CLINICAL STUDY PROTOCOL

Study Title:	A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Idelalisib with and without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	This is a non-IND study	
EudraCT Number:	2015-003909-42	
Clinical Trials.gov Identifier:	NCT02968563	
Indication:	Chronic Lymphocytic Leukemia	
Protocol ID:	GS-US-401-1958	
GCLLSG Protocol ID:	CLLRUmbrella1	
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Gilead CCI [redacted]:	Name: Telephone:	PPD PPD
GCLLSG Global Principal Investigator:	Name: Telephone:	PPD PPD
GCLLSG Coordinating Physician:	Name: Telephone:	PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5: Amendment 6:	01 June 2016 16 August 2016 16 September 2016 24 August 2017 15 January 2019 14 November 2019 28 May 2020

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Idelalisib with and without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia
IND Number:	This is a non-IND study
EudraCT Number:	2015-003909-42
Clinical Trials.gov Identifier:	NCT02968563
Study Centers Planned:	Approximately 25 centers in Germany
Objectives:	**Primary Objective:** • To determine the preliminary efficacy of the combination of tirabrutinib and idelalisib with obinutuzumab in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) **Secondary Objective:** • To evaluate the safety and tolerability of the combination of tirabrutinib and idelalisib with and without obinutuzumab CCI [redacted]
Endpoints:	**Primary Endpoint:** The primary endpoint is the rate of complete remission (CR) per modified International Workshop on CLL (IWCLL) 2008 criteria {Hallek 2008} at Week 25 **Secondary Endpoints:** • Rate of complete response (CR) with bone marrow minimal residual disease (MRD) negativity (CR/BM MRD-) at Week 25 • Rate of CR with MRD negativity ($<10^{-4}$) in peripheral blood (CR/PB MRD-) at Week 25

- Overall response rate (ORR) at Week 25including CR, CR with incomplete bone marrow recovery (CRi), partial remission (PR), and PR with lymphocytosis
- Type, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs)

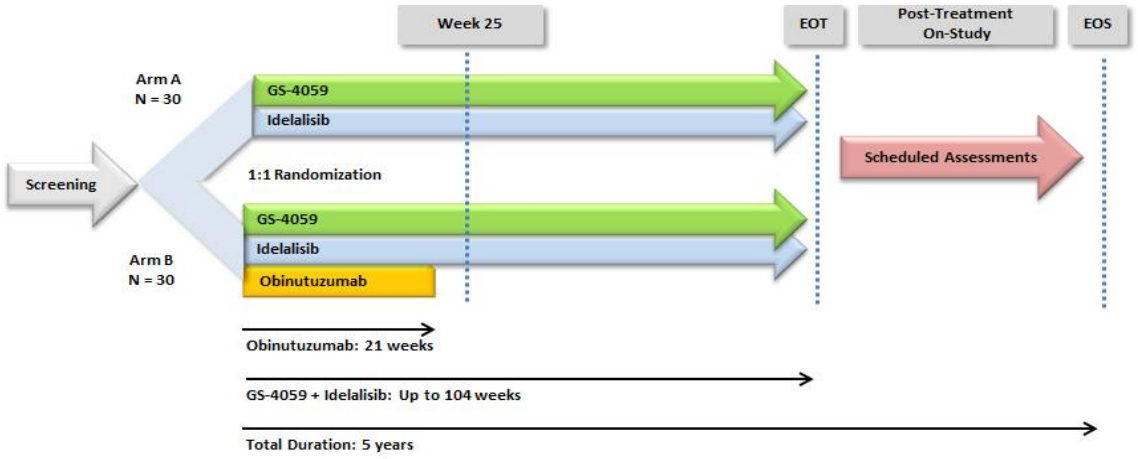
CCI [redacted]

Study Design:

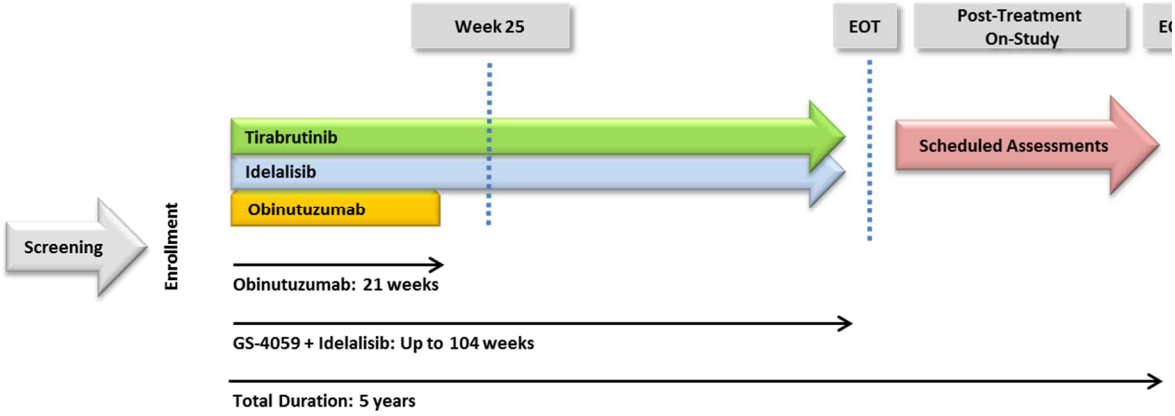
This is a Phase 2, prospective, open-label, multicenter trial to evaluate the safety and efficacy of the combination of tirabrutinib and idelalisib with and without obinutuzumab in subjects with relapsed or refractory CLL.

Eligible subjects will be treated with the combination of tirabrutinib and idelalisib and stratified by the presence of 17p deletion/ TP53 mutation (del17p/TP53mut) in CLL cells. Following stratification, subjects will be randomized 1:1 to treatment with the combination of tirabrutinib and idelalisib with or without obinutuzumab.

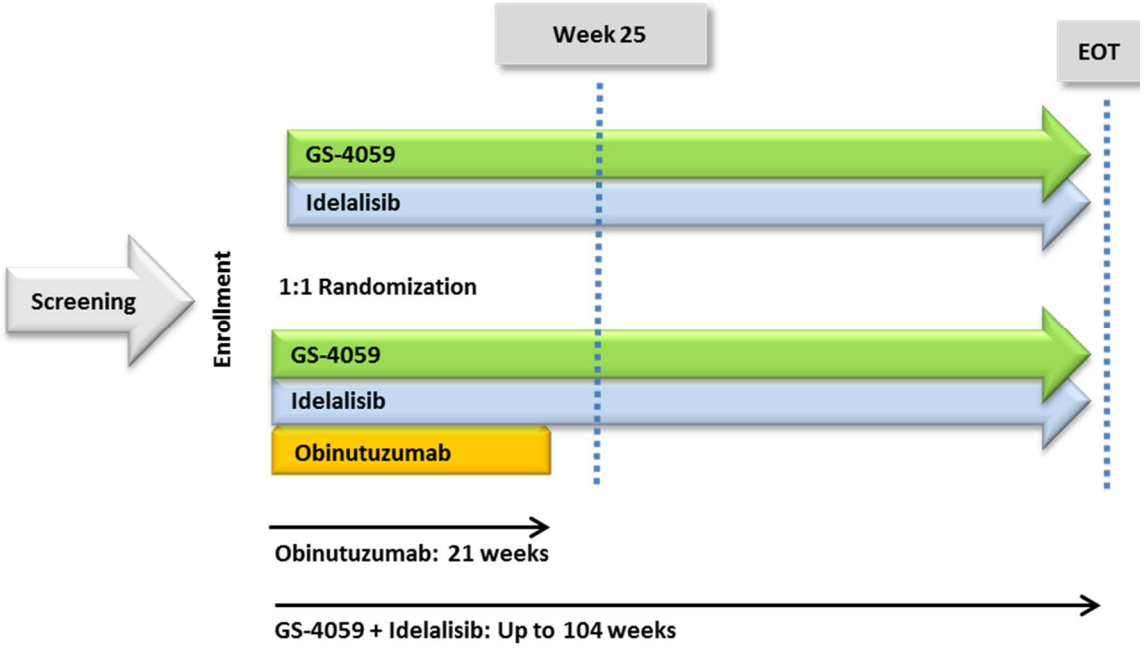
- Arm A: tirabrutinib + idelalisib
- Arm B: tirabrutinib + idelalisib + obinutuzumab



With Amendment 3, randomization was discontinued. All subsequently enrolled subjects will enter Arm B (tirabrutinib + idelalisib + obinutuzumab).



With Amendment 4, the Post Treatment period will no longer be applicable.



Enrollment will be paused following enrollment of the first 6 subjects into Arm B, who will be observed for safety for 28 days following the first dose of study treatment including weekly clinical evaluation through that period. Additional subjects may be enrolled into the safety cohort if any of the first 6 subjects in Arm B discontinue therapy during the initial 28 days for reasons unrelated to toxicity. A Safety Review Team (SRT) will review 28-day safety data from the first 6 subjects in Arm B and determine whether enrollment may resume and if weekly clinical evaluation through the first 28 days should continue or may be reduced in frequency for the remainder of subjects enrolled in the study. The safety review will include assessment of the following:

- Grade ≥ 4 hematological toxicities persisting for > 7 days or non-hematologic laboratory abnormalities except for asymptomatic AST/ALT elevation
- Grade ≥ 3 non-hematological toxicities (except alopecia or the following that resolve within 72 hours with medical intervention: tumor lysis, nausea, vomiting, diarrhea, or constipation)
- Grade ≥ 2 non-hematologic treatment-emergent adverse events (TEAE) that in the opinion of the investigator are of potential clinical significance such that further dosing would expose subjects to unacceptable risk

	A decision to prematurely terminate the study will be made by the sponsor in consultation with the investigators in accordance with regulatory and ethical principles. Criteria for termination of the study are: 1) An unacceptable safety profile or incidence of AEs or SAEs revealed in this or any other study in which the combination of agents is administered 2) Any other factor that in the view of the sponsor constitutes an adequate reason for terminating the study As agreed with the German Federal Institute for Drugs and Medical Devices Agency (BfArM), a safety report including the cumulative safety results and summary of the conclusion of the SRT following assessment of the safety cohort was submitted to BfArM. The study steering committee, including representatives from the German CLL Study Group (GCLLSG) and Gilead, will review ongoing safety data at least quarterly throughout the treatment period and regularly for the complete duration of the study.
Number of Subjects Planned:	Approximately 36 evaluable in total; 30 evaluable in Arm B and approximately 6 in Arm A
Target Population:	Adults with relapsed or refractory CLL
Duration of Treatment:	Obinutuzumab will be administered for up to 8 doses over 21 weeks to subjects randomized or enrolled to treatment with tirabrutinib + idelalisib + obinutuzumab (Arm B). Combination treatment with the oral agents (tirabrutinib and idelalisib) will continue for all subjects for up to 104 weeks in the absence of disease progression, unacceptable toxicity or documentation of CR/BM MRD-. If CR/BM MRD- is documented on study, treatment will stop after the earlier of: i) an additional 3 months of therapy or ii) 104 weeks of total treatment.
Long-Term Follow-Up After End of Study:	Consenting subjects for inclusion in the German CLL Study Group (GCLLSG) registry is requested at screening or as soon as possible thereafter.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

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

1) Documentation of relapsed or refractory CLL
2) Have an indication for treatment per modified IWCLL 2008 criteria; subjects without radiographically measureable disease (defined as ≥ 1 lesion > 1.5 cm in diameter as assessed by computed tomography (CT) or magnetic resonance imaging [MRI]) must have bone marrow evaluation at screening
3) Adequate hematologic function as indicated by a platelet count ≥ 50×10^9/L, a neutrophil count ≥ 1×10^9/L and a hemoglobin ≥ 8 g/dL unless lower values are directly attributable to documented bone marrow burden of CLL
4) Adequate renal function as indicated by a CrCl ≥ 50 mL/min calculated by the modified Cockcroft-Gault formula or from a 24h urine collection
5) Adequate liver function as indicated by total bilirubin ≤ 1.5× institutional upper limit of normal (ULN) unless attributed to Gilbert's syndrome and AST/ALT ≤ 2.5×ULN
6) Male or female ≥ 18 years of age
7) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2
8) Absence of active HBV infection (serological testing within 6 weeks prior to randomization or enrollment with the following results: HBsAg negative AND anti-HBcAb negative, or if anti-HBcAb positive, HBV DNA PCR negative)
9) HCV Ab negative or if Ab positive, negative HCV RNA PCR within 6 weeks prior to randomization or enrollment
10) Negative testing for HIV within 6 weeks prior to randomization or enrollment
11) Satisfies the following criteria:
    a) For female subjects of childbearing potential, willingness to abstain from sexual intercourse or use a protocol-specified method of contraception as described in Appendix 4
    b) Male subjects of reproductive potential who engage in sexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4

12) Ability and willingness to provide written informed consent and adhere to protocol requirements including study visit schedule, drug administration plan, imaging studies, laboratory testing, other study procedures and restrictions including mandatory prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP)

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible for participation in this study:

1) Known transformation of CLL (ie, Richter's transformation, prolymphocytic leukemia)
2) Known CNS involvement
3) Progression on treatment with any inhibitor of BTK, SYK, PI3K, BCL-2, or obinutuzumab. The treatment and disease response history of subjects with prior treatment with agents in these classes should be reviewed by the sponsor or the GCLLSG study office prior to enrollment to clarify sensitivity to these treatments.
4) Any treatment for CLL other than corticosteroids for symptomatic management within 28 days of the start of study treatment
5) Participation on a concurrent therapeutic clinical trial unless all treatment is complete with only ongoing surveillance
6) Diagnosis of or concern for progressive multifocal leukoencephalopathy
7) History of myelodysplastic syndrome or another malignancy other than CLL, *except* for the following: any malignancy that has been in complete remission for 3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to start of study therapy
8) Active infection requiring systemic therapy
9) Pregnant or nursing women (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment and monthly during therapy)
10) Active autoimmune disease including autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura requiring a higher corticosteroid equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped > 14 days prior to randomization or enrollment;

exceptions may be made for corticosteroids prescribed specifically for management of CLL symptoms after discussion with the study medical monitor.

11) Diagnosis of inflammatory bowel disease or ongoing symptomatic pneumonitis

12) Ongoing CMV infection, treatment or prophylaxis for CMV within the past 28 days

13) History of stroke or intracranial hemorrhage within 12 months of randomization or enrollment; subjects requiring therapeutic anticoagulation for any indication should be discussed with the GCLLSG coordinating physician and/or medical monitor prior to screening.

14) Legal incapacity, prisoners or subjects institutionalized by regulatory or court order, or any individual in dependence to study sponsor or any investigator

15) Use of a strong CYP3A4 or a strong P-gp inducer within 2 weeks of first dose of study treatment or anticipated chronic use while on study

16) Demonstration of QTc interval > 450 milliseconds or requirement for ongoing treatment with concomitant medications that prolong the QT interval

17) Known hypersensitivity to obinutuzumab, idelalisib, tirabrutinib, or any of the excipients

Test Product, Dose, and Mode of Administration:

Tirabrutinib and Idelalisib:

Tirabrutinib 80 mg and idelalisib 100 mg will be self-administered orally once daily. Dosing of both agents will begin on Week 1, Day 1 of the study and continue at approximately the same time each day until the earlier of i) 3 months after documentation of CR/MRD- or ii) completion of 104 weeks of treatment. Tirabrutinib is supplied as 20 mg (4 × 20 mg) tablets, 40 mg (2 x 40 mg) tablets, or 80 mg tablets. Idelalisib is supplied as 100 mg tablets.

Obinutuzumab:

Obinutuzumab will be administered as 8 intravenous infusions of 1000 mg each over 21 weeks. A test dose of 100 mg will be administered on Week 1 Day 1. If this dose is tolerated, the remainder of the full dose will be administered on Day 1. Alternatively, the remaining 900 mg will be administered on Day 2.

Subsequent infusions will be administered on Week 2 Day 1, Week 3 Day 1, Week 5 Day 1, and then every 4 weeks through Week 21.

Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessing AEs and monitoring of clinical laboratory tests.
Efficacy:	Efficacy will be assessed per modified IWCLL 2008 criteria {Hallek 2008}: • Lymph node, spleen and liver measurements by physical examination • Complete blood count • Lymph node, spleen and liver measurements by CT or MRI • Peripheral blood MRD assessment • Bone marrow assessment including standard histopathology and MRD assessment
CCI [redacted]	[redacted]

Sample Size Determination:

The primary goal of the study is to evaluate the efficacy of the aforementioned combination treatment. The evaluation will be based on the estimation of the CR rate and its corresponding exact confidence interval. Approximately 30 subjects will be enrolled into Arm B, which will result in the 90% confidence interval of the observed CR rate to be within ±17.0%. The 90% confidence interval for a given observed CR rate is provided in the table below.

90% Confidence Intervals at Different CR Rates

Sample Size	Observed CR Rate	90% Confidence Interval using Clopper-Pearson Method
30	20%	(9.1%, 35.7%)
30	30%	(16.6%, 46.5%)
30	40%	(25.0%, 56.6%)
30	50%	(33.9%, 66.1%)
30	60%	(43.4%, 75.1%)

With Amendment 3, randomization was discontinued. All subsequently enrolled subjects will enter Arm B. A total of approximately 6 subjects in Arm A and 30 subjects in Arm B will be enrolled, thus the total sample size for the study will be approximately 36 subjects.

Statistical Methods:

The Full Analysis Set (FAS) consists of all subjects randomized or enrolled to each study arm who received at least 1 dose of any study treatment. The per-protocol (PP) analysis set consists of all randomized or enrolled subjects who received at least 1 dose of any study treatment and have a baseline disease assessment and at least 1 post-baseline response measurement. The safety analysis set consists of all randomized or enrolled subjects who received at least 1 dose of any study treatment.

All efficacy analyses will be based on the FAS and the analyses of response endpoints will be repeated using the PP analysis set.

Tumor response will be based on investigator's assessment according to modified IWCLL 2008 criteria (see Appendix 6). CR rate, ORR, rate of CR/BM MRD-, and rate of CR/PB MRD- will be estimated for each arm and their associated 90% confidence intervals will be calculated using the exact method.

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Adverse events will be coded using the current version of MedDRA and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria and will be summarized by system organ class and preferred term and by severity and relationship to study treatment. Clinical laboratory tests and their changes from baseline will be summarized descriptively.

