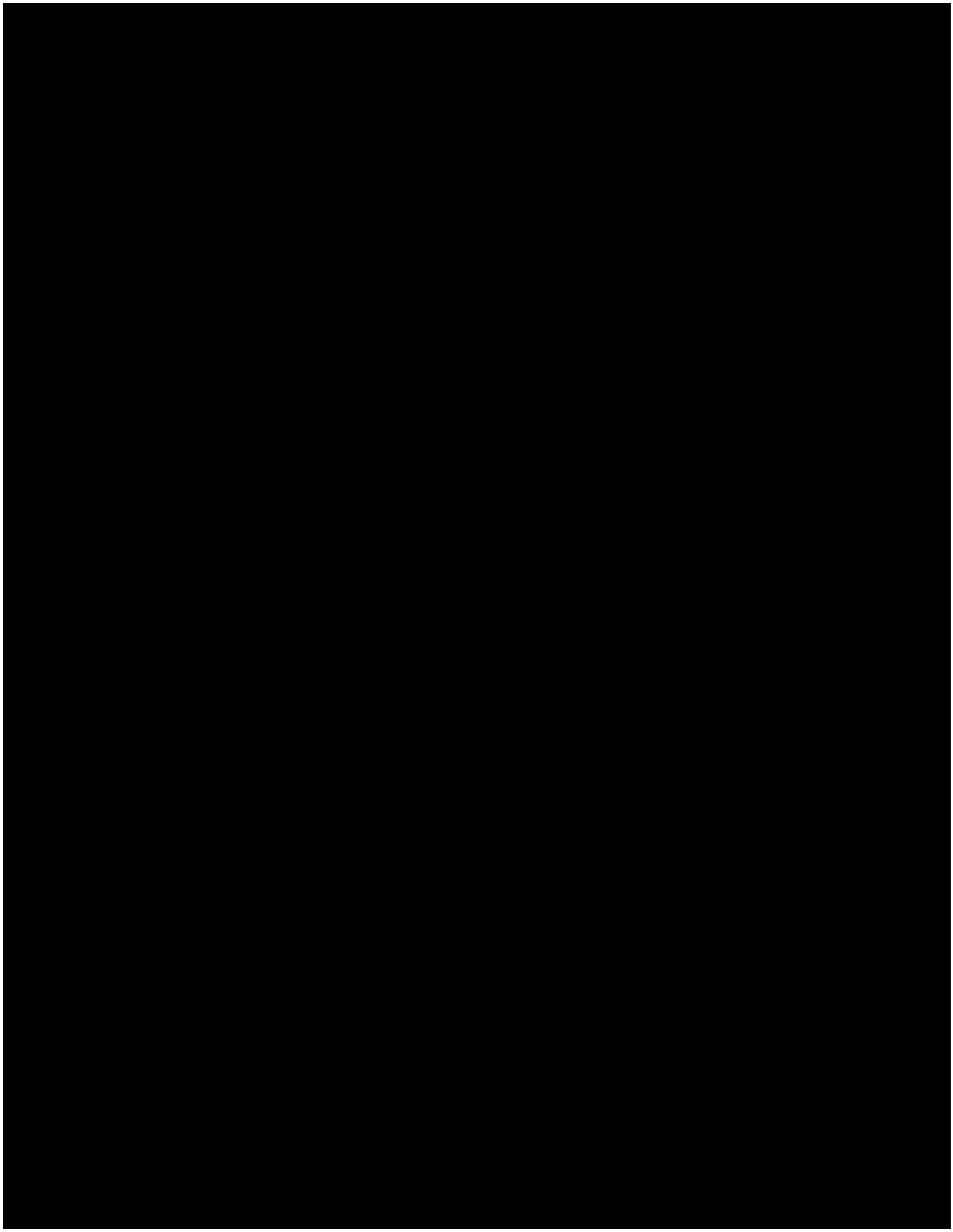
7.1.2 CENTRAL LABORATORY ASSESSMENTS

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

1. Fluorescence in situ hybridization (FISH) of peripheral blood for 13q deletion, 11q deletion, 17p deletion, trisomy 12, IgHV, and P53 gene mutation status. Central FISH analysis can be performed on UTX-IB-301 study or the TGTX-LAB-001 screening protocol.

2. Minimal Residual Disease (MRD) assessment for all patients in PR or CR at response assessment intervals beginning at the Cycle 6 response assessment.