Subject enrollment and disposition will be summarized descriptively by treatment arms. Reasons for premature discontinuation from study treatment will be provided.

Subject demographics and baseline characteristics as well as baseline disease characteristics will be summarized descriptively by treatment arms using the FAS. Medical history and concomitant medication use will be summarized using the safety analysis set. In general, continuous variables will be summarized by sample size, mean, standard deviation, median, quartiles, minimum and maximum and categorical variables will be summarized by counts and percentages.

Treatment exposure and compliance will be summarized descriptively using treatment duration, number of doses, average dose, dose modifications, and treatment adherence rate based on the safety analysis set.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ANC	absolute neutrophil count
AST	aspartate transaminase
$AUC_{0\text{-}24h}$	mean exposure
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BID	twice daily
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CIRS	cumulative illness rating scale
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma/serum concentration of drug
CMV	Cytomegalovirus
CNS	central nervous system
CR	complete response/complete remission
CR/BM MRD-	complete response with bone marrow minimal residual disease negativity ($<10^{-4}$ CLL cells present)
CR/PB MRD-	complete response with peripheral minimal residual disease negativity ($<10^{-4}$ CLL cells present)
CrCl	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
C_{tau}	observed drug concentration at the end of the dosing interval
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
del17p	deletion of short arm of chromosome 17
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
EU	European Union
eSAE	electronic serious adverse event
FAS	full analysis set
FDA	Food and Drug Administration
FL	follicular lymphoma
FSH	follicle stimulating hormone
GCB	germinal center B-cell lymphoma
GCLLSG	German CLL Study Group
GCP	good clinical practice
GGT	gamma-glutamyltransferase
HBcAb	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest toxic dose
IB	Investigator's Brochure
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IMP	investigational medicinal product
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
IP	investigational product
IWCLL	International Workshop on CLL
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MRD	minimal residual disease, with positivity defined as $>1/10^{-4}$ CLL cells present in a sample
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction

PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetics
PP	per protocol
PS	performance status
PR	partial response/partial remission
PT	prothrombin time
PVE	(Gilead) Pharmacovigilance and Epidemiology
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	stable disease
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TEN	Toxic Epidermal Necrolysis
TLR	Toll-like receptor
TP53mut	mutation within TP53 genomic locus
TTNT	time to next therapy
ULN	upper limit of normal
US	United States
WBC	white blood cell
WM	Waldenstrom's macroglobulinemia

1. INTRODUCTION

1.1. Background

1.1.1. Chronic Lymphocytic Leukemia

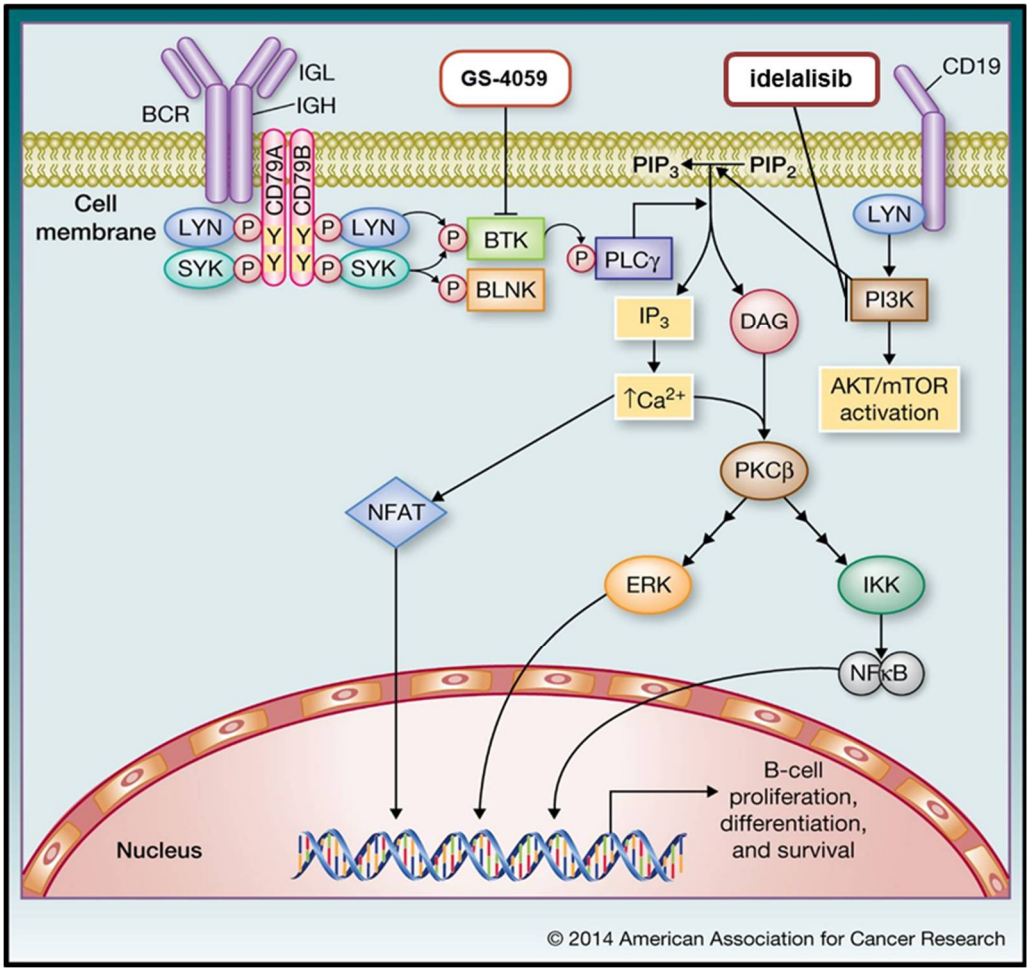
Chronic lymphocytic leukemia (CLL) is the most commonly occurring leukemia in Europe and the United States (US) with an estimated lifetime risk of 1:167 in the US (NIH SEER database) {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. CLL is marked by the progressive accumulation of functionally impaired monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver {Dighiero 2008}. Symptoms include fever, night sweats, and weight loss, and disease progression is often accompanied by lymphadenopathy, splenomegaly, or hepatomegaly. The course of CLL is highly variable, with a median survival of more than 10 years in low-risk patients compared with 2 years in high-risk subjects. CLL is largely a disease of the elderly; at diagnosis, 70% of subjects are ≥ 65 years of age and the median age is 71 years {National Cancer Institute (NIH) 2016}.Subjects with CLL harboring a deletion of the short arm of chromosome 17 (del17p) or an inactivating mutation in the TP53 gene (TP53mut) are a particularly high risk CLL population and have shorter intervals prior to disease progression and shorter overall survival (OS) {Stephens 2015}.

For the majority of patients, chemoimmunotherapy remains the current standard of care for initial treatment {Gribben 2011}. The CLL8 study of the German CLL Study Group (GCLLSG) comparing FC (fludarabine and cyclophosphamide) vs FCR (FC and CD20) {Hallek 2010} established the benefit of addition of an anti-CD20 monoclonal antibody to a combination of a purine analog and alkylating agent in achieving a durable remission and prolonging survival {Byrd 2005, Catovsky 2007, Hallek 2010, Robak 2010}. The subsequent CLL-10 study of FCR vs BR (bendamustine and CD20) {Eichhorst 2016} clarified the role of both regimens in the initial treatment of CLL. However, for the overwhelming majority of subjects, these treatments are not curative; the disease will usually relapse and further intervention is required to obtain and maintain tumor control. While repeat treatment with chemoimmunotherapy can be pursued at the time of disease relapse, it has toxicity, including myelosuppression and fatigue. These toxicities limit the suitability of FCR and BR in subjects with significant comorbidities or limited functional status. Similarly, subjects with a limited response to initial therapy (refractory) and those who have recurrent disease within 3 years are poorly served by repeated treatment with chemoimmunotherapy.

The approval and ongoing development of new, effective, oral small molecule targeted agents for the treatment of relapsed and refractory CLL has changed the treatment landscape. For subjects with del17p or TP53mut who respond poorly to chemoimmunotherapy in the frontline setting, these agents have yielded meaningful improvements in response rate and duration of response.

How best to combine targeted agents remains an area of interest due to the potential to achieve deeper and more durable responses in the treatment of CLL.

Figure 1-1. Inhibition of the BCR Pathway



Adapted from {Herrera 2014}

1.2. Idelalisib

Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling enzymes mediate the effects of multiple receptors including the B-cell receptor (BCR). The class I PI3K containing the p110δ catalytic subunit (PI3Kδ) is critical for primary survival, proliferation, and homing of malignant B cells. Idelalisib is a potent competitive inhibitor of the adenosine triphosphate (ATP) binding site of the PI3Kδ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Okkenhaug 2003, Vanhaesebroeck 2005}. The effects of p110δ on lymphocyte activation/function, cellular proliferation, and protection from apoptosis provide the rationale for targeting this isoform as a therapy for hematologic malignancies.

Idelalisib (Zydelig®) is an inhibitor of PI3Kδ which was first approved in the US on 23 July 2014 for the treatment of relapsed CLL, follicular lymphoma (FL), and small lymphocytic lymphoma (SLL), followed by approval in the European Union (EU) on 18 September 2014 (centrally authorized). Zydelig is currently approved in 40 countries worldwide.

In CLL, the hazard ratio for PFS was 0.18 (95% CI; 0.10, 0.32) compared to rituximab alone {Brown 2014a, Flinn 2014, Furman 2014}. Idelalisib as monotherapy or in combination with other agents (bendamustine, chlorambucil) and immunotherapy (rituximab, ofatumumab) has been shown to be tolerable and demonstrated clinical efficacy in clinical trials in subjects with CLL and other hematological malignancies.

The approved idelalisib dosing regimen is 150 mg twice daily administered as monotherapy (FL) or in combination with rituximab (CLL). Dose modification to 100 mg twice daily due to toxicity is included within prescribing guidelines. For combination therapy outlined in this protocol, the dose of idelalisib has been reduced to 100 mg once daily. At 50 mg twice daily, idelalisib has demonstrated clinical benefit and acceptable safety in the prior single-agent and combination treatment settings for CLL. The 50 mg twice daily and 100 mg once daily idelalisib dosing regimens are predicted to have a comparable reduction in exposure of > 50% from 150 mg twice daily (C_{max}, AUC) with a further reduction of C_{tau} by once daily rather than twice daily dosing.

Information on the preclinical pharmacology, toxicology, metabolism, and PK of idelalisib can be found in the idelalisib Investigator's Brochure (IB).

1.3. Tirabrutinib

1.3.1. General Information

Tirabrutinib (also known as GS-4059, ONO-4059HCL, ONO-1973, and ONO-WG-307) is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) that is being jointly developed by Gilead Sciences, Inc. (Gilead) and Ono Pharmaceutical Co, Ltd. (ONO) for oral administration in the treatment of B-cell malignancies.

1.3.2. BTK in B-cell Malignancies

BTK was originally identified in 1993 as a non-receptor intracellular protein tyrosine kinase that is defective in the inherited immunodeficiency disease X-linked agammaglobulinaemia (XLA) {Tsukada 1993, Vetrie 1993}. XLA is characterized by low levels of immunoglobulin production and the absence of peripheral B cells, indicating a specific role for BTK in B-cell development and function. BTK is a member of the TEC family of tyrosine protein kinases. BTK is primarily expressed in hematopoietic cells, particularly in B cells, but not in plasma cells or T cells {de Weers 1993, Genevier 1994, Smith 1994}. BTK is also found in specific cells of the myeloid lineage, including monocytes, macrophages, neutrophils, and mast cells, where its biological role remains to be fully explored.

BTK plays a crucial role in the development and activation of B cells through its activation via the BCR {Aoki 1994, Hendriks 2014, Honigberg 2010}. Signaling through the BCR regulates cellular proliferation and activation and promotes survival, differentiation, and clonal expansion of B cells (Figure 1-1) {Rickert 2013}. In addition to BCR signaling, BTK is activated by Toll-like receptors (TLR) which contribute to B-cell activation {Jefferies 2003}. BTK also plays a critical role in signaling pathways triggered by the C-X-C chemokine receptor type 4 and type 5 (CXCR4 and CXCR5) which mediate homing of B cells to lymph nodes and bone marrow and control integrin-mediated adhesion and B-cell survival to vascular adhesion molecule 1 (VCAM1) and fibronectin {de Rooij 2012, Hendriks 2014}.

Signaling through the BCR has been established to have a key oncogenic role in many B-cell malignancies, including (CLL, SLL, diffuse large B-cell lymphoma [DLBCL], mantle cell lymphoma [MCL], and lymphocytic lymphoma/Waldenstrom's macroglobulinemia [WM]). A first-in-class BTK inhibitor, ibrutinib (Imbruvica®), provides clinical benefit to subjects with CLL, MCL, and WM {Pharmacyclics Inc. 2015}. Additionally, transient clinical responses were observed in a study of relapsed DLBCL, primarily in the non-GCB subtype {Wilson 2012}.

1.3.3. Nonclinical Pharmacology and Toxicology of Tirabrutinib

Please refer to the tirabrutinib IB for information regarding the nonclinical pharmacology, absorption, distribution, metabolism, and elimination (ADME) and nonclinical toxicity of tirabrutinib.

1.3.4. Clinical Trials of Tirabrutinib

Tirabrutinib is an orally administered, potent and selective inhibitor of BTK initially evaluated in a Phase 1 single agent dose escalation study, ONO-4059POE001, conducted in the United Kingdom (UK) and France {Walter 2015}. This study enrolled and treated 90 subjects with relapsed CLL, non-GCB DLBCL, MCL, SLL, and other indolent non-Hodgkin's lymphomas (iNHLs). Tolerability and efficacy of tirabrutinib monotherapy have been demonstrated in subjects with CLL at doses ranging from 20 to 600 mg once daily with no maximum tolerated dose (MTD) identified. Responses were observed in subjects in the NHL cohort at doses from 40 to 480 mg. Dose limiting toxicities (DLTs) of rash and non-immune reaction were observed at 600 mg once daily in the NHL cohort. For CLL patients, the most common AEs were contusion, neutropenia, anemia, and nasopharyngitis and the most frequent AEs attributed to tirabrutinib were hematoma, macule, dry skin, neutropenia, pruritus, diarrhea, and contusion. The most frequent ≥ Grade 3 AEs were neutropenia, anemia, thrombocytopenia, and lower respiratory tract infection.

All subjects continuing on tirabrutinib treatment have been transitioned to the GS-US-401-1787 continuation study; as of 01 June 2016, 27 subjects (18 with CLL) are continuing on treatment with tirabrutinib at doses ranging from 80 to 600 mg once daily with a median duration on study of 799 days.

Study ONO-4059-01 is an ongoing open-label, multi-center, non-randomized Phase 1 dose-escalation study of tirabrutinib monotherapy in Japanese subjects with relapsed/refractory B-NHL and CLL. This study utilizes a 3+3 design with dose levels ranging from 160 to 600 mg daily. As of 05 May 2016, 17 subjects had enrolled. The only AEs attributable to study drug were Mallory-Weiss syndrome (1), HBV reactivation (1), and pneumonitis (1; subject had pre-existing organizing pneumonia). All subjects resumed treatment with lower doses of study drug. Rash, anemia, lymphopenia, hypophosphatemia, hypokalemia and emesis were the only AEs reported in more than 1 subject (n 2 for all except n 5 for rash).

Study GS-US-401-1767 is a Phase 1, partially-blinded, single-dose, crossover, multiple-cohort study of capsule and tablet formulations of tirabrutinib to evaluate the relative bioavailability (rBA), food effect, and interaction with a proton pump inhibitor (PPI), omeprazole, in healthy subjects. PK data from this study show no difference in plasma exposure (C_{max} and AUC) of tirabrutinib between the capsule formulation and the low and high drug load (10% and 33% w/w, respectively) formulation tablets when administered as a single 100-mg dose in the fasted state. This data supports switching from capsules to tablets without adjusting dosage. There was no clinically relevant effect of food (high-fat meal) on the PK of a single 100-mg dose of tirabrutinib administered as the low and high drug load formulation tablets; as such, tirabrutinib tablets may be administered without regard to food. There was no clinically relevant effect of multiple doses of omeprazole on the PK of a single 100-mg dose of tirabrutinib administered as the low drug load formulation tablet. Tirabrutinib tablets may be co-administered with PPIs such as omeprazole.

Study GS-US-401-1765 is an open-label, crossover, Phase 1 study to evaluate the effects of an OATP1B1/1B3 inhibitor, single dose rifampin, and a strong CYP3A4/p-gp inducer, multiple doses of rifampin, on the PK of tirabrutinib in healthy subjects. The slight increase in tirabrutinib exposure observed in combination with single dose rifampin is not considered clinically relevant and does not preclude coadministration of OATP1B1/1B3 inhibitors. The half-life of tirabrutinib was unchanged and the exposure (C_{max} and AUC) of tirabrutinib was significantly decreased (~70%) following multiple doses of the inducer rifampin. Strong CYP3A4/P-gp inducers such as rifampin have the potential to decrease efficacy by reducing exposure.

Study GS-US-401-1768 is a single-center, open-label, Phase 1, mass-balance study of tirabrutinib administered as a single, oral dose of radiolabeled ^{14}C-tirabrutinib in healthy subjects with preliminary results showing extensive metabolism after oral administration by oxidation, reduction, hydrolysis, *N*-acetylation, sulfation, glutathione conjugation, and glucuronidation.

Study GS-US-401-1757, an ongoing Phase 1b dose-escalation study of tirabrutinib in combination with other anti-cancer therapy, provides the primary supportive data for this Phase 2 trial. This study used a 3+3 dose-escalation and dose-expansion design to establish a safe and well-tolerated dose of tirabrutinib in combination with idelalisib. Tirabrutinib once daily up to 160 mg combined with idelalisib 50 mg twice daily or 100 mg once daily has been well tolerated with no DLTs. As of 01 September 2016, a total of 23 subjects have been treated with either idelalisib 50 mg twice daily or idelalisib 100 mg once daily in combination with a range of once daily tirabrutinib doses from 20 to 80 mg. Adverse events of any grade occurring in more than 10 % of subjects are as follows: diarrhea (35%), neutropenia (30%), back pain (26%), constipation (26%), decreased appetite (22%), nausea (22%), contusion (17%), fatigue (17%), petechiae (17%), rash (17%), thrombocytopenia (17%), dyspepsia (13%), dyspnea (13%), herpes zoster (13%), oral candidiasis (13%), and vomiting (13%). The only Grade 3 or higher AEs that occurred in more than 1 subject were neutropenia (6), cellulitis (2), and sepsis (2), which are discussed along with investigator-assessed drug-related toxicities in the dose rationale Section 1.5.1.

For additional information and a summary of all clinical trials with tirabrutinib, refer to the tirabrutinib IB.

1.4. Obinutuzumab

Obinutuzumab (GA-101) is a humanized and glycoengineered monoclonal antibody (mAb), derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycol-engineering leading to the following characteristics {Mössner 2014}:

- High affinity binding to CD20 type II epitope.
- Increased antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP) {Herter 2014} related to an improved binding of the antibody to the different allotypes of FcγRIIIa expressed by natural killer (NK) cells and monocytes.
- Low complement-dependent cytotoxicity (CDC) activity related to the recognition of the CD20 type II epitope and the lack of CD20 localization into lipid rafts after binding of mAb to CD20.
- Increased direct cell death induction related to an elbow hinge amino exchange of the Fragment antigen-binding (Fab) region and the recognition of CD20 type II epitope.

The CLL 11 study, led by Roche and the GCLLSG, compared the safety and efficacy of 3 regimens: Chlorambucil vs. Rituximab + Chlorambucil (R/Chl) vs. Obinutuzumab (GA-101) + Chlorambucil (G/Chl) in previously untreated patients with CLL with either cumulative illness rating scale (CIRS) score >6 or CrCl <70 mL/min {Goede 2014}. The median age of subjects was 73 years. The results show superiority of G/Chl, with median PFS of 11, 16, and 27 months in Chl, R/Chl and G/Chl respectively. There was a statistically significant improvement in OS with G/Chl vs Chl (hazard ratio for death of 0.41; 95% CI, 0.23 to 0.74; P 0.002). The CR rate was 21% with G/Chl vs 7% with R/Chl. MRD negativity in the marrow was achieved in 19.5% of G/Chl subjects vs only 2.6% of those receiving R/Chl. Infusion-related reactions and neutropenia were more common with G/Chl than with R/Chl, but the risk of infection was not increased. Most infusion-related reactions occurred with the first infusion of both CD20 antibodies, with overall frequency of 65% with obinutuzumab (20% Gr 3/4) and 27% with rituximab (3% Gr 3/4). Due to the high frequency of Day 1 infusion-related reactions, the study was amended to split the first dose of 1000 mg over 2 days (100 mg on Day 1 and 900 mg on Day 2), this leading to partial amelioration of the reactions.

The safety and efficacy of obinutuzumab combined with idelalisib 150 mg twice daily was evaluated in a randomized, open-label Phase 3 study (GS-US-312-0118); this study was subsequently terminated due to safety concerns regarding the use of idelalisib at the dose of 150 mg twice daily in first-line treatment of CLL. A total of 57 subjects with previously untreated CLL were enrolled in Study GS-US-312-0118 at the time of study termination; of these, 33 were randomized to the combination of idelalisib with obinutuzumab and 32 were treated with this combination. Of the 32 subjects treated with the combination, the median duration of exposure was 9 weeks (range: 0.7 45 weeks). Treatment-emergent AEs reported

in >15% of these subjects were as follows (any grade/≥Grade 3): ALT increased (38%/31%); AST increased (38%/25%); neutropenia (31%/28%); anemia (25%/13%); diarrhea (25%/6%); and infusion-related reaction (19%/9%). A total of 14 subjects reported a treatment-emergent serious adverse event (SAE), of which the majority were due to infection (16%) [pneumonia (3%), sepsis (3%), bronchitis (3%), lung infection (3%), upper respiratory tract infection (3%)]; the remainder were due to anemia (6%), pneumonitis (6%), febrile neutropenia (3%), diarrhea (3%), enteritis (3%), pyrexia (3%), and chills (3%). A total of 3 subjects discontinued treatment with idelalisib due to an AE: 1 each for colitis (Grade 3), sepsis (Grade 3), and liver function test abnormality (Grade 4); 1 subject discontinued obinutuzumab due to sepsis (Grade 3). No deaths occurred on the study.

Obinutuzumab (Gazyva®/Gazyvaro®) is approved in the US and EU for use in combination with chlorambucil for the treatment of patients with previously untreated CLL.

For further information on obinutuzumab, refer to the local prescribing information (PI).

1.5. Rationale for This Study

Despite an increase in therapeutic options for CLL, few subjects are cured with current therapy. Small molecule targeted therapy for CLL avoids many of the toxicities of chemoimmunotherapy but requires chronic administration due to generally low CR rates. Novel regimens combining targeted therapy have the potential to improve CR rates, PFS, and OS while limiting toxicity.

Tirabrutinib and idelalisib each show significant single-agent clinical activity in CLL. The addition of an anti-CD20 antibody to CLL therapy has an established benefit {Hallek 2010} with the potential superiority of obinutuzumab in comparison with rituximab {Goede 2014}.

Preliminary *in vitro* data from primary CLL samples have shown additive or synergistic growth inhibition when combining tirabrutinib and idelalisib, suggesting the possibility of improved depth of response with combination treatment. While single mutations in drug targets have been shown to be sufficient for resistance to single-agent therapy, combination therapy has the potential to improve duration of response by creating a higher threshold for the emergence of drug-resistant malignant clones. Even with doses reduced from those used as single agents, combining tirabrutinib and idelalisib *in vitro* had striking efficacy, supporting the possibility of improving efficacy with low toxicity.

As of June 7, 2017, 14 subjects with CLL have been treated on Phase 1b Study GS-US-401-1757 with the combination of tirabrutinib and idelalisib with a median exposure of 67 weeks (range: 22-96). All 14 subjects continue on study and treatment at this time; however, 0 of 10 evaluable CLL subjects have achieved a CR. Given the lack of CRs in the ongoing treatment experience with the combination of tirabrutinib and idelalisib, enrollment into Arm A (the doublet combination of tirabrutinib and idelalisib) was discontinued with Amendment 3. Arm B continued enrollment as the safety and preliminary efficacy of the combination with the addition of obinutuzumab retains the potential to be safe and achieve a high rate of deep response.

1.5.1. Rationale for Dose Selection

This Phase 2 study will evaluate the efficacy and safety of the combination of GS-4059 and idelalisib with and without obinutuzumab in subjects with relapsed or refractory CLL.

A maximum tolerated dose during single-agent treatment of CLL patients was not identified with tirabrutinib at up to 600 mg once daily (ONO-4059POE001) {Walter 2015} or with idelalisib at up to 350 mg twice daily {Brown 2014b}. Idelalisib at 100 mg once daily is expected to reduce idelalisib exposure by ~60% from the approved 150 mg twice daily dose with the potential for reducing idelalisib-associated toxicity. The combination was tested in the dose-ranging Phase 1b GS-US-401-1757 study. The combination of tirabrutinib at up to 80 mg once daily combined with idelalisib 50 mg twice daily was shown to be safe and tolerable with no DLTs during the 28-day safety review period. A subsequent cohort of tirabrutinib 80 mg once daily combined with idelalisib 100 mg once daily was also safe and tolerable. With convenient once daily dosing and comparable cumulative exposure, the combination of tirabrutinib 80 mg once daily and idelalisib 100 mg once daily will be evaluated in the current study.

Data from both the single-agent treatment experience and the combination Phase 1b GS-US-401-1757 study support the potential efficacy of the combination of tirabrutinib 80 mg once daily and idelalisib 100 mg once daily. Preliminary BTK occupancy data in peripheral blood mononuclear cells (PBMC) demonstrates full occupancy by tirabrutinib at doses of 40 mg once daily and higher. A total of 28 subjects with CLL were treated in the ONO-4059POE001 single-agent dose escalation study with tirabrutinib. With a minimum dose of 80 mg daily, 20 of 21 evaluable subjects had a PR or better; at a tirabrutinib dose of 20 or 40 mg, 2 of 3 subjects had a PR or better. In the Phase 1 CLL treatment experience with idelalisib, the 50 mg twice daily dose had an overall response rate of 40%, comparable to 46% observed at the approved dose of 150 mg twice daily.

Based on data as of 02 September 2016, the median time on study for 23 subjects with lymphoid malignancies treated with the combination of tirabrutinib and idelalisib in the GS-US-401-1757 study was 227 days (range: 37-437). Of these 23 subjects, 10 had CLL. No subject discontinued the study due to an AE. In total, 10 (43%) subjects had a Grade 3 or 4 AE that was attributed by the investigator to treatment. The only ≥Grade 3 AE attributed to treatment in more than 1 subject was neutropenia (6 subjects). Preliminary pharmacokinetic results from the GS-US-401-1757 study are consistent with the prediction that idelalisib 100 mg once daily is comparable to 50 mg twice daily in exposure as established by C_{max} and $AUC_{0\ 24h}$ with a ~2 fold reduction in C_{tau}. Of the 7 subjects in the GS-US-401-1757 study who have been on study for at least 24 weeks and undergone at least 1 CT scan (3 with FL, 2 with SLL, and 1 each with CLL and MCL), 4 have reported a PR. Two subjects progressed prior to 24 weeks (1 each with MZL and DLBCL).

Obinutuzumab will be used at the approved label 1000 mg dose and schedule. The combination of obinutuzumab with idelalisib has been evaluated in Study GS-US-312-0118. It is important to note that the dose of idelalisib has been reduced from 150 mg twice daily used in combination with obinutuzumab in Study GS-US-312-0118 to 100 mg once daily in the current study. In addition, the safety of tirabrutinib 80 mg once daily and idelalisib 100 mg once daily with and without obinutuzumab will be evaluated in 6 subjects per treatment arm in the safety run-in before additional subjects are enrolled.

1.6. Risk/Benefit Assessment for the Study

Tirabrutinib

In the completed Phase 1 study ONO-4059POE001, 90 subjects with either NHL or CLL received tirabrutinib at doses ranging from 20 to 600 mg per day for up to 3 years. Observed AEs were mainly Grades 1 and 2 in severity, and were most commonly infections, hematological abnormalities, skin disorders, gastrointestinal disorders, and general disorders. The majority of AEs were assessed by the investigator as not related to tirabrutinib. Hematological disorders and infections have been observed; irrespective of severity, the majority of these events did not preclude ongoing treatment. Grade 1 and 2 diarrhea, respectively, was observed in 20% and 4% of study participants. No Grade 3 or higher diarrhea attributed to tirabrutinib by the investigator was reported. Bruising was observed frequently; however, clinically-significant bleeding events (such as those requiring transfusions) were unusual and hemorrhage did not limit the ability to continue on therapy for the majority of subjects.

In ongoing Study GS-US-401-1787 (rollover from Study ONO-4059POE001), AEs ≥ Grade 3 assessed cumulatively from the beginning of Study ONO-4059POE001 (N 90) were reported for 61 subjects (67.8%), most frequently neutropenia and thrombocytopenia (each 16 subjects, 17.8%) followed by anemia (10 subjects, 11.1%) and lower respiratory tract infection (8 subjects, 8.9%). Overall, SAEs were reported for 44 subjects (48.9%).

Please refer to the IB for more information.

Idelalisib

Idelalisib (Zydelig®) is a PI3Kδ inhibitor which is approved in 40 countries, including those in the EU, for the treatment of relapsed/refractory FL and CLL. Please refer to the SmPC for further information.

In an embryo-fetal development study of idelalisib in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations, and lower fetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo fetal development were not investigated in a second species.

Based on data from the clinical development programs and post-marketing pharmacovigilance for idelalisib and other PI3K inhibitors {Flinn 2013} alone or in combination with chemotherapy or anti-CD20 antibodies, AEs including infection, diarrhea/colitis, transaminase elevation, rash, neutropenia, organizing pneumonia, and pneumonitis may be observed in subjects treated with idelalisib. Guidelines for managing these AEs have been incorporated into this protocol. The monitoring to be performed and the actions to be taken in response to toxicity are based on experience with interruption, dose modification, rechallenge, and re-escalation with idelalisib treatment.

A recent aggregate analysis of three Phase 3 trials in front-line CLL (1) and early-line relapsed iNHL (2) demonstrated an increase in SAEs and deaths, primarily due to infections, with the addition of idelalisib to standard therapy, particularly in the first 6 months of therapy. The risk of death was higher in bendamustine containing regimens. In light of this additional idelalisib safety data, pneumocystis prophylaxis, CMV surveillance, and increased monitoring for neutropenia in the first 6 months have been instituted in conjunction with idelalisib therapy, including in this study protocol.

In contrast to the studies in which increased deaths from infection in idelalisib treated patients were noted, this study is limited to subjects with previously-treated CLL there is a clear benefit of idelalisib treatment in this population. Two large Phase 3 clinical trials {Furman 2014, Zelenetz 2015} have shown improved PFS and OS for previously-treated CLL patients with the addition of idelalisib to either the combination of bendamustine and rituximab or rituximab alone. Furthermore, the decreased dose of idelalisib 100 mg once daily used in the combination setting, including in this study, is predicted to reduce idelalisib exposure (AUC and C_{min}) by ~50% and has the potential to reduce idelalisib-associated toxicities while maintaining efficacy when administered in combination.

Please refer to the IB for more information.Obinutuzumab

Obinutuzumab (Gazyva®/Gazyvaro®) is an anti-CD20 mAb which is approved in the US and EU for use in combination with chlorambucil for the treatment of patients with previously untreated CLL. The safety reference documents for obinutuzumab will be the Summary of Product Characteristics (SmPC). Please refer to the SmPC for further information.

In a Phase 3 trial, patients were treated with chlorambucil alone, GAZYVARO in combination with chlorambucil, or rituximab product in combination with chlorambucil. The Stage 1 analysis compared GAZYVARO in combination with chlorambucil vs. chlorambucil alone, and Stage 2 compared GAZYVARO in combination with chlorambucil vs. rituximab product in combination with chlorambucil.

The most common Grade 3 to 4 adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVARO containing arm of clinical trials were neutropenia, infusion reactions, and thrombocytopenia.

The most common adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVARO containing arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

The most common obinutuzumab-related events are infusion-related reactions and tumor lysis syndrome, most commonly during the initial administration, hypersensitivity (immediate or delayed onset), and worsening of pre-existing cardiac conditions. Some patients receiving obinutuzumab have experienced cytopenias or infections. Obinutuzumab use has been associated with hepatitis B virus (HBV) reactivation and very rare cases of progressive multifocal leukoencephalopathy.Mitigation strategies are defined in this protocol. To reduce the incidence and severity of obinutuzumab-related infusion reactions, established premedication regimens and infusion modification algorithms have been included (Section 5.3.2). To mitigate the risk of *Pneumocystis jirovecii* pneumonia, antibiotic prophylaxis is required (Section 5.4.1).

To mitigate the risk of HBV reactivation in subjects treated with an anti-CD20 antibody, HBV screening will be performed. Subjects who are hepatitis B core antibody positive at screening may be enrolled only if the plasma DNA PCR test is negative, and will be monitored for potential HBV reactivation (manifested as detectable HBV DNA by quantitative PCR). Subjects will be tested monthly for the duration of obinutuzumab therapy and every 3 months thereafter for 1 year from the last dose of obinutuzumab therapy in this study. Specific instructions for supportive care in response to myelosuppression are described. Investigators are instructed to institute prophylaxis and monitoring for tumor lysis syndrome for subjects with a high tumor burden, high circulating lymphocyte count (>25 × 10^9/L) or renal impairment (CrCl <70mL/min).

Combination therapy

Although new toxicities due to the combination of agents remains a possibility, the safety and tolerability of tirabrutinib combined with idelalisib has been previously evaluated in a Phase 1b dose-escalation study (GS-US-401-1757). Idelalisib does not increase the exposure of tirabrutinib significantly based on preliminary pharmacokinetic data from this study. The combination of idelalisib and obinutuzumab has been previously evaluated in Phase 3 Study GS-US-312-0118 (results discussed in Section 1.4). The patient population enrolled in Study GS-US-312-0118 (previously untreated CLL) is distinct from that in the current study (relapsed/refractory CLL). The recommendations from the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), which were issued on 07 July 2016 and adopted by the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2016, reflect a favorable benefit-risk assessment for the treatment of patients with relapsed/refractory CLL with the combination of idelalisib and rituximab. Furthermore, the CHMP re-issued a positive opinion on 21 July 2016 for a Type II variation based on data from Study GS-US-312-0119, which also supported a favorable benefit-risk assessment and an update to the Zydelig SmPC to include treatment of patients with relapsed/refractory CLL with the combination of idelalisib and ofatumumab. The dose of idelalisib has been reduced from the currently approved 150 mg twice daily dose used in Study GS-US-312-0118 to 100 mg once daily in the current study.

The safety of the combination of tirabrutinib 80 mg once daily and idelalisib 100 mg once daily with and without obinutuzumab will be evaluated in this Phase 2 study through a review of the safety data for the initial 6 subjects in each treatment arm after 28 days of therapy prior to enrollment of additional subjects. The dose of tirabrutinib used in the current study is 13% of the highest safe dose identified for CLL patients in Phase 1 Study ONO-4059POE0001 and the dose of idelalisib is 33% of the approved dose in relapsed/refractory CLL patients. Study visits including laboratory monitoring will occur weekly for the first 28 days of treatment for close monitoring. Following evaluation of the safety data for the first 6 subjects in each treatment arm, the SRT will determine if weekly visits for the first 28 days should continue or may be reduced in frequency for the remainder of subjects enrolled in the study.