[redacted]



8 TREATMENT PLAN

8.1 TREATMENT SUMMARY

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

Patients randomized to Arm A will receive ublituximab and ibrutinib, while patients randomized to Arm B will receive ibrutinib alone. Treatment schema is outlined below.

Treatment Schema Overview

Cycle 1:

Arm A				*Arm B*
Ublituximab			**Ibrutinib**	**Ibrutinib**
Day 1	Day 2	Day 8 & 15	Daily	Daily
≤150mg	750 mg	900 mg	420 mg	420 mg

Cycles 2 through 6:

Arm A		*Arm B*
Ublituximab	**Ibrutinib**	**Ibrutinib**
Day 1 Cycles 2, 3, 4, 5, 6	Daily	Daily
900 mg	420 mg	420 mg

Beyond Cycle 6:

Arm A		*Arm B*
Ublituximab	**Ibrutinib**	**Ibrutinib**
Day 1 every 3 months thereafter (e.g. cycle 9, 12, etc)	Daily	Daily
900 mg	420 mg	420 mg

8.2 AGENT ADMINISTRATION

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

8.2.1 GUIDELINES FOR ADMINISTRATION OF UBLITUXIMAB

- *Method of Administration:* Ublituximab will be administered as an intravenous infusion through a dedicated line.
- *Potential Drug Interactions*: No Drug Interactions have been reported to date.
- *Pre-medications:* Pre-medicate approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). Use of corticosteroids as a premedication after cycle 6 is at the discretion of the investigator.
    - Use of oral acetaminophen should be restricted to patients 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.
- *Patient Care Implications*:
  - Ublituximab should not be administered as an IV push or bolus.
  - Ublituximab should only be diluted in 0.9% NaCl.
  - Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if does not conform to the specifications. Immediately inform the Monitor/Sponsor with any product quality concerns or questions.
  - It is recommended that ublituximab be administered immediately after dilution.
  - No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
  - Concurrent glucocorticoid therapy as long as started for at least 7 days prior to study entry (≤ 10 mg per day of prednisone or equivalent) is allowed as clinically warranted.
  - Since infusion-related hypotension may occur, **antihypertensive medications should be withheld 24 hours prior to and throughout infusion of ublituximab**
  - For patients at risk for tumor lysis syndrome in the opinion of the treating investigator, prophylaxis with allopurinol or per recommended institutional standards should be considered.

8.2.1.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE - UBLITUXIMAB

Infusion related reactions, including severe reactions, have been reported with ublituximab administration in patients with CLL. Guidelines are provided below for patients 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 patients 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 patient, institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the Investigator, and provided the patient is stable, the infusion may be resumed at no more than half the previous rate.
- If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate at the treatment cycle dose (see Section 8.2.1.2).

3rd Infusion Interruption (same day):

- Discontinue infusion for that day – monitor patient for resolution of all symptoms. Patient 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 patient 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 of 750 mg according to the protocol dosing schedule.

8.2.1.2 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

Cycle 1 Day 1 & 2 infusion over 4 hours

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

Cycle 1 Day 8 & 15 infusions over 3 hours

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

Cycle 2 and remaining infusions over 90 minutes

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

8.2.1.3 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or his/her representative must check that ublituximab is in accordance with the product specifications and the product is within the re-test date.

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

The pharmacist or his/her representative should complete the accountability forms with information concerning the dispensation of ublituximab. Preparation should be done by the Pharmacist or his/her representative according to instructions for sterile dilution provided below.

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

8.2.1.3.1 DILUTIONS OF UBLITUXIMAB

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

[redacted]

Dilutions for Cycle 1 Day 1 & Day 2 Infusions

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 8 Infusions

Dose of ublituximab for infusion	[redacted]
900 mg	

8.2.2 GUIDELINES FOR ADMINISTRATION OF IBRUTINIB

Guidelines for the administration of ibrutinib are per the FDA approved prescribing information. Please refer to www.imbruvica.com for the most up to date information.