Benefits from combination therapy include the potential to achieve higher rates of response and improve DOR and the potential for reduced toxicity with increased efficacy by the use of lower individual study drug doses in combination, particularly in the case of idelalisib.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To determine the preliminary efficacy of the combination of tirabrutinib and idelalisib with obinutuzumab in subjects with relapsed or refractory CLL

The secondary objective of this study is:

- To evaluate the safety and tolerability of the combination of tirabrutinib and idelalisib with and without obinutuzumab

CCI

3. STUDY DESIGN

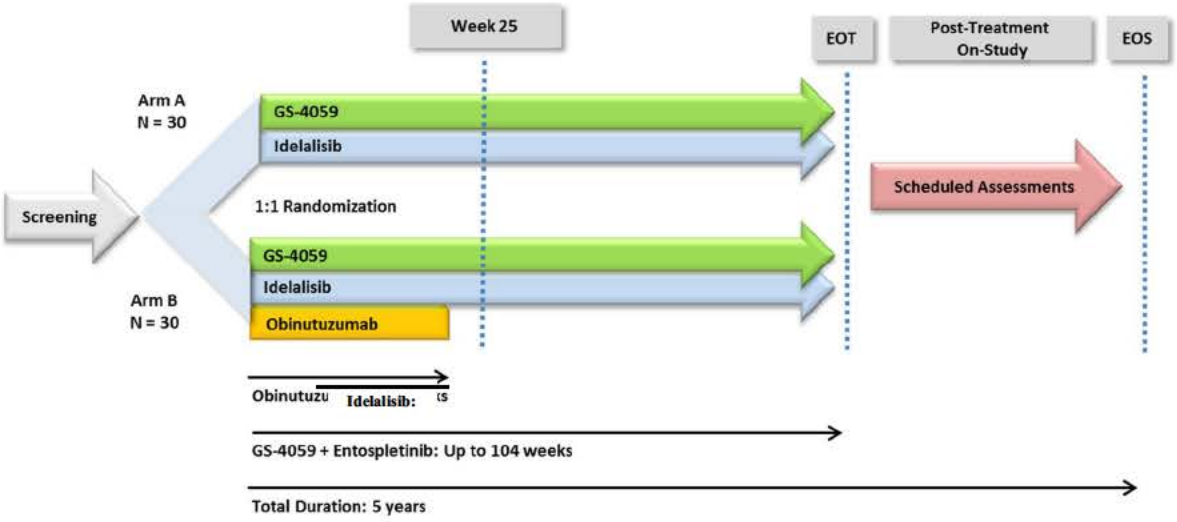
3.1. Study Design

This is a Phase 2, prospective, open-label, multicenter trial to evaluate the safety and efficacy of the combination of tirabrutinib and idelalisib with and without obinutuzumab in subjects with relapsed or refractory CLL.

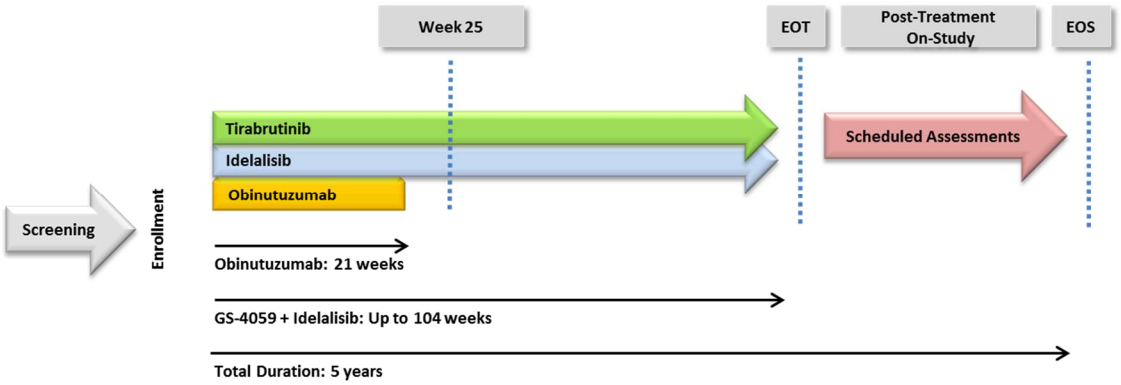
3.2. Study Treatments

Combination therapy of tirabrutinib (BTK inhibitor) 80 mg once daily and idelalisib (PI3Kδ inhibitor) 100 mg once daily with and without obinutuzumab will be evaluated for efficacy, safety, and tolerability.

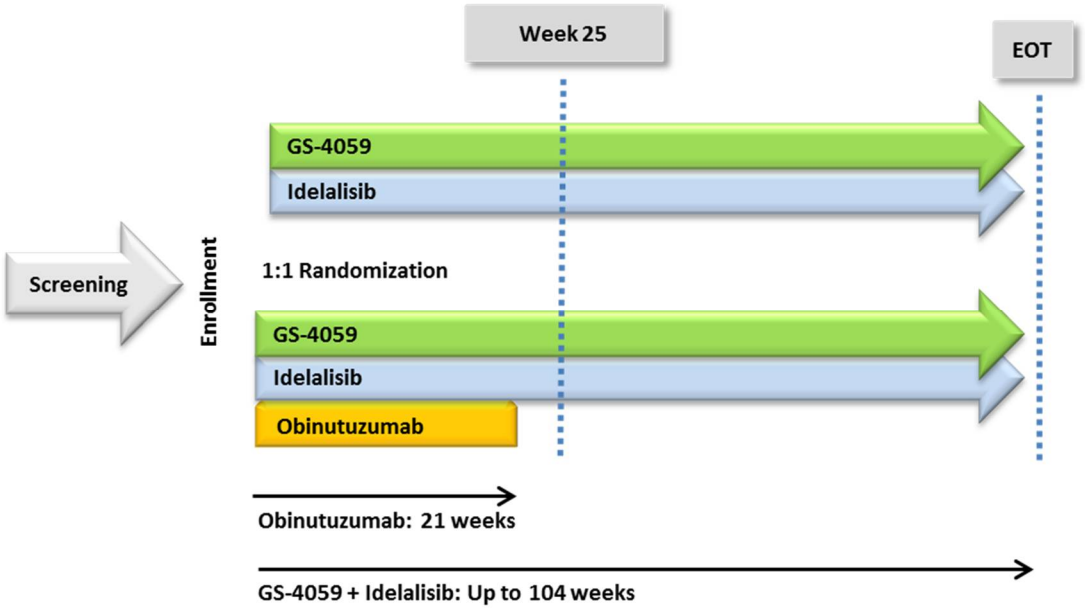
Eligible subjects will be treated with the combination of tirabrutinib and idelalisib and stratified by the presence of del17p/TP53mut in CLL cells. Following stratification, subjects will be randomized 1:1 to treatment with the combination of tirabrutinib and idelalisib with or without obinutuzumab.



With Amendment 3, randomization was discontinued. All subsequently enrolled subjects entered Arm B (tirabrutinib + idelalisib + obinutuzumab).



With Amendment 4, the Post Treatment period will no longer be applicable.



Enrollment will be temporarily paused following enrollment of the first 6 subjects into Arm B, who will be observed for safety for 28 days following the first dose of study treatment including weekly clinical evaluation through that period. Additional subjects may be enrolled into the safety cohort if any of the first 6 subjects in Arm B discontinue therapy during the initial 28 days for reasons unrelated to toxicity. A Safety Review Team (SRT) will review 28-day safety data from the first 6 subjects in Arm B and determine whether enrollment may resume and if weekly clinical evaluation through the first 28 days should continue or may be reduced in frequency for the remainder of the subjects enrolled in the study.

The SRT will consist of at least one investigator from the GCLLSG and Gilead study team members including but not limited to: the medical monitor, representatives from Pharmacovigilance and Epidemiology (PVE), and Biostatistics.

The safety review will include the assessment of the following:

- Grade ≥ 4 hematological toxicities persisting for > 7 days or non-hematologic laboratory abnormalities except for asymptomatic AST/ALT elevation
- Grade ≥ 3 non-hematological toxicities (except for alopecia or the following that resolve within 72 hours with medical intervention: tumor lysis, nausea, vomiting, diarrhea, or constipation)
- Grade ≥ 2 non-hematologic treatment-emergent adverse events (TEAE) that in the opinion of the investigator are of potential clinical significance such that further dosing would expose subjects to unacceptable risk

Criteria for termination of the study are:

1) An unacceptable safety profile or incidence of AEs or SAEs revealed in this or any other study in which the combination of agents is administered

2) Any other factor that in the view of the sponsor constitutes an adequate reason for terminating the study

As agreed with the German Federal Institute for Drugs and Medical Devices Agency (BfArM), safety report including the cumulative safety results and summary of the conclusion of the SRT following assessment of the safety cohort was submitted to the BfArM.

The study steering committee, including representatives from the GCLLSG and Gilead, will review ongoing safety data at least quarterly throughout the treatment period and regularly for the complete duration of the study.

3.3. Duration of Treatment

Obinutuzumab will be administered for up to 8 doses over 21 weeks to subjects randomized or enrolled to Arm B (tirabrutinib + idelalisib + obinutuzumab). Combination treatment with the oral agents (tirabrutinib and idelalisib) will continue for all subjects for up to 104 weeks in the absence of disease progression, unacceptable toxicity, or documentation of CR/BM MRD-. If CR/BM MRD- is documented on study, treatment will stop after the earlier of:

A) an additional 3 months of therapy or

B) 104 weeks of total treatment

3.4. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Documented progression of CLL
- Non-study treatment for CLL
- Development of malignant disease requiring systemic therapy
- Pregnancy
- Investigator discretion
- Non-compliance with study treatment
- Severe protocol violation
- Subject request to discontinue for any reason
- Lost to follow-up
- Death
- Study termination by the sponsor
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol (Section 6.5), or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

3.5. Duration of Study

This study will continue to monitor subjects for up to 30 days post end of treatment, or up to Week 25 should a subject discontinue treatment prior to Week 25 for reasons other than disease progression.

3.6. Criteria for Discontinuation from Study

Subjects may be removed from the study for the following reasons:

- Death
- Investigator discretion
- Withdrawal of consent
- Study termination by the sponsor

3.7. GCLLSG CLL Registry

Consenting subjects for inclusion in the GCLLSG registry is requested at screening or as close thereafter as possible.

3.8. Post Study Care

At this time, there is no plan to provide post-study care to subjects who have participated in this study.

4. SUBJECT POPULATION

4.1. Number of Subjects

The study will enroll approximately 36 subjects in total; 30 evaluable subjects in Arm B and approximately 6 subjects in Arm A.

4.2. Inclusion Criteria

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

1) Documentation of relapsed or refractory CLL

2) Have an indication per modified IWCLL 2008 criteria for treatment; subjects without radiographically measurable disease (defined as ≥ 1 lesion > 1.5cm in diameter as assessed by CT or MRI) must have bone marrow evaluation at screening

3) Adequate hematologic function as indicated by a platelet count ≥ 50×10^9/L, a neutrophil count ≥ 1×10^9/L and a hemoglobin ≥ 8g/dL unless lower values are directly attributable to documented bone marrow burden of CLL

4) Adequate renal function as indicated by a CrCl ≥ 50 mL/min calculated by the modified Cockcroft-Gault formula or from a 24 hour urine collection

5) Adequate liver function as indicated by total bilirubin ≤ 1.5× institutional upper limit of normal (ULN) unless attributed to Gilbert's syndrome and AST/ALT ≤ 2.5×ULN

6) Male or female ≥ 18 years of age

7) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2

8) Absence of active HBV infection (serological testing within 6 weeks prior to randomization or enrollment with the following results: HBsAg negative AND anti-HBcAb negative, or if anti-HBcAb positive, HBV DNA PCR negative)

9) HCV Ab negative or if Ab positive, negative HCV RNA PCR within 6 weeks prior to randomization or enrollment

10) Negative testing for HIV within 6 weeks prior to randomization or enrollment

11) Satisfies the following criteria:

    a) For female subjects of childbearing potential, willingness to abstain from sexual intercourse or use a protocol-specified method of contraception as described in Appendix 4

    b) Male subjects of reproductive potential who engage in sexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4

12) Ability and willingness to provide written informed consent and adhere to protocol requirements including study visit schedule, drug administration plan, imaging studies, laboratory testing, other study procedures and restrictions including mandatory prophylaxis for PJP

4.3. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible for participation in this study:

→ Known transformation of CLL (ie, Richter's transformation, prolymphocytic leukemia)

→ Known CNS involvement

→ Progression on treatment with any inhibitor of BTK, SYK, PI3K, BCL-2, or obinutuzumab. The treatment and disease response history of subjects with prior treatment with agents in these classes should be reviewed by the sponsor or the GCLLSG study office centrally prior to enrollment to clarify sensitivity to these treatments.

→ Any treatment for CLL other than corticosteroids for symptomatic management within 28 days of the start of study treatment

→ Participation on a concurrent therapeutic clinical trial unless all treatment is complete with only ongoing surveillance

→ Diagnosis of or concern for progressive multifocal leukoencephalopathy

→ History of myelodysplastic syndrome or another malignancy other than CLL, *except* for the following: any malignancy that has been in complete remission for 3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to start of study therapy

→ Active infection requiring systemic therapy

→ Pregnant or nursing women (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment and monthly during therapy)

→ Active autoimmune disease including autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura requiring a higher corticosteroid equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped >14 days prior to randomization or enrollment; exceptions may be made for corticosteroids prescribed specifically for management of CLL symptoms after discussion with the study medical monitor.

→ Diagnosis of inflammatory bowel disease or ongoing symptomatic pneumonitis

→ Ongoing CMV infection, treatment or prophylaxis for CMV within the past 28 days

→ History of stroke or intracranial hemorrhage within 12 months of randomization or enrollment; subjects requiring therapeutic anticoagulation for any indication should be discussed with the GCLLSG coordinating physician and/or medical monitor prior to screening

→ Legal incapacity, prisoners or subjects institutionalized by regulatory or court order, or any individual in dependence to study sponsor or any investigator

→ Use of a strong CYP3A4 or a strong P-gp inducer within 2 weeks of first dose of study treatment or anticipated chronic use while on study

→ Demonstration of QTc interval > 450 milliseconds or requirement for ongoing treatment with concomitant medications that prolong the QT interval

→ Known hypersensitivity to obinutuzumab, idelalisib, tirabrutinib, or any of the excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

It is the responsibility of the Investigator to ensure that subjects are eligible for the study prior to randomization or enrollment. Subjects will be assigned a unique screening number at the time of consent. A medical review of selected screening data will be performed by members of the GCLLSG to confirm eligibility and must be completed prior to randomization or enrollment.

Once eligibility is confirmed, subjects will be assigned a unique subject number from the interactive web response system (IWRS), randomized in a 1:1 ratio to treatment with the combination of tirabrutinib and idelalisib with and without obinutuzumab. The randomization will be stratified by the presence of del17p/TP53mut in CLL cells. Once a subject number is assigned to a subject, it will not be reassigned to another subject. This is an open-label study.

With Amendment 3, randomization of subjects will no longer be performed as only Arm B of the study will continue to enroll.

All Day 1 tests and procedures must be completed prior to the dispensation and administration of the first dose of study treatment on Week 1 Day 1.

5.2. Description and Handling of Tirabrutinib, Idelalisib, and Obinutuzumab

5.2.1. Tirabrutinib

5.2.1.1. Formulation

Tirabrutinib film-coated tablets, 20 mg, contain the equivalent of 20 mg tirabrutinib as the hydrochloride salt (GS-4059-01) and utilize a 10% w/w drug load formulation. The 20 mg tablet is a blue, plain-faced, round, film-coated tablet and contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C blue #2/indigo carmine aluminum lake.

Tirabrutinib film-coated tablets, 40mg, contain the equivalent of 40 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The 33% drug load formulation tablet is an orange, plain-faced, round, film-coated tablet. The tirabrutinib film-coated tablets, 40 mg, contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6/sunset yellow FCF aluminium lake, and iron oxide yellow.

Tirabrutinib film-coated tablets, 80 mg, contain the equivalent of 80 mg tirabrutinib as the hydrochloride salt (GS-4059-01) and utilize a 33% drug load formulation. The 80 mg tablet is a yellow, plain-faced, modified capsule-shaped, film-coated tablet and contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

5.2.1.2. Packaging and Labeling

Tirabrutinib tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drug(s) shall be labeled to meet applicable requirements of the EU Guideline to Good Manufacturing Practice Annex 13 (Investigational Medicinal Products) and/or other local regulations.

5.2.1.3. Storage and Handling

Study drug tirabrutinib should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.2. Idelalisib

5.2.2.1. Formulation

Idelalisib will be provided in tablets intended for oral administration. Each tablet contains 100 mg of active idelalisib. The 100 mg tablets are oval, debossed with “100” on one side and “GSI” on the other, and film-coated orange. The tablets include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide (50 mg tablets only), FD&C Yellow #6/Sunset Yellow FCF aluminum lake (100 mg tablets only), polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide.

5.2.2.2. Packaging and Labeling

Idelalisib tablets are packaged in white, HDPE bottles. Each bottle contains 60 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Idelalisib to be distributed to centers in the EU shall be labeled to meet applicable requirements of the EU Guideline to Good Manufacturing Practice Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.2.3. Storage and Handling

Idelalisib bottles should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handing idelalisib.

5.2.3. Obinutuzumab

5.2.3.1. Formulation

Please refer to the Gazyvaro (obinutuzumab) SmPC.

5.2.3.2. Packaging and Labeling

Commercially available product of obinutuzumab will be used for this study.

Obinutuzumab to be distributed to centers in the EU shall be labeled to meet applicable requirements of the EU Guideline to Good Manufacturing Practice Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3.3. Storage and Handling

Commercially available obinutuzumab will be used for this study. Further information regarding storage and handling are available in the Gazyvaro (obinutuzumab) SmPC.

5.3. Dosage and Administration of Tirabrutinib, Idelalisib, and Obinutuzumab

5.3.1. Tirabrutinib and Idelalisib

Tirabrutinib and idelalisib will be provided by Gilead. Tirabrutinib tablets (4 × 20 mg, 2 x 40 mg, or 1 x 80 mg) and idelalisib tablets (1 x 100 mg) will be self-administered orally once daily. Dosing with both agents will begin on Week 1 Day 1 of the study and thereafter at approximately the same time each day until end of treatment. Study drugs should be swallowed whole with water. Tirabrutinib and idelalisib may be administered without regard to food.

For patients assigned to the 20 mg tirabrutinib dose, 20 mg tirabrutinib tablets may be exchanged for 40 mg tirabrutinib tablets leading to an increase in total daily dose from 20 mg to 40 mg. Based on the range of exposures of tirabrutinib observed in subjects with B-cell malignancies, the slight increase in daily dose is not considered clinically relevant.

If the subject misses a dose, he/she should be instructed to take the study drug as soon as he/she remembers, unless more than 12 hours has elapsed since the scheduled time of the missed dose for study drugs administered once daily or 6 hours for study drugs administered twice daily. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time.

5.3.2. Obinutuzumab

Liquid concentrate of obinutuzumab intended for IV infusion is prepared by diluting the drug product to the final concentration into an infusion bag containing 0.9 % Sodium Chloride (NaCl).

All patients should receive premedication before administration of obinutuzumab as follows:

First infusion of obinutuzumab

The following premedication should be administered (unless contraindicated) prior to the start of the first dosage of obinutuzumab (Days 1 [and 2 in case of dose splitting]) to avoid infusion related reactions (IRRs):

- Prednisolone or prednisone 100 mg IV ≥ 1 hrs before starting the obinutuzumab infusion (an equivalent dose of dexamethasone [20 mg] or methylprednisolone [80 mg] is permitted, but hydrocortisone should not be used)
- Acetaminophen/paracetamol 1000 mg p.o. ≥ 30 min before starting the obinutuzumab infusion
- Antihistamines including a H1-antagonist (eg, dimentindene 4 mg IV) and a H2-antagonist (eg, ranitidine 50 mg IV) ≥ 30 min before starting the obinutuzumab infusion

Please note that withholding of antihypertensive treatments should be considered for 12 hours prior to, throughout, and for the first hour after each obinutuzumab infusion as hypotension may occur as a result of an IRR. Antihypertensive treatment can still be used to treat IRR triggered hypertension, if required.

Subsequent infusions of obinutuzumab

All patients should receive oral acetaminophen/paracetamol (1000 mg) p.o. ≥ 30 min ahead of every obinutuzumab infusion (unless contraindicated). The antihistamine premedication may be omitted at the investigator's discretion for the following obinutuzumab infusions if the previously administered obinutuzumab infusion did not result in an IRR CTCAE Grade > 1 (ie, no medication was required to treat the IRR and there was no interruption of the infusion). A corticosteroid should be administered for premedication if the patient experienced a Grade 3 IRR during the previous infusion, the patient´s lymphocyte count is > 25,000/µl and at the investigator‘s discretion. As during the first cycle, the investigator should consider withholding antihypertensive medication 12 hours prior and until 1 hour after the obinutuzumab infusion.

Patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Patients with a high tumor burden (leukocyte counts ≥ 25 × 10^9/L and/ or bulky lymphadenopathy) and/or renal impairment (CrCl <70 mL/min) are at risk for developing a tumor-lysis syndrome (TLS). These patients with a high tumor burden and also all other patients considered at risk for TLS by the investigator must receive prophylaxis for TLS prior to the initiation of treatment with obinutuzumab and ahead of all subsequent administrations of obinutuzumab until the tumor burden is reduced and risk for development of a TLS is minimized. Possible preventive measures include:

- adequate hydration (eg, intravenous administration of 1000 4000 mL NaCl 0.9% starting 12 24 hours before treatment),
- prophylactic administration of an uric acid reducer (eg, allopurinol 300 mg once daily starting 12 24 hours prior to initiation of treatment) and/or
- rasburicase (*Fasturtec*®).

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium and uric acid levels must be performed. Patients with TLS should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, administration of supportive care, including dialysis as indicated).

Infusion Rates

First infusion: All subjects will receive an infusion of the fixed dose of 100 mg obinutuzumab administered at a fixed rate of 25 mg/hr over 4 hours. If the first 100 mg obinutuzumab is tolerated well and completed without interruptions or adjustments of infusion rate and it is possible from an organizational and medical point of view (enough time, medical supervision available throughout the infusion), patients are allowed to continue with the remaining 900 mg infusion on the same day. Otherwise the remaining 900 mg should be infused the next day. The infusion with 900 mg obinutuzumab should be started at a rate of 50 mg/hr in all patients and the infusion rate may be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

Subsequent infusions: If the first infusion of obinutuzumab was well tolerated (defined by an absence of IRRs during a final infusion rate of ≥100 mg/hr), subsequent infusions will be administered at an initial rate of 100 mg/hr. The infusion rate may be increased by 100 mg/hr increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hr. Alternatively, if an IRR was present during the first infusion, the administration may be per the guidance from the first infusion with a maximum rate that which has been previously tolerated by the subject. At the investigator's discretion, obinutuzumab infusions may be split and administered over 2 days.

	Dose of Obinutuzumab	Rate of Infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)
Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
Day 1 or 2	900 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
Subsequent	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Management of infusion-related reactions (IRRs)

In case of IRR, the following measures should be considered depending on the severity of the IRR:

- Acetaminophen/paracetamol 1000 mg if not administered during the last 4 hrs
- Antihistamines including a H1- (eg, dimetindene 4 mg IV) and a H2-antagonist (eg. ranitidine 50 mg IV) if not administered during the last 4 hours
- Prednisolone or prednisone 100 mg IV in case of urticarial, bronchospasm and dyspnea
- Intravenous fluids
- Bronchodilators and oxygen in case of bronchospasm and dyspnea
- Vasopressors in case of hypotension

Once symptoms have resolved completely, obinutuzumab may be resumed at 50% of the infusion-rate used prior to the interruption. If no infusion related symptoms occur, the rate of the infusion may be escalated stepwise with 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr, except for the first administration of obinutuzumab. The first obinutuzumab administration (100 mg) may be re-started at half initial rate (12.5 mg/hr) upon complete resolution of symptoms; if this is tolerated well for an hour, the rate may be increased to a maximum of 25 mg/hr.

It needs to be stressed that in the event of a life-threatening (which may include pulmonary or cardiac events), prolonged or recurrent IRR, obinutuzumab should be discontinued immediately and no further obinutuzumab should be administered.

Patients experiencing Grade 3 or 4 IRRs twice should receive aggressive symptomatic treatment and will be discontinued from further study treatment with obinutuzumab. Treatment with oral agents should be continued with the subject remaining on study.

For guidance on the management of infusion-related reactions (IRRs) see the following table:

IRR Severity (NCI CTCAE v4.0)	**Recommendation**
Grade 1-2	Reduce the infusion rate or hold infusion Administer supportive treatment Upon symptom resolution, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose
Grade 3	Discontinue infusion immediately Administer supportive treatment Upon symptom resolution, may resume infusion rate escalation, at the investigator's discretion Treatment must be permanently discontinued, if same adverse event recurs with same severity.
Grade 4	Discontinue infusion immediately Treat symptoms aggressively Do not restart obinutuzumab

Reductions in obinutuzumab dosing are not planned. Repeat obinutuzumab administrations may be delayed to allow subjects to recover from obinutuzumab-related AEs or intercurrent illness.

5.4. Prior and Concomitant Medications

Subjects must not have previously progressed on treatment with inhibitors of BTK, SYK, PI3K, BCL-2 or obinutuzumab.

Subjects should not have had treatment or prophylaxis for CMV within 28 days of starting therapy with idelalisib or obinutuzumab.

Subjects should not be treated with a strong CYP3A4 or a strong P-gp inducer within 2 weeks of study treatment initiation; if chronic administration of such an agent is needed after study initiation, this situation should be immediately discussed with the study medical monitor.

5.4.1. *Pneumocystis (carinii) jirovecii* Pneumonia Prophylaxis

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis should continue for a period of 2 to 6 months after the last dose of idelalisib. The duration of prophylaxis should be based on clinical judgment of the investigator and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

Immunization with live or attenuated viral vaccines is not recommended while on treatment during this study.

5.4.2. IVIg and G-CSF

Administration of IVIg or G-CSF is permitted per institutional standard of care.

5.4.3. Prior and Concomitant Medications with Tirabrutinib

In vitro data indicate tirabrutinib is a substrate of CYP3A4 and P-gp. Co-administration of CYP3A4 inhibitors may increase tirabrutinib exposure. However, preliminary PK data from study GS-US-401-1757 indicate idelalisib, a CYP3A4 inhibitor, does not cause a clinically relevant increase in tirabrutinib exposure indicating tirabrutinib is not a sensitive CYP3A4 substrate. As such, co-administration of strong CYP3A4 inhibitors with study drug is allowed in this study, but caution should be exercised. Co-administration of the strong CYP3A4 and P-gp inducer, rifampin, resulted in a significant decrease in tirabrutinib exposure (~70%). As such, potent CYP3A4 or P-gp inducers are prohibited while subjects are on study drug and within 2 weeks prior to study drug administration. Examples of strong CYP3A4 or P-gp inducers are provided in the table below.

In vitro data indicate tirabrutinib has the potential to inhibit several CYPs and transporters. Therefore, tirabrutinib may affect the plasma concentrations of their substrates. Caution should be exercised when co-administering concomitant medications that are metabolized by CYP3A4/5 and transported by OAT3, OATP1B1, MATE1, OCT1, OCT2, or P-gp.

Table 5-1. Examples of Concomitant Medications Prohibited in this Study

	Strong
CYP3A4/P-gp Inducer	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide

5.4.4. Prior and Concomitant Medications with Idelalisib

The major metabolite of idelalisib, GS-563117, is a competitive and time dependent inhibitor of CYP3A; accordingly coadministration of idelalisib 150 mg twice daily with midazolam, a probe CYP3A substrate, resulted in an approximately 5-fold increase in midazolam systemic exposure (AUC). At the planned dose of idelalisib in this study (100 mg once daily), idelalisib is predicted to be a moderate CYP3A4 inhibitor. Coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 (PDE5) inhibitors, and warfarin, see Table 5-1). Particular caution is recommended during coadministration of idelalisib with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine see Table 5-1) with idelalisib. The investigator should review the prescribing information of the concomitant medication for guidance on coadministration with a CYP3A inhibitor.

5.4.5. Prior and Concomitant Medications with Obinutuzumab

In accordance with current obinutuzumab prescribing information, subjects should be premedicated with an antipyretic and an antihistamine to reduce the incidence and severity of infusion reactions. A recommended regimen is diphenhydramine, 25 to 50 mg orally, and acetaminophen (paracetamol) 650 to 1000 mg orally, both given approximately 30 minutes prior to each obinutuzumab administration. In addition, an intravenous corticosteroid should also be administered as a premedication on Days 1, 2, 8, and 15 for all subjects, completed at least 1 hour prior to administration of obinutuzumab, and then only as indicated per the prescribing information. Local practices and guidelines may be followed.

5.4.5.1. Tumor Lysis Syndrome

Subjects with a high tumor burden (WBC $\geq 25 \times 10^9$/L or bulky lymphadenopathy) must receive prophylaxis for tumor lysis syndrome (TLS) prior to the initiation of treatment. Prophylaxis for subjects with renal impairment (CrCl < 70mL/min) should also be considered. Subjects must be well hydrated. It is desirable to maintain a fluid intake of approximately 3 liters per day, 1-2 days before the first dose of obinutuzumab. All subjects with high tumor burden must be treated with allopurinol (≥300 mg p.o./day) or a suitable alternative treatment (eg, rasburicase) starting 12-24 hours prior to the first infusion. Subjects should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator. Older and frail subjects will need special individualized care in fluid management, as 3 liters per day may not be tolerated. Rasburicase may be particularly indicated in such subjects. For all subjects, electrolytes should be monitored and corrected, fluid balance and renal function should be monitored, and supportive care should be administered, including dialysis as indicated. Hospitalization, particularly for older and frail subjects, should be considered.

5.4.5.2. Antihypertensive Medication

As infusion related reactions may include hypotension, the investigator should consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after completion of the infusion.

5.5. Accountability for Tirabrutinib, Idelalisib, and Obinutuzumab

The investigator is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP bottles dispensed to subjects must be returned to the site.

Tirabrutinib, idelalisib, and obinutuzumab accountability records will be provided to each study site to:

- Record the date received and quantity of IMP bottles and vials
- Record the date, subject number, subject initials, and the quantity of IMP bottles and vials dispensed
- Record the date, quantity of used and unused IMP bottles returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Study drug should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. All study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

Please see Section 9.1.7 for more information.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

The study steering committee, including representatives from the GCLLSG and Gilead, will meet at least monthly throughout the treatment period and regularly for the complete duration of the study to review ongoing safety data.

6.1. Subject Enrollment, Randomization and Treatment Assignment

It is the responsibility of the Investigator to ensure that each subject is eligible for the study before enrollment or randomization. Please refer to Section 5.1 for details about randomization and treatment assignment. With Amendment 3, all subsequent subjects will be enrolled in Arm B.

6.2. Study Procedure Descriptions

During the treatment period, all visits may be performed within the specified window for that study visit (see Appendix 2).

6.2.1. Informed Consent

All subjects must sign and date the most recent IEC approved informed consent form before any study procedures are performed. CCI [redacted]

Subjects who screen fail must re-sign the informed consent, if any screening procedures will be performed outside of the 28-day screening window from the time of the first informed consent.

6.2.2. Medical and Medication History

A complete medical history will be obtained by the Investigator or designee. Medical history will include information on the subject's significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent illnesses. CIRS score should be determined at screening.

6.2.3. Physical Examination

The Investigator or qualified designee will perform a physical examination at screening and time points outlined in the Study Procedures Tables (Appendix 2). Screening and End of Treatment (EOT) will be a complete physical examination. Beginning at Week 1 Day 1, a modified physical examination will be performed to monitor for any changes (lymph nodes, size of liver and spleen, lung, cardiac, abdomen, skin, neurologic, and any systems, as clinically indicated). Physical examination findings will either be reported as medical history or AEs based on the requirements in Section 7.

Weight should be measured with each physical examination.

Height will be measured at screening only.

6.2.4. Vital Signs

Vital signs, including blood pressure, respiratory rate, pulse, and temperature will be measured at the time points listed in the Study Procedures Tables in Appendix 2. Only the screening measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.2.5. ECOG Performance Status/B-Symptoms

ECOG PS and B-Symptoms will be performed at the time points listed in the Study Procedures Tables (Appendix 2). ECOG will be scored using the scale index in Appendix 5.

6.2.6. 12-lead ECG

A 12-lead ECG will be obtained at the time points listed in the Study Procedures Table (Appendix 2).

6.2.7. Binet and Rai Staging

Binet and Rai staging will be assessed at the time points listed in the Study Procedures Table (Appendix 2). CLL staging will be evaluated using the table in Appendix 9.

6.2.8. Geriatric assessment

The G8 screening questionnaire (Appendix 10) will be used for assessment for subjects aged > 70 years as outlined in the Study Procedures Table (Appendix 2).

6.2.9. Prior and Concomitant Medications

At screening, all medication taken up to 30 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (eg, anti-emetics), and vitamins and minerals.

In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and recorded on the eCRF.

6.2.10. Adverse Events

Subjects will be assessed for AEs per guidelines in the NCI CTCAE (version 4.03) at the time points outlined in the Study Procedures Tables (Appendix 2). After informed consent, but prior to initiation of study medication, the following types of events should be reported on the electronic case report form eCRF: AEs related to protocol-mandated procedures, and all SAEs.

Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. Please refer to Appendix 3 for CTCAE grading criteria.

Please refer to Section 7 for additional information on AE reporting.

6.2.10.1. Evaluation for Gastrointestinal Events/Colitis

For subjects who report diarrhea or colitis, obtain history of onset and duration, including description of the number of stools and stool composition (watery, bloody, nocturnal), travel history, diet changes and medication review to identify possible causes. Perform physical examination, including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration). If unclear, consider upper and lower tract endoscopy with biopsy. Laboratory evaluation for infectious causes of diarrhea should be performed and in the absence of a diagnosis, endoscopy should be considered with evaluation for CMV and other infectious pathology.

6.2.11. Radiology Assessment

The radiology assessment in this study is consistent with the European Society for Medical Oncology (ESMO) clinical practice guidelines for CLL {Eichhorst 2015}. Imaging of the neck, chest, abdomen and pelvis by CT scan (preferred) or MRI will be performed at screening. Scans already completed up to 42 days prior to the first dose of treatment may be used for the screening assessment. One additional radiologic evaluation is specified per protocol, at the Week 25 visit, with evaluation of areas affected by CLL during the screening evaluation. During the treatment phase, if an improvement in clinical response is noted following the Week 25 assessment or if disease progression is suspected, additional scans may be performed if clinically indicated. Scans should continue to be performed at Week 25 for subjects who stop study treatment but did not

have disease progression (e.g. experienced unexpected toxicity) unless radiographic progression is previously documented or unless the subject starts on subsequent therapy for CLL.

6.2.12. Blood and Urine Samples

Blood and urine for laboratory safety tests will be collected according to the Study Procedures Tables (Appendix 2). The volume of blood phlebotomized will be roughly 100 mL at screening and subsequently is not to exceed 200 mL every 3 months. CCI [redacted] The tests will be analyzed using standard procedures. All laboratory tests must be reviewed for clinical significance by the Investigator or qualified designee.

The analytes listed in Table 6-1 will be tested.

6.2.13. Bone Marrow Assessment

For subjects without radiographic evidence of disease at screening, a bone marrow biopsy including aspirate is required within the screening window.

A bone marrow biopsy including aspirate is required at Week 25 for subjects who otherwise would meet criteria for a CR or complete remission with incomplete bone marrow recovery (CRi).

An additional bone marrow biopsy, including aspirate, may be obtained on protocol per investigator discretion following evidence of an improvement in clinical response.

Any bone marrow aspirate obtained should be sent for central MRD assessment, immunophenotyping, bio-banking, and follow-up research.