- *Method of Administration:* Ibrutinib will be administered orally once daily in accordance with prescribing information
- *Potential Drug Interactions*: Avoid co-administration with strong CYP3A inhibitors/inducers. If a moderate CYP3A inhibitor/inducers must be used, see ibrutinib prescribing information for dose reduction guidelines and further information. For this reason, patients requiring treatment with strong inhibitors of CYP3A are excluded from enrollment. Also avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A and can alter ibrutinib pharmacokinetics. See Appendix D – HEPATITIS B SEROLOGIC TEST RESULTS.
- *Pre-medications:* None

Ibrutinib should be obtained via standard commercial channels. Ibrutinib should be self-administered (by the patient). Starting on Cycle 1 Day 1 the patient should maintain a daily diary recording the time and date of the administration of ibrutinib. Tablets should be taken at approximately the same time each day, except for days when the patient has a scheduled visit to the site. Patients should be instructed to swallow the tablets as a whole and should not chew or crush them. If a dose of ibrutinib is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

Study drug compliance (i.e. the patient's daily diary) should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented in the appropriate eCRF. Patients should record the dose of ibrutinib taken for each dose in a drug diary.

For patients having surgery, hold ibrutinib for at least 7 days prior to planned surgery and for 7 days following surgery.

8.3 CRITERIA FOR ONGOING TREATMENT

Continue treatment as per protocol provided that patient has:

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

8.4 DOSE DELAYS/DOSE MODIFICATIONS

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

A maximum four (4) week delay of treatment for recovery from toxicity is allowed to recover from hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If greater than a four (4) week delay is necessary, then the patient should discontinue treatment and continue to be followed for progression. If a patient withdraws consent or has documented progression, an end of study visit should be completed.

8.4.1 DOSE DELAY: UBLITUXIMAB

No reduction in the dose of ublituximab is permitted. Please refer to Section 8.2.1.1 and 8.2.1.2 for detailed information on infusion rate guidance for infusion related reactions related to ublituximab. Supportive care should be considered for any patient who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. A maximum four (4) week delay for recovery from toxicity is allowed for both study drugs (individually or together) to allow recovery of hematologic toxicities to ≤ Grade 3 or non-hematologic toxicities to ≤ Grade 2 or to baseline level. If greater than a four (4) week delay is necessary for both study drugs, then the patient should discontinue treatment and continue to be followed for progression. If the patient withdraws consent or has documented progression, an end of study visit should be completed.

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

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. If delay is > 4 weeks, discontinue ublituximab. *(If the underlying cause for the ANC reduction is considered to be disease related and is Grade ≤3, treatment hold is at the discretion of the treating investigator).*

Grade 4 thrombocytopenia: Delay ublituximab until Grade ≤ 3; consider intervention with supportive care as warranted; thereafter resume at full dose. If delay is > 4 weeks, discontinue ublituximab.

Grade ≥3 non-hematological adverse event: Withhold ublituximab until Grade ≤2 at the discretion of the investigator; consider supportive care as warranted. Resume at full dose or if delay > 4 weeks, discontinue ublituximab.

8.4.2 DOSE DELAYS/MODIFICATIONS: IBRUTINIB

Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Once reduced, the dose of ibrutinib may not be re-escalated. If further evaluation of the toxicity reveals the event was not treatment related, 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.

For adverse events related to ibrutinib, refer to Table 3: Study Drug Dose Reduction Levels: Ibrutinib provided below. Please refer to the FDA approved prescribing information for all safety updates and dose modifications for ibrutinib. For the most up to date information please see www.imbruvica.com.

TABLE 3: STUDY DRUG DOSE REDUCTION LEVELS: IBRUTINIB

Toxicity Occurrence	CLL Dose Modification After Recovery (Starting Dose = 420 mg)
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Fourth	Discontinue ibrutinib

8.5 ORDERING UBLITUXIMAB AND IBRUTINIB

Once the clinical study site receives regulatory approval (IRB/IEB), and the Sponsor and/or Sponsor designee performs the Site Initiation Visit and inspection of pharmacy, and determines the site to be officially open for enrollment, and once a patient is identified, a shipment of pre-determined quantity of ublituximab 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 ublituximab. If any abnormality on the supplied boxes is observed, the Pharmacist or the appropriate person should document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

Ibrutinib should be prescribed via commercial supply by the treating investigator.

8.6 DURATION OF THERAPY

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

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

During the study period, patients will be evaluated for response by CT and/or MRI after the completion of cycles 2, 4, and 6, then after the completion of every 3 cycles thereafter if under treatment or every 3 months if in follow up. The best clinical response as well as disease progression will be determined by an independent review committee (IRC). Patients will remain on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons. Patients who discontinue from study treatment (either for toxicity or physician choice) and have not progressed will continue to be followed for progression.

9 STUDY MEDICATIONS

9.1 UBLITUXIMAB

Chemical Name: ublituximab

Other Names: TG-1101

Classification: Recombinant chimeric anti-CD20 monoclonal antibody

Mode of Action: Targets CD20 antigen on B-cells

Description: Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.