CCI [redacted]

[redacted] CCI [redacted]

CCI [redacted]

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- [redacted]
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- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

[redacted]

[redacted]

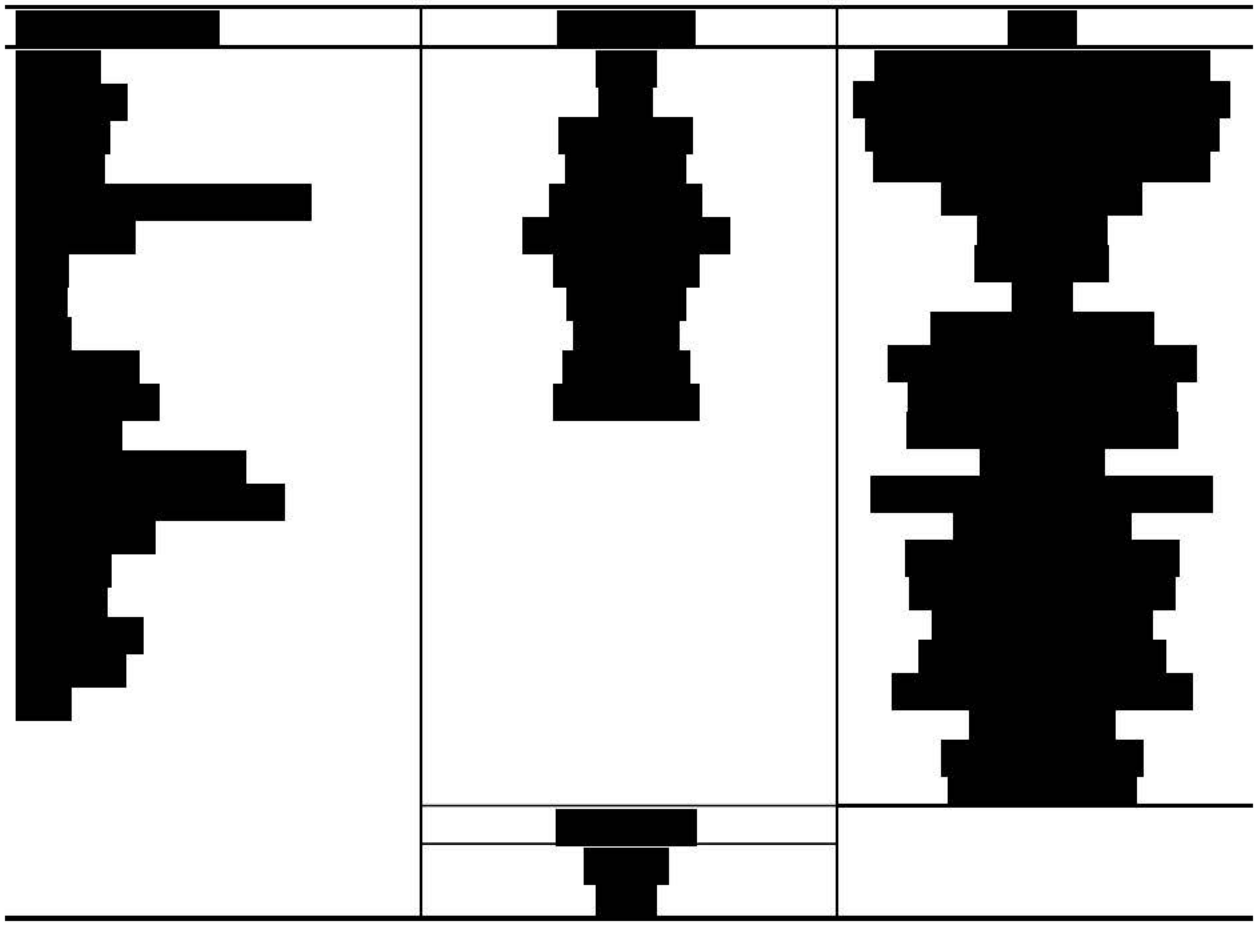
6.2.16. Pregnancy Test for Females of Childbearing Potential

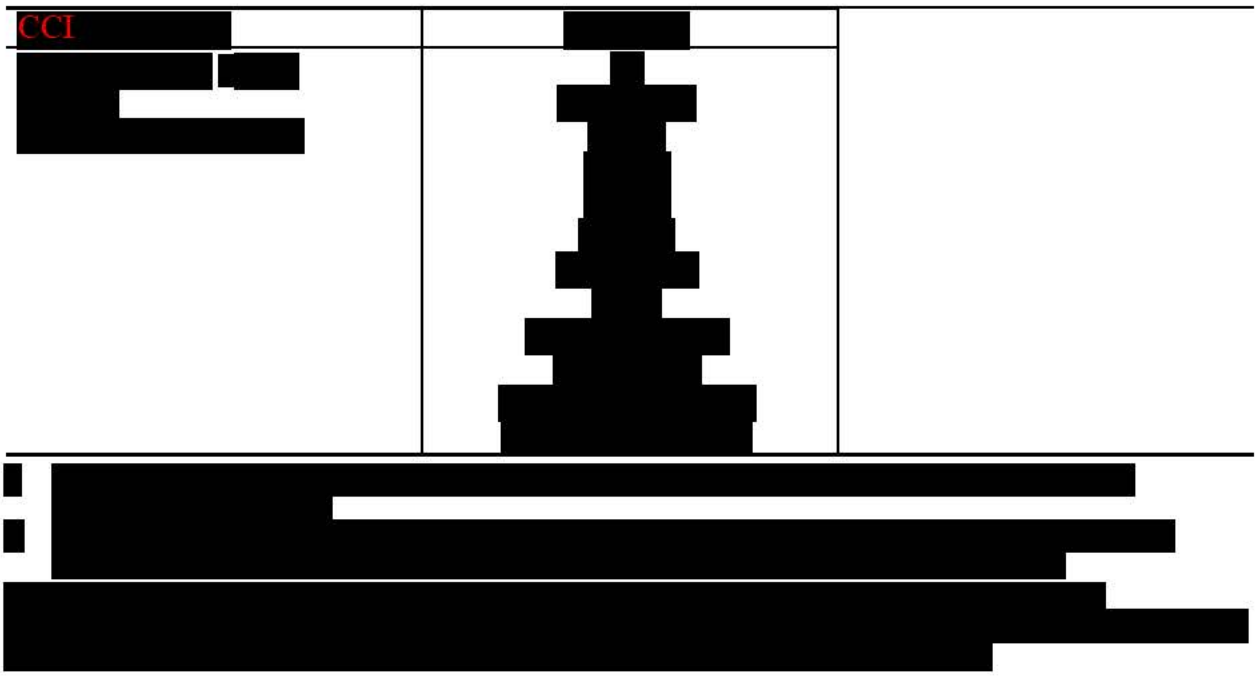
All female subjects of childbearing potential (as defined in Appendix 4) will have a serum pregnancy test at screening and a urine pregnancy test prior to Week 1 Day 1 dosing and throughout the study as indicated in the Study Procedures Table (Appendix 2). The results must be confirmed as negative prior to continued administration of study drug.

CCI [redacted]

[redacted]

CCI [redacted]





6.3. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.4 Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. Long-term follow-up within the GCLLSG registry is recommended.

6.4. Criteria for Discontinuation of Study Treatment

See Sections 3.4 and 3.5 for discontinuation criteria.

6.5. Dose Interruption and Reduction

The following are the guidelines for dose interruption and/or reduction. If an AE is attributed to study drug, the investigator's discretion will be used to determine if the drug not attributed to the AE will be withheld based on the investigator's assessment of risk-benefit of withholding the study drug.

Subjects who experience Grade 3 or 4 neutropenia whilst on idelalisib treatment must have their neutrophil count measured weekly until resolution to ≤ Grade 2, per Table 6.2.

An interruption of tirabrutinib and/or idelalisib administration of up to 2 weeks will be acceptable to allow for any reversal of toxicity between doses of tirabrutinib and/or idelalisib. If the toxicity does not resolve to CTC Grade ≤ 2 within 2 weeks, additional doses of the interrupted drug(s) will not be administered unless the toxicity is deemed related to the subject's underlying disease in the opinion of the investigator. If the toxicity is deemed to be related to one agent (tirabrutinib or idelalisib), the subject may resume the other drug as a single agent, however, the discontinued drug may not be re-initiated on this study.

A subject who discontinues obinutuzumab for any reason other than progression may remain on study receiving the combination of tirabrutinib and idelalisib as assigned.

Subjects experiencing a related or non-related AE at any point during the study that takes longer than 2 weeks to resolve will be reviewed on a case-by-case basis by the investigator and the sponsor. Upon resolution of the AE, or in the opinion of the Investigator if the AE is considered to be well controlled and if the subject is deemed to be gaining clinical benefit from treatment with tirabrutinib and/or idelalisib, a subject may continue to receive tirabrutinib and/or idelalisib at their assigned dose or at a lower dose (and consistent with Table 6-2). The dose may subsequently be increased back to the original dose level if considered safe to do so by the treating investigator and upon approval by the sponsor.

The dose modification instructions focus on the types of events most commonly attributed to each of the study agents. The recommendations provided in Table 6-2, and Table 6-3 comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject. **The exceptions are SJS/TEN or DRESS, Grade 4 ALT/AST with Bilirubin elevation, organizing pneumonia, symptomatic (Grade ≥2) pneumonitis, PJP infection, and bowel perforation where idelalisib must be discontinued**

Table 6-2. Dose Adjustments, Withholding and Discontinuation Related to Idelalisib and/or Tirabrutinib

NCI CTCAE Grade	Recommendation	
	Idelalisib	**Tirabrutinib**
HEMATOLOGICAL ADVERSE EVENTS		
Neutropenia[a]		
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule. Blood counts ***must*** be monitored at least weekly until Grade ≤ 2.	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Withhold until resolved to Grade ≤2. Consider G-CSF support. Tirabrutinib and idelalisib may be reinitiated either together or sequentially. Blood counts ***must*** be monitored at least weekly until ANC ≤ Grade 2. If the toxicity recurs, consider discontinuing idelalisib.	Withhold tirabrutinib until resolved to Grade ≤ 2. Consider G-CSF support. If the toxicity recurs, consider a decrease in tirabrutinib to 40 mg. If toxicity persists following discontinuation of idelalisib alone, discontinue tirabrutinib as well.
Thrombocytopenia		
Grade ≤ 3 Thrombocytopenia	Withhold for clinically significant bleeding.	
Grade 4 Thrombocytopenia	Withhold tirabrutinib and idelalisib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and idelalisib may be reinitiated at the previous dose. If the toxicity recurs, consider a decrease in tirabrutinib to 40 mg or discontinuing tirabrutinib. If toxicity persists following discontinuation of tirabrutinib, discontinue idelalisib as well.	
NON-HEMATOLOGICAL ADVERSE EVENTS		
Rash		
Grade ≤ 2	Maintain current dose level and schedule.	
Grade 3 or 4	Withhold tirabrutinib and idelalisib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and idelalisib may be resumed and a dose reduction to tirabrutinib 40 mg may be considered if multiply recurrent. If toxicity recurs following repeated rechallenge, discontinue tirabrutinib and/or idelalisib.	
Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).		
Any Grade	Discontinue Idelalisib and concomitant medications that have been associated with SJS/TEN and drug reaction with eosinophilia and systemic symptoms (DRESS). Institute systemic immunosuppression per institutional standards.	-

NCI CTCAE Grade	Recommendation	
	Idelalisib	**Tirabrutinib**
Bowel Perforation		
Any Grade	Discontinue idelalisib.	Maintain current dose level and schedule.
Progressive Multifocal Leukoencephalopathy (PML)		
Any Grade	Withhold idelalisib until PML is excluded. Refer to section 6.6.11	-
Diarrhea		
Grade ≥ 1	In the absence of evidence of infection, provide anti-diarrheal (eg, loperamide) and maintain current tirabrutinib and idelalisib dose level and schedule.	
Grade 2	Withhold idelalisib until Grade ≤ 1. Consider anti-diarrheal (eg, loperamide). Resume idelalisib at previous dose level. If rechallenge results in recurrence, discontinue idelalisib. Consider addition of anti-inflammatory (eg, budesonide).	Withhold tirabrutinib until resolved to Grade ≤ 1. If resolution occurs within 7 days, tirabrutinib may be reinitiated at the previous dose. If the toxicity recurs or is persistent with corticosteroid therapy, decrease to 40 mg.
Grade 3 or 4	Withhold idelalisib until resolved to Grade 1 or baseline (recovery). Rule out infectious etiology including CMV (see Section 6.2.10.1). Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). If toxicity persists or recurs upon repeated rechallenge, permanently discontinue idelalisib. Refer to Section 6.2.10.1 for evaluation.	Withhold tirabrutinib until Grade ≤ 1. Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).
Hepatic Adverse Events (elevations in ALT, AST or bilirubin)		
Grade 1 (ALT/AST ≤ 3×ULN) (Bilirubin ≤ 1.5×ULN)	Maintain current dose level and schedule.	
Grade 2 (ALT/AST > 3-5×ULN) (Bilirubin>1.5 -≤ 3×ULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1× per week.	
Grade 3 (ALT/AST > 5-20×ULN) (Bilirubin > 3-10×ULN)	Withhold all study medication. Monitor ALT, AST, ALP, and bilirubin at least 1× per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib and idelalisib at previous dose level and resume obinutuzumab. If bilirubin abnormality was Grade ≥ 3, discontinue idelalisib and obinutuzumab.	
Grade 4 (ALT/AST > 20×ULN) (Bilirubin > 10×ULN)	Withhold all study medication. Monitor ALT, AST, ALP, and bilirubin at least 1× per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib only. If bilirubin was Grade 4, discontinue all study medication.	

NCI CTCAE Grade	Recommendation	
	Idelalisib	Tirabrutinib
Organizing Pneumonia		
Any Grade	Discontinue idelalisib permanently. Institute supportive care as appropriate.	
Pneumonitis		
Grade 1	Withhold all study medication until resolution to baseline. May resume therapy at investigator discretion.	
Grade 2	Discontinue all study medication. Supportive care, including oxygen or mechanical ventilation, should be considered early and provided as necessary. May consider resuming therapy with tirabrutinib alone after discussion with medical monitor.	
Grade 3 or 4	Discontinue all study medication permanently, institute systemic corticosteroids and supportive care per institutional standard.	
PJP infection		
Any Grade	Discontinue idelalisib. Consider discontinuation of tirabrutinib until the infection has resolved.	
Unequivocal CMV infection[a]		
Any Grade	Discontinue idelalisib. Consider discontinuation of tirabrutinib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.	
Hypersensitivity		
Any Grade	Consider interrupting or discontinuing tirabrutinib treatment (see Section 6.6.2).	
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS		
Grade 1	Maintain current dose level and schedule	
Grade 2	Withhold tirabrutinib and idelalisib until Grade ≤ 1 or baseline. May resume idelalisib with tirabrutinib at initial or lower dose level or discontinue tirabrutinib and idelalisib at investigator discretion.	
Grade 3	Withhold tirabrutinib and idelalisib until Grade ≤ 1 or baseline. May resume idelalisib with tirabrutinib at lower dose level or discontinue tirabrutinib and idelalisib at investigator discretion.	
Grade 4	Discontinue tirabrutinib and idelalisib.	

a) CMV should be diagnosed using clinical or laboratory criteria per established institutional standard

Table 6-3. Dose Adjustment Guidelines for Subjects Receiving Obinutuzumab

	Recommendation
NCI CTCAE Grade	**Toxicity attributable to obinutuzumab**
HEMATOLOGICAL ADVERSE EVENTS*	
Neutropenia[a]	
Grade ≤ 2 neutropenia	Maintain current dose level and schedule.
Grade 3 neutropenia	Maintain current dose level and schedule. Consider G-CSF support.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Delay obinutuzumab until Grade ≤ 2 (ANC ≥ 1×10^9/L) and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider G-CSF support to avoid delays. If delay is > 4 weeks, discontinue obinutuzumab.
Thrombocytopenia	
Grade ≤3	Maintain current dose level and schedule.
Grade 4	Delay obinutuzumab until Grade ≤ 3 (platelets ≥ 25×10^9/L); thereafter, resume at full dose. If delay is > 4 weeks, discontinue obinutuzumab, unless the Grade 4 thrombocytopenia occurred after the first 3 weekly doses.
Hemorrhage	
N/A	Hold obinutuzumab in case of platelets < 20,000/μL. If Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved). If Day 15 is delayed then skip Day 15 dosing and administer Day 29 of obinutuzumab as scheduled. At the discretion of the study investigator, for subjects who are on low molecular weight heparin (LMWH), when thrombocytopenia with platelets <20,000/μL develops, reduce the dose of LMWH or new oral anticoagulants (NOAC) used. Hold tirabrutinib and obinutuzumab for clinically significant bleeding (irrespective of platelet count) until it resolves.
NON-HEMATOLOGICAL ADVERSE EVENTS	
Cutaneous	
Grade ≤2	Maintain current dose level and schedule.
Grade 3 or 4	Delay obinutuzumab until Grade ≤ 1; thereafter, may resume at full dose or discontinue obinutuzumab at investigator discretion.
Gastrointestinal Inflammation/Diarrhea	
Grade ≤1	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.
Grade 3	Hold idelalisib and obinutuzumab until subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. If recurrent with rechallenge, consider treatment with tirabrutinib alone.
Grade 4	Delay all study medication until subject is sufficiently stable to receive further treatment; if recurrent with rechallenge, consider treatment with tirabrutinib alone.

NCI CTCAE Grade	Recommendation Toxicity attributable to obinutuzumab
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)	
Grade ≤1 (ALT/AST≤3×ULN) (Bilirubin≤1.5×ULN)	Maintain current dose level and schedule.
Grade 2 (ALT/AST>3-5×ULN) (Bilirubin>1.5-≤3×ULN)	Maintain current dose level and schedule.
Grade 3 (ALT/AST>5-20×ULN) (Bilirubin>3-10×ULN)	Withhold all study medication. Monitor ALT, AST, ALP, and bilirubin at least 1× per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib and idelalisib at previous dose level, resume obinutuzumab. If bilirubin abnormality was Grade ≥ 3, discontinue idelalisib and obinutuzumab.
Grade 4 (ALT/AST>20×ULN) (Bilirubin>10×ULN)	Withhold all study medication. Monitor ALT, AST, ALP, and bilirubin at least 1× per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib. If bilirubin was grade 4, discontinue all study medication.
Pneumonitis	
Grade ≤1	Maintain current dose level and schedule.
Grade 2	Withhold all study medication until Grade ≤ 1, consider systemic corticosteroids. May consider resuming therapy with tirabrutinib alone
Grade ≥3	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue obinutuzumab at investigator discretion.
Hypersensitivity	
Any Grade	Stop the infusion and discontinue obinutuzumab treatment (see section 6.6.2)
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS	
Grade ≤2	Maintain current dose level and schedule.
Grade ≥3	If felt to be related to obinutuzumab, delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue obinutuzumab at investigator discretion.

Abbreviations: ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, ANC absolute neutrophil count, CTCAE Common Terminology Criteria for Adverse Events, G CSF granulocyte colony stimulating factor, NCI National Cancer Institute, ULN upper limit of normal

a Neutropenia and thrombocytopenia should not necessarily lead to delay in dosing of obinutuzumab or idelalisib if it is believed that the cytopenia is due to CLL, and not to the drug(s).

6.6. Recommendations for Evaluation, Intervention, and Drug Discontinuation for Specific Adverse Events or Conditions

6.6.1. Hemorrhage

Bleeding events have occurred in subjects with relapsed/refractory chronic lymphocytic leukemia (CLL) and relapsed/refractory non-Hodgkin's lymphoma (NHL) who received tirabrutinib as monotherapy. These include minor hemorrhagic events such as contusion, hematoma, and petechiae, and major hemorrhagic events such as small intestinal hemorrhage and subdural hematoma.