How Supplied: Concentration of 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 area at a temperature ranging +2°C / + 8°C. Ublituximab must not be frozen.

Stability: Once a vial of ublituximab has been opened it must be diluted immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions, 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 unit boxes. Each unit box 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.

9.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

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

9.1.1.1 COMMON (>20%)

- **Blood and lymphatic system disorders:** Neutropenia, Thrombocytopenia
- **General disorders and administration site conditions:** Infusion-related reaction, Pyrexia, Chills
- **Nervous system disorders:** Headache

9.1.1.2 LESS COMMON (10%-20%)

- **Blood and lymphatic system disorders:** Anemia
- **Gastrointestinal disorders:** Diarrhea, Nausea, Abdominal Pain Upper
- **General disorders and administration site conditions:** Fatigue, Asthenia

9.1.1.3 UNCOMMON (≥5% - <10%)

- **Blood and lymphatic system disorders:** Febrile neutropenia, Pancytopenia
- **General disorders and administration conditions:** Pain
- **Infections and infestation:** Bronchitis
- **Investigations:** Blood bilirubin increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Elevated liver enzymes
- **Musculoskeletal and connective tissue disorders:** Muscular weakness
- **Nervous system disorder:** Dysguesia
- **Respiratory, thoracic and mediastinal disorders:** Throat irritation/tightness, Dyspnea
- **Skin and subcutaneous tissue disorders:** Pruritus
- **Vascular disorders:** Hypertension

9.1.1.4 EVENTS REPORTED IN AT LEAST ONE SUBJECT

- **Blood and lymphatic system disorders**: Lymph Node Pain
- **Cardiac disorders**: Supraventricular Arrhythmias
- **Gastrointestinal disorders:** Constipation, Gastroesophageal Reflux Disease, Oral Pruritus
- **General disorders and administration conditions:** Edema
- **Immune system disorders:** Serum Sickness, Hypocomplementemia
- **Infections and infestations:** Herpes Zoster, Paronychia, Pneumonia, Urinary Tract Infection, Pyuria
- **Investigations**: Blood Creatinine Increase, Blood Potassium Increase, Blood Urea Increase, Heart Rate Irregular, Urine Output Decrease, Weight Increase
- **Metabolism and nutrition disorders**: Hypoalbuminemia
- **Musculoskeletal and connective tissue disorders**: Arthralgia, Groin Pain, Muscle Spasms
- **Nervous system disorders**: Ageusia, Dizziness, Sciatica, Cognitive Disorder
- **Renal and urinary disorders:** Hematuria, Proteinuria, Acute Kidney Failure, Tubulointerstitial Nephritis
- **Respiratory, thoracic and mediastinal disorders**: Cough, Lung Infiltration, Pneumonitis, Wheezing
- **Skin and subcutaneous tissue disorders**: Cold Sweat, Hyperhidrosis, Rash

- **Vascular Disorders**: Flushing

9.2 IBRUTINIB

Classification:	Covalent inhibitor of the enzyme Bruton's tyrosine kinase (Btk)
Formulation:	See Prescribing Information
How Supplied:	140 mg strength capsules
Storage:	See ibrutinib prescribing information
Route of Administration:	Oral
Potential Drug Interactions:	Avoid co-administration with strong and/or moderate CYP3A inhibitors/inducers. If a moderate CYP3A inhibitor/inducers must be used, see ibrutinib prescribing information for dosingguidelines and further information. Also, avoid grapefruit and Seville oranges during treatment, as these contain strong or moderate inhibitors of CYP3A and can alter ibrutinib pharmacokinetics.
Availability:	Ibrutinib is available commercially from Pharmacyclics and Janssen.

9.2.1 ADVERSE REACTIONS - IBRUTINIB

The data described below reflect adverse reactions in ≥ 20% of patients who received ibrutinib in three clinical trials; an open-label, single-arm clinical trial (Study 1102) that included 51 patients with previously treated CLL, a randomized clinical trial (RESONATE) that included 391 (195 on ibrutinib) patients with previously treated CLL or SLL, and a randomized clinical trial (RESONATE-2) that included 267 (135 on ibrutinib) patients ≥ 65 years old with previously treated CLL or SLL (Janssen Biotech, Inc. & Pharmacyclics LLC, 2017).

To ensure reference to the most up to date adverse reaction profile, please refer to the full IMBRUVICA® (ibrutinib) full prescribing information. The prescribing information can be found at www.imbruvica.com.

9.2.1.1 COMMON (≥ 20%)

- **Blood and lymphatic system disorders:** Anemia, Neutropenia, Thrombocytopenia
- **Gastrointestinal disorders:** Diarrhea, Constipation, Nausea, Stomatitis
- **General disorders and administrative site conditions:** Fatigue, Pyrexia, Peripheral edema
- **Infections and infestations:** Upper respiratory tract infection, Sinusitis
- **Skin and subcutaneous tissue disorders:** Rash, Bruising
- **Musculoskeletal disorders:** Musculoskeletal pain, Arthralgia
- **Nervous system disorders:** Dizziness
- **Respiratory, thoracic and mediastinal disorders:** Cough

9.2.1.2 IBRUTINIB – WARNINGS AND PRECAUTIONS (JANSSEN BIOTECH INC. & PHARMACYCLICS LLC, 2017)

Hemorrhage

Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib.

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and treat appropriately.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) occurred in patients with B-cell malignancies treated with ibrutinib.

Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of ibrutinib treatment and dose modification in the prescribing information.

Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with ibrutinib with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate**.**

Second Primary Malignancies

Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with ibrutinib therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

9.2.2 ADVERSE REACTIONS – UBLITUXIMAB IN COMBINATION WITH IBRUTINIB

The following adverse events were observed in at least 1 of the 62 patients treated with ublituximab in combination with ibrutinib in an ongoing Phase II clinical trial, and were considered at least possibly related to ublituximab. See the ublituximab investigator brochure for a complete list of all adverse events.

9.2.2.1 COMMON >20%

- **General disorders and administration site conditions:** Infusion related reaction

9.2.2.2 LESS COMMON ≥10% - ≤20%

- **Blood and lymphatic system disorders:** Neutropenia, Thrombocytopenia
- **Gastrointestinal disorders**: Nausea, Diarrhea
- **General disorders and administration site conditions**: Fatigue
- **Musculoskeletal and connective tissue disorders:** Muscle spasms

9.2.2.3 UNCOMMON ≥1% - <10%

- **Blood and lymphatic system disorders**: Anemia, Lymph node pain
- **Ear and labyrinth disorders:** Tinnitus
- **Gastrointestinal disorders:** Stomatitis, Abdominal pain, Dyspepsia, Gastroesophageal reflux disease, Abdominal distension, Constipation, Oral pain
- **General disorders and administration conditions:** Malaise, Pyrexia, Chills, Non-cardiac chest pain
- **Hepatobiliary disorders:** Hyperuricemia
- **Infections and infestations:** Wound infection
- **Injury, poisoning, and procedural complications:** Contusion
- **Investigations:** Aspartate aminotransferase increased, Blood creatinine increased, Alanine aminotransferase increase
- **Metabolism and nutrition disorders:** Hypomagnesaemia, Decreased appetite, Hypercalcemia, Hyperglycemia,
- **Musculoskeletal and connective tissue disorders:** Back pain, Pain in extremity, Myalgia, Arthralgia, Joint swelling
- **Nervous system disorders:** Dysgeusia, Headache, Neuropathy peripheral, Memory impairment, Tremor, Dizziness, Dementia Alzheimer's type
- **Psychiatric disorders:** Insomnia
- **Renal and urinary disorders:** Hematuria
- **Respiratory, thoracic and mediastinal disorders:** Cough, Dysphonia, Epistaxis, Nasal congestion, Sinus congestion, Upper-airway cough syndrome, Hiccups
- **Skin and subcutaneous tissue disorders:** Onychoclasis, Alopecia, Rash, Rosacea
- **Vascular disorders:** Hypotension

10 MEASUREMENT OF EFFECT

During the study period, all patients will be evaluated for response by CT and/or MRI after the completion of cycles 2, 4, and 6 then after the completion of every 3 cycles thereafter while under protocol treatment. If a patient is off study in follow up, assess for response every 3 months. All efficacy assessments have a +/- 7 day window. The determination of response and progression will be based on IWCLL criteria (Hallek M, 2008). Radiographic and clinical tumor assessments will be subject to independent confirmation by the Independent Review Committee (IRC) which will be blinded to treatment assignment. The findings of the IRC will be considered primary for analyses of ORR, PFS, and other tumor control 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 tumor 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.

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

10.1 METHOD OF ASSESSMENT

In addition to clinical examination, imaging-based evaluation will be used in this study in all patients enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in patients 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 patients 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, scanner, patient position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a patient is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the patient cannot tolerate the contrast.