Consider interrupting treatment with tirabrutinib for up to 7 days prior to surgery or other interventions associated with a significant risk of bleeding and resuming treatment once hemostasis is achieved.

Subjects should be monitored for signs of bleeding and treated appropriately.

6.6.2. Dermatological and Hypersensitivity Events

Subjects receiving idelalisib and tirabrutinib with ≥ Grade 3 rash have generally presented with a maculopapular rash on the trunk and extremities that is occasionally associated with fever and/or pruritus and responded to treatment with diphenhydramine and/or topical or oral corticosteroids.

For subjects who develop a severe rash for which an underlying etiology cannot be identified (e.g., infection, co-suspect drug), study drug should be interrupted. Resumption of study drug should be considered once rash resolves.

Hypersensitivity symptoms can occur after previous exposure and very rarely with the first infusion. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated. Subjects receiving obinutuzumab may also experience hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness); these may be difficult to distinguish from infusion related reactions.

If a hypersensitivity reaction is suspected during or after an obinutuzumab infusion, the infusion must be stopped and treatment permanently discontinued.

If patients experience a hypersensitivity reaction whilst on tirabrutinib, consideration should be given to interruption or discontinuation.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**, have been reported in subjects receiving idelalisib and anti-CD20 antibody therapy. If SJS, TEN or DRESS is suspected, all coadministered medications associated with SJS, TEN or DRESS including (if applicable) those for prophylaxis of pneumocystis jirovecii or tumor lysis, should be interrupted and the subject treated accordingly.

6.6.3. Gastrointestinal Events

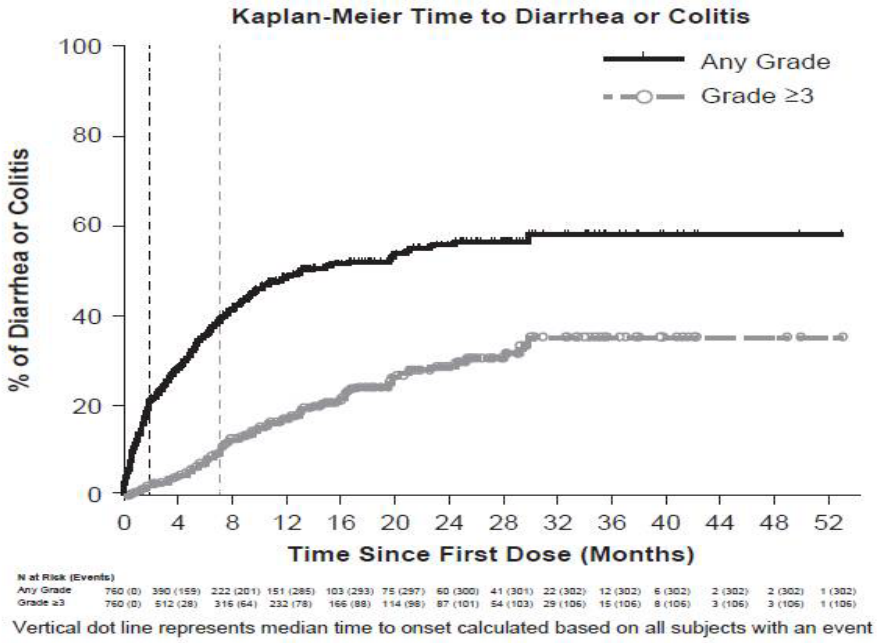
Isolated cases of gastrointestinal inflammation (eg, stomatitis, colitis, cecitis) have been noted in subjects receiving idelalisib or anti-CD20 therapy. Rare cases of gastrointestinal perforation have occurred, generally in the setting of occult carcinoma, mesenteric embolus or diverticular disease. Study treatment should be discontinued in subjects who experience bowel perforation.

Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that idelalisib played a contributory role. In such subjects, rechallenge with idelalisib has been possible and has not been associated with other severe adverse events. Subjects who have developed evidence of diarrhea or colitis during idelalisib therapy have been successfully treated with antidiarrheals (eg, loperamide) and with enteric steroidal (eg, budesonide) or non-steroidal (eg sulfasalazine [Azulfidine®]) anti-inflammatory agents and have been able to continue or resume idelalisib.

For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered. Upon recovery, rituximab may be resumed.

Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0 29.8), of grade 1 or 2 was 1.5 months (range, 0.0 15.2) and of grade 3 or 4 was 7.1 months (range, 0.5 29.8). Kaplan Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib- treated patients in Figure 6-1 {Coutre 2015}.

Figure 6-1. Kaplan-Meier Curve of Time to Diarrhea or Colitis



Idelalisib-associated severe diarrhea responds poorly to antimotility agents however, median time to resolution ranged between 1 week and 1 month across trials following interruption of idelalisib treatment and, in some instances, initiation of corticosteroid treatment {Gilead Sciences Inc 2014}.

For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as Clostridium difficile (particularly for patients recently treated with broad spectrum antibiotics), Shigella, Campylobacter, Yersinia and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral IHC staining should be considered. In the event that an infectious cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In some subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events.

6.6.4. Hepatic Events

Transaminase Elevations: Reversible asymptomatic ALT/AST increases have been observed with idelalisib in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. Transaminase elevations are most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

HBV Reactivation: HBV reactivation can occur with treatment, most commonly in patients treated with obinutuzumab. The risk is very low among patients with negative anti-HBc serology and/or undetectable HBV DNA as assessed by quantitative PCR. Although some subjects who are HBc antibody positive with negative PCR may have had passive transfer of antibody from intravenous IgG, it cannot be known for certain that any such subject did not have natural HBV infection. Therefore, all subjects who are HBc antibody positive at screening will be monitored for potential HBV reactivation (manifest as detectable HBV DNA by quantitative PCR). Surveillance of subjects who test positive for HBc antibody for HBV reaction will be performed according to the Study Procedures Table (Appendix 2). If there is evidence of HBV reactivation immediately stop study treatment and start appropriate treatment for HBV. In the event of HBV reactivation, please contact the Medical Monitor prior to re-initiation of study treatment.

6.6.5. Hematological Events

In the Phase 1 experience with idelalisib in patients with NHL and CLL, subjects with Grade ≥3 neutropenia, anemia, and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during idelalisib administration were largely due to minor fluctuations in these parameters among subjects with pre-existing hematological abnormalities due to disease or prior therapy. Thus, idelalisib did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed. Treatment-emergent Grade 3 or 4 neutropenia events including those accompanied by fever or infection have occurred in subjects treated with idelalisib, most commonly in the context of myelosuppressive agents such as bendamustine. All subjects will have their absolute neutrophil count monitored at least every two weeks for the first 24 weeks of idelalisib treatment.

Neutropenia and anemia have also occurred in subjects treated with tirabrutinib. The anemia in subjects treated with tirabrutinib has generally been self-limiting, without the requirement for intervention and with improvement on continued therapy.

Management of neutropenia, including administration of G-CSF should be per established clinical guidelines and institutional standard of care.

6.6.6. Infectious Events

Patients with lymphoid cancers receiving tirabrutinib, idelalisib or obinutuzumab have developed serious and fatal infections during therapy. Opportunistic infections, most notably *Pneumocystis jirovecii* pneumonia (PJP) and CMV infection, have most frequently occurred within the first 6 months of treatment with idelalisib and are increased in the context of concurrent myelosuppressive therapy such as bendamustine.

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a period of 2 to 6 months after the last dose of idelalisib. The duration of prophylaxis should be based on clinical judgment of the investigator and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

CMV surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every 4 weeks through week 33 and every 12 weeks thereafter through the course of idelalisib treatment. CMV viral load testing should be performed from the same specimen type whenever possible and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must permanently discontinue idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines.

6.6.7. Pulmonary Events

Documented bacterial, fungal, viral, and pneumocystis pneumonias have been observed in patients receiving idelalisib, primarily in patients with CLL. Some study subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis and organizing pneumonia, respectively, without documented pulmonary infection. Given the potential for infectious or drug-related pulmonary adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of ≥5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT) should be evaluated. Potential bacterial, fungal, or viral etiologies should be assessed. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

Cases of organizing pneumonia, some with fatal outcome, have occurred with idelalisib. In subjects presenting with serious lung events, idelalisib should be interrupted and the subject assessed for an explanatory etiology. If organizing pneumonia is diagnosed, treatment with idelalisib should be permanently discontinued and the subject treated accordingly.

6.6.8. Pregnancy, Lactation, and Reproduction

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. However, definitive reproductive toxicology studies in animals have not yet been performed and the specific effects of idelalisib on human embryogenesis or fetal development are unknown. Whether idelalisib is excreted in human breast milk is unknown. General toxicology studies of idelalisib in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

6.6.9. Ultraviolet Exposure

In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite of idelalisib) are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern. Although specific clinical correlates for these nonclinical data are not available, investigators and study subjects should be observant for the possibility that study participants may have exaggerated sunburn reactions (eg, burning, erythema, exudation, vesicles, blistering, edema) involving areas of skin exposed to ultraviolet light.

6.6.10. Stevens-Johnson syndrome, Toxic epidermal necrolysis and Drug reaction with eosinophilia and systemic symptoms.

Stevens-Johnson syndrome and Toxic epidermal necrolysis are severe blistering rashes that can include redness, swelling and blistering of the lining of the mouth, throat, nose, genitals, and/or eye. They have been reported in some people who have received idelalisib at the same time as other medicines known to cause these conditions. The peeling away of the skin can allow serious infection that can be life-threatening or fatal. Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement may indicate a serious condition named Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or drug hypersensitivity syndrome. If subjects develop such symptoms, you must seek medical attention immediately.

6.6.11. Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported following the use idelalisib within the context of prior or concomitant immunosuppressive therapies (including fludarabine and select anti-DC20 mAbs [e.g. rituximab]) that have been associated with PML. Investigator should consider PML in the differential diagnosis in subjects with new or worsening neurological, cognitive or behavior signs or symptoms. If PML is suspected then appropriate diagnostic evaluations (referral to neurologist including MRI scan preferably with contrast, cerebrospinal fluid [CSF] testing JC viral DNA) should be undertaken and treatment needs to be suspended until PML is excluded.

6.6.12 Further Safety Information

Further safety information regarding the study drug may be found in the IBs for idelalisib and tirabrutinib and the current product labeling for obinutuzumab.

6.7. End of Treatment

The EOT visit should be scheduled for 30 days following discontinuation of all study treatment to satisfy the requirement for a 30-day post-treatment safety assessment. Please consider enrollment of subjects at EOT in the non-interventional GCLLSG CLL registry for subjects that did not enroll at screening.

For subjects that permanently discontinue all study treatment prior to the Week 25 visit without experiencing disease progression, the Week 25 Day 1 visit should be performed on schedule per the Study Procedures Table (Appendix 2).

6.8. Unscheduled Procedures

Unscheduled procedures will be recorded on the applicable eCRFs.

6.9. Post Study Care

At this time there is no plan to provide post-study care to subjects who have participated on this study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be recorded and graded according to the NCI CTCAE, Version 4.03, published 14 June 2010.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met 1 of the criteria for serious events listed in Section 7.1.2**.**

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: adverse events related to protocol-mandated procedures, and all SAEs.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required 30 day post treatment follow-up period, which concludes at the EOT visit, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs beyond the end of study; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline. Electronic Serious Adverse Event (eSAE) Reporting Process.

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead PVE:	Fax: E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results. Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor or designee.

Please refer to the current tirabrutinib or idelalisib IB and local obinutuzumab prescribing information for information related to toxicity management. See Section 6.4 for more information related to recommended dose modifications associated with toxicities.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to or Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE.

Gilead PVE:	Fax: E-mail:	PPD

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To determine the preliminary efficacy of the combination of tirabrutinib and idelalisib with obinutuzumab in subjects with relapsed or refractory CLL

The secondary objective of this study is:

- To evaluate the safety and tolerability of the combination of tirabrutinib and idelalisib with and without obinutuzumab

CCI [redacted]

8.1.2. Primary Endpoint

The primary endpoint is the rate of CR per modified IWCLL 2008 criteria {Hallek 2008} at Week 25.

8.1.3. Secondary Endpoints

The secondary endpoints of this study are:

- Rate of CR/BM MRD- at Week 25
- Rate of CR/PB MRD- at Week 25
- ORR at Week 25 including CR, CRi, PR, and PR with lymphocytosis
- Type, frequency, and severity of AEs and SAEs

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), which is defined as all subjects randomized or enrolled to each study arm who received at least 1 dose of any study treatment. Subjects are analyzed according to the study treatment they are assigned to at randomization or enrollment.

The PP analysis set is defined as all randomized or enrolled subjects who received at least 1 dose of any study treatment and had disease assessment at baseline and at least 1 evaluable response assessment post baseline. Study treatment assignment will be designated according to the actual treatment received. This analysis set will be used in the supplementary analysis of response endpoints.

8.2.1.2. Safety

The primary analysis set for safety analyses is the safety analysis set, which is defined as all randomized or enrolled subjects who received at least 1 dose of any study treatment, with study treatment assignment designated according to the actual treatment received.

CCI [redacted]

CCI [redacted]

8.3. Data Handling Conventions

By-subject listings will be presented for all randomized or enrolled subjects in the FAS and sorted by subject ID number, visit date, and time if applicable. Data collected on log forms, such as AEs, will be presented in chronological order within subject. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, and percentage.

The baseline value is generally defined as the last (most recent) pre-treatment value in safety analyses and the last (most recent) pre-randomization value for efficacy analyses. Data from all sites will be pooled for all analyses. If there is a significant degree of non-normality, analyses may be performed on log-transformed data, as appropriate.

In general, missing data will not be imputed. For response endpoints, if a subject is missing baseline or post baseline assessments, the subject will be treated as non-responders. CCI [redacted] Methods for imputing partially missing dates and laboratory results beyond limit of quantification will be provided in the SAP.

8.4. Demographic Data and Baseline Characteristics

Subject demographic variables (age, sex, race and ethnicity), baseline characteristics (including body weight, height, body mass index, and ECOG Performance Status) as well as baseline disease characteristics (including time since initial diagnosis, disease staging at study entry, cytogenetic risk group, refractory and relapse status) will be summarized descriptively by treatment arms and overall based on the FAS. Medical history and concomitant medication use will be summarized using safety analysis set.

In general, continuous variables will be summarized by sample size, mean, standard deviation, median, quartiles, minimum and maximum and categorical variables will be summarized by counts and percentages.

8.5. Efficacy Analysis

8.5.1. Primary Endpoint

Tumor response will be based on investigator's assessment according to the modified IWCLL 2008 criteria (see Appendix 6).

Rate of CR will be calculated by treatment arms using the FAS. The 2-sided 90% exact confidence interval (CI) of CR will be estimated using the Clopper-Pearson method.

No inferential test will be performed. The goal of this analysis is to obtain preliminary estimates of the CR rate.

In addition, the analysis of the primary endpoint will be performed using the PP analysis set.

8.5.2. Secondary Endpoints

ORR and rate of CR/MRD- will be estimated for each arm and their associated 90% confidence intervals will be calculated using the exact method.

CCI [redacted]

CCI [redacted]

8.6. Safety Analysis

8.6.1. Extent of Exposure

Treatment exposure and compliance will be summarized descriptively by treatment group based on safety analysis set. Summaries will include treatment duration, number of doses, average dose, dose modifications, and treatment adherence rate.

8.6.2. Adverse Events

Clinical and laboratory adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the NCI-CTCAE, Version 4.03. The relationship of the AE to the study treatment will be assessed by the investigator as related or unrelated.

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs (TEAEs). A TEAE is defined as an AE that occurs or worsens in severity on or after the date of the first dose of study treatment but no later than 30 days after the last dose of study treatment.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided by treatment group:

- All TEAEs
- TEAEs of Grade 3 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- All treatment-emergent SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of study drug
- All AEs leading to dose modification or temporary interruption of study drug
- All SAEs leading to death (ie, outcome of death)

8.6.3. Laboratory Evaluations

Safety laboratory results will be graded according to NCI-CTCAE Version 4.03. Summaries of laboratory data will be provided for the safety analysis set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units.

Descriptive statistics will be provided by treatment groups for each safety laboratory test as follows:

- Baseline values (defined as the last measurement obtained on or prior to the date/time of first dose of study drug)
- Post baseline maximum value
- Change from baseline to post baseline maximum value
- Post baseline minimum value
- Change from baseline to post baseline minimum value

In addition, treatment-emergent laboratory abnormalities will be summarized descriptively using number and percentages of subjects by treatment group for the following:

- Grade 3 or 4 laboratory abnormalities
- Shift from baseline in laboratory toxicity grade

Subjects will be categorized according to the most severe post baseline abnormality grade for a given lab test.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

8.9. Sample Size

The primary goal of the study is to evaluate the efficacy of the combination treatment described above. The evaluation will be based on the estimation of the CR rate and its corresponding exact confidence interval for each arm. Approximately 30 subjects will be enrolled into Arm B, which will result in the 90% confidence interval of the observed CR rate to be within ±17.0%. The 90% confidence interval for a given observed CR rate is shown in the table below.

Table 8-1. 90% Confidence Intervals at Different CR Rates

Sample Size	CR Rate	95% Confidence Interval using Clopper-Pearson Method
30	20%	(9.1%, 35.7%)
30	30%	(16.6%, 46.5%)
30	40%	(25.0%, 56.6%)
30	50%	(33.9%, 66.1%)
30	60%	(43.4%, 75.1%)

With Amendment 3, randomization was discontinued. All subsequently enrolled subjects will enter Arm B. A total of approximately 6 subjects in Arm A and 30 subjects in Arm B will be enrolled, thus the total sample size for the study will be approximately 36 subjects.

8.10. External Data Monitoring Committee

No external independent Data Monitoring Committee is used in this study.

8.11. Endpoint Adjudication Committee

No independent endpoint adjudication committee is used in this study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the EU Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators" 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study subject activities until approval from the IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Aoki Y, Isselbacher KJ, Pillai S. Bruton tyrosine kinase is tyrosine phosphorylated and activated in pre-B lymphocytes and receptor-ligated B cells. Proc Natl Acad Sci U S A 1994;91 (22):10606-9.