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

10.2 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 tumor status. CLL response and progression data collected from the study will be subjected to review by the IRC. The

patient should continue study treatment pending confirmation of progression status by the IRC. CT/MRI should be attempted in order to document definitive disease progression by the IRC.

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. The findings of the IRC will be considered primary for analyses of ORR, PFS, and other tumor control endpoints.

See IRC manual for instructions on process for submission of scans.

10.3 IDENTIFICATION AND MEASUREMENT OF TUMOR LESIONS AND ORGANOMEGALY

10.3.1 TARGET LESIONS

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

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

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

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

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

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

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

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

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the liver in its

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

10.3.3 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 at the stipulated intervals during treatment. If present at baseline, up to 6 non-target lesions should be recorded. The non-target disease at baseline will be used as a general reference to further characterize regression or progression of CLL during assessments of the objective tumor response during treatment. Measurements are not required and these lesions should be followed as “present” or “absent”.

10.4 DEFINITIONS OF TUMOR RESPONSE AND PROGRESSION

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

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

10.5 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 $<4 \times 10^9$/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 $>1.5 \times 10^9$/L without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count $\geq 100 \times 10^9$/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)

Patients 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).

10.6 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 patient with baseline lymphocytosis (ALC $\geq 4 \times 10^9$/L), a decrease in peripheral blood ALC by ≥50% from baseline or a decrease to $<4 \times 10^9$/L
  - A decrease by ≥50% from the baseline in the SPD of the target nodal lesions
  - In a patient with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 10.3.2
  - In a patient with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 10.3.2
  - 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)

10.7 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

10.8 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 patient 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 patient 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 patients, 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 patient has experienced persistent definitive CLL progression, then the date of progression should be the time point at which progression was first objectively documented.

10.9 NON-EVALUABLE

In a patient 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 patient known to have undergone splenectomy).

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

10.10 LYMPHOCYTOSIS DURING THERAPY

Upon initiation of ibrutinib, 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 ibrutinib therapy and usually resolves by a median of 8 weeks. Patients 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. New or increasing lymphocytosis after 6 months of starting treatment may be considered disease progression and should be confirmed as per the response criteria.

10.11 MINIMUM RESIDUAL DISEASE

In patients who achieve a PR or CR, minimum residual disease will also be assessed first by peripheral blood. If a patient is determined to be MRD negative by peripheral blood, a bone marrow aspirate will be obtained to assess MRD in the bone marrow. Patients will be defined as having a clinical remission in the absence of MRD (i.e. "MRD negative") when they have blood or marrow with less than one CLL cell per 10,000 leukocytes.

11 STATISTICAL CONSIDERATIONS

11.1 SAMPLE SIZE AND POWER

[redacted]

11.2 GENERAL ANALYSIS CONVENTIONS

Statistical analyses will be conducted by TG Therapeutics or its designee. Statistical analysis will be performed on the intent-to-treat (ITT) population for primary efficacy endpoints and the Treated Population for primary and secondary efficacy endpoints and for safety endpoints.

Baseline is defined as the last measurement for a variable prior to the initial dose of study treatment. Hypotheses will be tested at the 5%, two-sided statistical significance level, unless otherwise specified. Efficacy and safety analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC), or comparable software.

All data collected on the eCRF will be listed. Routine data listing or tabulation review during the study conduct will be performed to identify missing data, anomalies, outliers, etc. A complete description of data handling rules and planned statistical analyses is detailed in a separate statistical analysis plan (SAP) prior to conducting any planned analysis.

11.3 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will include all randomized patients. The Treated Population will include all randomized patients who received at least one dose of study medication.

11.4 PATIENT DISPOSITION

The disposition of patients includes the number and percentage of patients for the following categories: patients enrolled, patients in the ITT and Treated Population, and patients discontinued from the study. The reasons for study discontinuation will also be summarized in this table. Only one primary reason for study discontinuation will be reported in the summary. However, all reasons will be presented in the listing.

A listing will present data concerning patient disposition.

11.5 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

11.6 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 ITT and Treated Population.

11.7 EXTENT OF EXPOSURE

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

11.8 EFFICACY ANALYSES

All patients included in the study should have a baseline tumor assessment within 30 days of Cycle 1/Day 1. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

The primary analyses of efficacy variables that include measures of tumor response (e.g., ORR, CR rate) will involve response as determined by the IRC. Supportive analyses of these variables will involve response as determined by the investigators.

11.9 MISSING VALUE HANDLING PROCEDURES

Missing data will not be imputed, except for missing dates concerning major efficacy or safety parameters. The algorithms for imputation of partial dates vary depending upon the parameter and are presented in the Statistical Analysis Plan.

11.10 STATISTICAL ANALYSES

11.10.1 PRIMARY EFFICACY VARIABLES

The ORR is defined as the proportion of patients with a best overall response of partial response (PR) or complete response (CR). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the ORR. For the ITT analysis, for each treatment group, the number of patients achieving a response will be divided by the total of patients in the ITT population to yield the proportion responding.

The primary efficacy variable (i.e. ORR) will be analyzed in the ITT population first and then will also be analyzed for the Treated Population.

The ORR will be compared between treatment groups by a Fisher's Exact Test. Testing of ORR will be at the 5%, 2-sided statistical significance level.

ORR will also be analyzed based on Per Protocol patients. Additional sensitivity analyses will also be performed as appropriate.

11.10.2 SECONDARY EFFICACY VARIABLES

11.10.2.1.1 COMPLETE RESPONSE RATE

The CR rate is defined as the proportion of patients with a best overall response of complete response (CR). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the CR rate. For each treatment group, the number of patients achieving a CR will be divided by the total of patients in the Treated Population to yield the proportion responding.

The CR rate will be compared between treatment groups at the 5%, two-sided statistical significance level using the same methodology as that described in Section 11.10.1 found for ORR.

11.10.2.1.2 DURATION OF RESPONSE

The Duration of Response (DOR) is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression or death from any cause. The DOR rate will be compared between treatment groups at the 5%, two-sided statistical significance level using an ANOVA model with treatment effect.

11.10.2.1.3 TIME TO RESPONSE

The Time to Response (TTR) is defined as the interval from the start of study drug to the first documentation of CR or PR. The TTR rate will be analyzed via Kaplan-Meier methodology using a stratified Cox regression model with treatment effect and stratification effect to compare the treatment groups to generate the treatment group HR and 95% CI.

11.10.2.1.4 MINIMAL RESIDUAL DISEASE NEGATIVITY RATE

The MRD negativity rate is defined as the proportion of patients who are MRD negative post-baseline. MRD negativity rate is defined as the proportion of the patients in the Treated Population who are MRD negative, excluding any patients who remain on study treatment at the time of the analysis and have a Cycle 1/Day 1 start date less than 6 months from the time of the analyses. For the sake of clarity, the MRD negative analysis will exclude those patients that are too early to evaluate because MRD negativity is only tested for patients on study $\geq$ 6 months. Patients who drop off study for any reason prior to their 6 month visit will be included in the analysis.

The MRD negativity rate will be compared between treatment groups at the 5%, two-sided statistical significance level using the same methodology as that described in Section 11.10.1 for ORR.

11.10.2.1.5 SAFETY

Safety analyses will be performed on the Treated Population. Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented by study drug actually received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

11.10.2.1.6 PROGRESSION-FREE SURVIVAL

Progression-free survival is defined as the time from the date of randomization until the date of first documentation of definitive disease progression or date of death from any cause, whichever occurs first. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress or are lost to follow-up will be censored at the day of their last tumor response assessment. If no baseline or post-baseline assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after 2 or more consecutive missing tumor response assessments, censoring will occur at the date of the last response assessment prior to the missed assessments. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last tumor response assessment prior to initiation of new therapy.

This variable will be analyzed via Kaplan-Meier methodology. The median PFS will be estimated for each arm, however no formal hypothesis testing will be conducted.

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12 SAFETY REPORTING AND ANALYSIS

12.1 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 patient's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the Treated Population. Safety variables will be tabulated and presented by the dose of ublituximab and/or ibrutinib actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

The number of dose reductions of ibrutinib due to toxicity (adverse events) in each treatment arm will be compared.

12.2 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. Please refer to the ibrutinib prescribing information for a listing of expected AEs.

12.3 DEFINITIONS OF ADVERSE EVENTS

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

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

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

- **Grade 5**: Death related to AE.

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

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

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

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

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

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

12.5 ADVERSE EVENTS/SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

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

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

12.5.1 RECORDING OF ADVERSE EVENTS

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

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

12.5.2 ABNORMAL LABORATORY VALUES AND VITAL SIGNS

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

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

12.5.3 HANDLING OF ADVERSE EVENTS

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

12.6 SERIOUS ADVERSE EVENTS

12.6.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

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

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

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

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

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

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

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

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

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

12.6.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

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

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

To report an SAE, see the appropriate form.

All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to the sponsor as SAEs within the eCRF 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).

12.7 SPONSOR SAE REPORTING REQUIREMENTS

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

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

12.8 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

12.9 DIAGNOSIS VS. SIGNS AND SYMPTOMS

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

12.9.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

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

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

12.9.2 ABNORMAL LABORATORY VALUES

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

signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

12.9.3 DEATHS

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

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

12.9.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

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

12.9.5 PRE-EXISTING MEDICAL CONDITIONS

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

12.9.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

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

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

During the course of the study, all female patients 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 patient may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug(s), and must be discontinued from the study.

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

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

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

Study Drug Overdose

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

Secondary Malignancy

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

13 DATA SAFETY MONITORING BOARD (DSMB)

Upon first assessment scan or confirmation scan if necessary, of the last randomized study patient, and following site submission of all required efficacy and safety data, the independent DSMB will review the primary and secondary efficacy analyses and safety data.

14 CLINICAL DATA COLLECTION AND MONITORING

14.1 SITE MONITORING PLAN

A Sponsor representative or designee will have made a site visit to each trial site within 12 months prior to initiating the protocol to inspect the drug storage area, and fully inform the Investigator of his/her responsibilities for studies and the procedures for assuring adequate and correct documentation. A study initiation site visit, a teleconference and/or a planned investigator meeting will be performed to review investigator responsibilities and protocol requirements. During the initiation, the electronic case report forms (eCRFs) and other pertinent study materials will be reviewed with the investigator's research staff. During the course of the study, the Sponsor will make visits to the sites as necessary in order to review protocol compliance, examine eCRFs, and individual patient medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

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

14.2 AMENDMENTS TO THE PROTOCOL

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

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

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

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

Items requiring a protocol amendment with IRB and Ethics Committee and/or FDA and Competent Authority approval may include the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase of more than 20%

- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

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

14.3 CURRICULA VITAE AND FINANCIAL DISCLOSURES

All Principal Investigators will be required to submit to the Sponsor or its designee a signed up-to-date 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 a signed up-to-date CV, current within two years, a current copy of their medical license, and a completed financial disclosure statement.

14.4 DATA OWNERSHIP AND PUBLICATION

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

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

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

15 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

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

15.1 IRB APPROVAL

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

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

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

15.2 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 will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

15.3 INSURANCE AND INDEMNITY

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

15.4 INFORMED CONSENT

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

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

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

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

15.5 CONFIDENTIALITY

Patient Confidentiality

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

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

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

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

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

15.6 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.

15.7 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.

16 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

16.1 DOCUMENTATION REQUIRED TO INITIATE STUDY

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

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

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

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

16.2 STUDY DOCUMENTATION AND STORAGE

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

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

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

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21 CFR 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 21 CFR Part 56.115 for at least 3 years after completion of the research.

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

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

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

16.3 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 patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

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

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

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

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

16.4 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 patients' status throughout the course of the study.

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

16.5 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.

16.6 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.

16.7 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.

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18 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.

19 APPENDIX B- CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

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

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 30 days after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment**.**
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
4. 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:

- Oral contraception, injected or implanted hormonal methods are not allowed as IBRUTINIB potentially decreases the effectiveness of hormonal contraceptives.
- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

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

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use a condom during treatment, for 30 days after discontinuation of study treatment, and should for an additional 12 weeks (3 months in total after study drug discontinuation), and should not father a child in this period.

Pregnancies

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

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

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

20 APPENDIX C – NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

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

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

Interpretation of Hepatitis B Serologic Test Results

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

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

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

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

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

CDC

www.cdc.gov/hepatitis

22 APPENDIX E – INHIBITORS OF CYP3A

Examples of inhibitors of CYP3A4/5 can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx and http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables.

The list below reflects information obtained from the website on May 6, 2014. Please refer to the ibrutinib prescribing information for all updates at www.imbruvica.com.

Inhibitors of CYP3A4/5

Strong inhibitors:	**Moderate inhibitors:**
Indinavir	Aprepitant
Nelfinavir	Erythromycin
Ritonavir	Fluconazole
Clarithromycin	Grapefruit juice
Itraconazole	Verapamil
Ketoconazole	Diltiazem
Nefazodone	
Saquinavir	
Suboxone	
Telithromycin	