Brown JR, Byrd JC, Coutre SE, Benson DM, Flinn IW, Wagner-Johnston ND, et al. Idelalisib, an inhibitor of phosphatidylinositol 3 kinase p110d, for relapsed/refractory chronic lymphocytic leukemia [Prepublished Manuscript]. Blood 2014a:1-28.

Brown JR, Byrd JC, Coutre SE, Benson DM, Flinn IW, Wagner-Johnston ND, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood 2014b;123 (22):3390-7.

Byrd JC, Rai K, Peterson BL, Appelbaum FR, Morrison VA, Kolitz JE, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 2005;105 (1):49-53.

Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJ, Bezares RF, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007;370 (9583):230-9.

Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30 (23):2820-2.

Coutre SE, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, et al. Management of adverse events associated with idelalisib treatment - expert panel opinion. Leuk Lymphoma 2015:1-20.

de Rooij MF, Kuil A, Geest CR, Eldering E, Chang BY, Buggy JJ, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012;119 (11):2590-4.

de Weers M, Verschuren MC, Kraakman ME, Mensink RG, Schuurman RK, van Dongen JJ, et al. The Bruton's tyrosine kinase gene is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages. European journal of immunology 1993;23 (12):3109-14.

Dighiero G, Hamblin TJ. Chronic lymphocytic leukaemia. Lancet 2008;371 (9617):1017-29.

Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17 (7):928-42.

Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v78-84.

Flinn IW, Kahl BS, Leonard JP, Furman RR, Brown JR, Byrd JC, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-d, as therapy for previously treated indolent non-Hodgkin lymphoma. Blood 2014:1-35.

Flinn IW, Patel M, Horwitz S, Younes A, Foss FM, Oki Y, et al. Preliminary Safety and Efficacy Of IPI-145, a Potent Inhibitor Of Phosphoinositide-3-Kinase-δ,γ, In Patients With Chronic Lymphocytic Leukemia [Oral Presentation]. 12th International Conference on Malignant Lymphoma; 2013 June 19-22; Lugano, Switzerland.

Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014;370 (11):997-1007.

Genevier HC, Hinshelwood S, Gaspar HB, Rigley KP, Brown D, Saeland S, et al. Expression of Bruton's tyrosine kinase protein within the B cell lineage. European journal of immunology 1994;24 (12):3100-5.

Gilead Sciences Inc. ZYDELIG® (idelalisib) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. July 2014:

Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370 (12):1101-10.

Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. J Clin Oncol 2011;29 (5):544-50.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood 2008;111 (12):5446-56.

Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376 (9747):1164-74.

Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. Nature reviews. Cancer 2014;14 (4):219-32.

Herrera AF, Jacobsen ED. Ibrutinib for the treatment of mantle cell lymphoma. Clin Cancer Res 2014;20 (21):5365-71.

Herter S, Birk MC, Klein C, Gerdes C, Umana P, Bacac M. Glycoengineering of therapeutic antibodies enhances monocyte/macrophage-mediated phagocytosis and cytotoxicity. J Immunol 2014;192 (5):2252-60.

Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107 (29):13075-80.

Jefferies CA, Doyle S, Brunner C, Dunne A, Brint E, Wietek C, et al. Bruton's tyrosine kinase is a Toll/interleukin-1 receptor domain-binding protein that participates in nuclear factor kappaB activation by Toll-like receptor 4. J Biol Chem 2003;278 (28):26258-64.

Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct- and immune effector cell-mediated B-cell cytotoxicity. Blood 2014:1-26.

National Cancer Institute (NIH). SEER*Stat Databases: November 2015 Submission. Available at: http://seer.cancer.gov/data/seerstat/nov2015/. Accessed on 23 August. 2016:

Okkenhaug K, Vanhaesebroeck B. PI3K-signalling in B- and T-cells: insights from gene-targeted mice. Biochemical Society transactions 2003;31 (Pt 1):270-4.

Pharmacyclics Inc., Janssen Biotech Inc. IMBRUVICA® (ibrutinib) capsules, for oral use. US Prescribing Information. Revised January 2015:

Rickert RC. New insights into pre-BCR and BCR signalling with relevance to B cell malignancies. Nature reviews 2013;13 (8):578-91.

Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28 (10):1756-65.

Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116 (19):3724-34.

Smith CI, Baskin B, Humire-Greiff P, Zhou JN, Olsson PG, Maniar HS, et al. Expression of Bruton's agammaglobulinemia tyrosine kinase gene, BTK, is selectively down-regulated in T lymphocytes and plasma cells. J Immunol 1994;152 (2):557-65.

Stephens DM, Ruppert AS, Weirda WG, Jones JA, Woyach JA, Maddocks K, et al. Externally validated predictive clinical model for untreated del(17p13.1) chronic lymphocytic leukemia patients [Accepted Article]. Am J Hematol 2015.

Surveillance Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia. Available at: http://seer.cancer.gov/statfacts/html/clyl.html. Accessed 12 May 2011.

Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 1993;72 (2):279-90.

Vanhaesebroeck B, Ali K, Bilancio A, Geering B, Foukas LC. Signalling by PI3K isoforms: insights from gene-targeted mice. Trends Biochem Sci 2005;30 (4):194-204.

Vetrie D, Vorechovsky I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 1993;361 (6409):226-33.

Walter HS, Rule SA, Dyer MJ, Karlin L, Jones C, Cazin B, et al. A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. Blood 2015.

Wilson WH, Gerecitano JF, Goy A, de Vos S, Kenkre VP, Barr PM, et al. The Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity in the ABC Subtype of Relapsed/Refractory De Novo Diffuse Large B-Cell Lymphoma (DLBCL): Interim Results of a Multicenter, Open-Label, Phase 2 Study [Abstract 686]. American Society of Hematology (ASH) Annual Meeting; 2012 December 08-11; Atlanta, GA.

Zelenetz AD, Robak T, Coiffier B, Delgado J, Marlton P, Adewoye AH, et al. Idelalisib Plus Bendamustine and Rituximab (BR) is Superior to BR Alone in Patients with Relapse/Refractory Chronic Lymphocytic Leukemia: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study [Abstract LBA-5]. 57th Annual Meeting and Exposition of the American Society of Hematology (ASH); 2015 05-08 December; Orlando, FL.

11. APPENDICES

Appendix 1. **Investigator Signature Page**

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STUDY ACKNOWLEDGEMENT

A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Idelalisib with and without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia

GS-US-401-1958, Amendment 6, 28 May 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents

PPD

PPD

Name (Printed)
Author

June 22, 2020

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) | Signature

Date | Site Number

Appendix 2. Study Procedures Table

Visit Window (days)	Screening	24 Weeks														Week 25 Day 1[21]	Week 29 Day 1	Every 12 weeks starting Week 33 until Week 105	EOT[19]
	Day -28	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1[18]	Week 5 Day 1	Week 7 Day 1	Week 9 Day 1	Week 11 Day 1	Week 13 Day 1	Week 15 Day 1	Week 17 Day 1	Week 19 Day 1	Week 21 Day 1	Week 23 Day 1				
		0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7	±7	±7	±7
Informed Consent	X																		
Medical and Medication History[1]	X																		
Physical Examination[2]	X	X	X	X	X	X		X		X		X		X		X	X	X	X
Vital Signs	X	X	X	X	X	X		X		X		X		X		X	X	X	X
ECOG Performance Status / B symptoms	X	X				X		X		X		X		X		X	X	X	X
Binet/Rai Staging	X																		
G8 Screening Questionnaire[3]		X														X		X	X
12 lead ECG[4]	X	X				X		X		X		X		X		X			X
Adverse events/ Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tirabrutinib + idelalisib Dispensing[5]		X				X		X		X		X		X		X	X	X	
Tirabrutinib + idelalisib Accountability						X		X		X		X		X		X	X	X	X
Obinutuzumab Administration[6]		X	X	X		X		X		X		X		X					
Hematology[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[20]	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X
Coagulation (PT/INR, aPTT)	X																		X

Visit Window (days)	Screening	24 Weeks														Week 25 Day 1[21]	Week 29 Day 1	Every 12 weeks starting Week 33 until Week 105	EOT[19]
	Day -28	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1[18]	Week 5 Day 1	Week 7 Day 1	Week 9 Day 1	Week 11 Day 1	Week 13 Day 1	Week 15 Day 1	Week 17 Day 1	Week 19 Day 1	Week 21 Day 1	Week 23 Day 1				
		0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7	±7	±7	±7
Peripheral Blood MRD[8]		X								X						X		X	X
Urinalysis and Urine Chemistry	X																		
Pregnancy Testing[9]	X	X				X		X		X		X		X		X	X	X	X
Viral Serologies[10]	X																		
CMV Surveillance[11]	X	X				X		X		X		X		X		X	X	X	
CCI																			
CCI																			
CLL phenotyping[14]	X																		X
Radiographic Tumor evaluation[15]	X															X			
Bone marrow evaluation[16]	X															X			
Response Assessment[17]						X		X		X		X		X		X	X	X	X

1. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti cancer therapies, and any concurrent medical illnesses. CIRS score should be determined at screening.
2. Screening and End of Treatment will be complete physical examinations. Beginning at Week 1 Day 1, a modified physical examination will be a performed to monitor for any changes (eg, lymph nodes, size of the liver and spleen, lung, cardiac, abdomen, skin, neurologic, and any system clinically indicated). Weight should be measured at each PE. Height should be measured at screening only.
3. The G8 screening questionnaire will be used for assessment of subjects aged > 70 years at Week 1 Day 1 and every 6 months until EOT.
4. Subjects should be resting quietly in supine position for 5 minutes prior to ECG collection. The Investigator or qualified designee will review all ECGs.
5. Study drug is not dispensed at the Week 105 visit.
6. Obinutuzumab: 100 mg will be administered intravenously on Day 1 and 900 mg on either Day 1 or 2 (Week 1); then 1000 mg on Day 8 (Week 2), Day 15 (Week 3), and on Weeks 5, 9, 13, 17 and 21 for a total of 8 doses of 1000 mg over 21 weeks. If the 100 mg infusion on Day 1 is well tolerated, the remaining 900 mg (scheduled for Day 2) may be given on Day 1.
7. CBC with differential should be obtained every 2 weeks through Week 25 to evaluate for neutropenia and then at subsequent visits for assessment.

8. Peripheral blood MRD will be assessed on Day 1 of Weeks 1, 13, 25, 33, 45, 105, and EOT. EOT collection is not needed for subjects who complete the Week 105 visit.
9. Serum pregnancy test will be performed at screening for all women of childbearing potential (defined in Appendix 4). Urine pregnancy tests will be conducted prior to Week 1, Day 1 and then every 4 weeks until the EOT visit. Pregnancy kits may be provided for home testing The results must be confirmed as negative prior to continued administration of study drug.
10. Hepatitis serology includes HBsAg, HBcAb, HCV Ab; patients with positive HBcAb and negative HBsAg should have HBV DNA PCR performed prior to treatment start to rule out occult infection, then monthly through 6 months and then at subsequent clinic visits until EOT visit. HIV testing and CMV IgG and IgM testing should be performed at screening.
11. CMV antigen or quantitative PCR testing should be performed at screening and according to the schedule of assessments throughout the course of idelalisib treatment.

CCI [redacted]

CCI [redacted]

14. CLL immunophenotyping, karyotyping and FISH, TP53 and IgHV mutation status, CD38 and ZAP70 expression will be evaluated from peripheral blood at screening. In the event of disease progression, only FISH and TP53 will be evaluated.
15. Tumor evaluation by CT scan (preferred) or MRI of neck, chest, abdomen, and pelvis will be performed at screening (unless scan was already completed up to 42 days prior to first dose). At the Week 25 visit, the same type of evaluation should be performed on those body regions which showed involvement by CLL at screening. An additional CT may be obtained on protocol per investigator discretion following evidence of an improvement in clinical response if the response assessment at the Week 25 visit is less than a complete response or in the event of suspected disease progression.
16. A bone marrow evaluation is required in the screening window for subjects without radiographic evidence of disease. Bone marrow aspirate and biopsy should be performed at Week 25 for subjects fulfilling clinical response criteria for CR or CRi per the modified IWCLL 2008 criteria. MRD should be assessed from bone marrow aspirate at the reference laboratory in Kiel; CCI [redacted]
17. Qualitative treatment response assessment based on physical exam, laboratory parameters and presence of B symptoms should be performed every 4 weeks until Week 33 Day 1 and then at all scheduled visits thereafter following the modified IWCLL 2008 criteria, with the exception of lymphadenopathy, hepatomegaly, splenomegaly, and bone marrow. Assessment of response per modified IWCLL 2008 criteria should also be recorded at the completion of 24 weeks on treatment and subsequent to any CT and/or bone marrow biopsy that is repeated while on study.
18. Following evaluation of the safety data for the first 6 subjects enrolled in each treatment arm, the Safety Review Team (SRT) will determine if weekly clinical evaluation should continue for the duration of the study.
19. The EOT visit should be scheduled for approximately 30 days following discontinuation of all study treatment. For subjects that permanently discontinue all treatment prior to Week 25 Day 1, the Week 25 Day 1 visit should also be performed and may satisfy the requirement for the EOT visit if falling into the +30 days ± 7 day window from all study drug discontinuation.
20. Screening results should include creatinine clearance, serum thymidine kinase, serum beta2 microglobulin and serum quantitative immunoglobulins.
21. The window for bone marrow assessments is 7 days or +14 days as calculated from Week 1 Day 1.

Appendix 3. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v4.03 can be accessed from the below link:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

A) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

B) Definition of Male Fertility

For the purposes of this study, a male born subject is considered to be fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

C) Study Drug Effects on Pregnancy and Hormonal Contraception

Tirabrutinib is contraindicated in pregnancy as non-clinical studies in rats and rabbits have demonstrated embryo-fetal toxicity and reproductive failure. Idelalisib is contraindicated in pregnancy due to a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical studies in rats and rabbits that have demonstrated teratogenic effects.

Currently, insufficient data exists for any of the study investigational products to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen in this study. There are no data with obinutuzumab use in pregnant women to inform a drug-associated risk. For further information on obinutuzumab, refer to the SmPC.

For additional information on any of these study investigational products, please refer to the latest version of the relevant IB or label in the applicable country.

D) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Also, subjects must not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the Week 1, Day 1 visit prior to dosing. Pregnancy tests will be performed at the timepoints specified in the Study Procedures Table (Appendix 2). Female subjects of childbearing potential must agree to one of the following from screening until 30 days following the final dose of either tirabrutinib or idelalisib or 18 months from the last dose of obinutuzumab (whichever is later).

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Intrauterine device (IUD) with a failure rate of < 1% per year

  Tubal sterilization

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days following the final dose of either tirabrutinib or idelalisib or 18 months from the last dose of obinutuzumab (whichever is later).

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days following the final dose of either tirabrutinib or idelalisib or 18 months from the last dose of obinutuzumab (whichever is later). Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days following the final dose of either tirabrutinib or idelalisib or 18 months from the last dose of obinutuzumab (whichever is later).

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of the final dose of either tirabrutinib or idelalisib or 18 months from the last dose of obinutuzumab (whichever is later). Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Male subjects whose female partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 5. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg,, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 6. Modified IWCLL 2008 Response Criteria

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) 2008 criteria {Hallek 2008}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of small molecule targeted therapy {Cheson 2012}.

Complete remission (CR):

All below listed criteria must be fulfilled and no disease related symptoms should be present.

Complete remission with incomplete recovery of the bone marrow (CRi):

All below listed criteria must be fulfilled, except for an incomplete recovery of the bone marrow with persisting anemia, thrombocytopenia and/or neutropenia (related to toxicity of treatment and not due to CLL) and no disease related symptoms should be present.

Partial response (PR):

Among the below listed criteria at least 2 from group A and 1 from group B must be fulfilled.

Partial response with lymphocytosis (PR-L):

Among the below listed criteria at least 2 from group A and 1 from group B must be fulfilled, however, a lymphocytosis related to treatment may be present.

Nodular partial response (nPR):

All criteria for a CR/CRi are fulfilled, but the bone marrow shows lymphoid nodules. As in a lot of cases these nodules are related to bone marrow proliferation during recovery, efforts should be made to prove that these lymphocytes are no CLL cells by 4-colour-flow cytometry to be able to define these patients as CR/CRi. If this cannot be proved by either FACS or MRD from the bone marrow patients will be considered PR and therefore this category will not appear on the eCRF.

Stable disease (SD):

Failure to achieve a PR and absence of PD.

Progressive disease (PD):

Presence of at least 1 of the below enlisted criteria or appearance of new lymph nodes > 1.5 cm, hepato- or splenomegaly or organ infiltration by CLL.

Response criteria

Parameter	CR	CRi	PR	PR-L	PD
Group A (indicating tumor load)					
Lymphadenopathy[1]	none > 1.5 cm		decrease ≥ 50%		increase by ≥ 50% or new lymph nodes ≥ 1.5 cm
Hepatomegaly	none		decrease ≥ 50%		Increase by ≥ 50 %
Splenomegaly	none		decrease ≥ 50%		Increase by ≥ 50 %
Blood lymphocytes	< 4000/µL		decrease of ≥ 50% from baseline	increase	Increase by ≥ 50% over baseline[2] to ≥ 5000/µL
Bone marrow	Normocellular	hypocellular	50% reduction in BM infiltrates[3]		irrelevant
	30% lymphocytes, no B-lymphoid nodules				
Group B (indicating function of the hematopoietic system)					
Platelet count	≥ 100000/µL	Irrelevant	≥ 100000/µL or increase by ≥ 50% from baseline		Decrease by ≥ 50% due to CLL
Hemoglobin	> 11 g/dL	irrelevant	> 11 g/dL or increase by ≥ 50% from baseline		Decrease by > 2 g/dL
Neutrophil count	> 1500/µL	Irrelevant	> 1500/µL or increase by ≥ 50% from baseline		irrelevant

a Assessed as sum of the products of multiple lymph nodes, if available an indicator lymph node (the largest palpable) from every region should be compared in every staging.
b Patients with treatment related lymphocytosis should not be rated PD and remain on study treatment if other criteria for progressive disease are absent.
c In case of B lymphoid nodules a 4 colour flow cytometry is recommended to clarify if this is related to CLL, if FACS is negative these patients can be rated as CR/CRi, if all other criteria are fulfilled.

MRD response rate

The MRD response is assessed with four-color-flow cytometry (FACS) and MRD negativity is defined as one CLL cell per 10,000 leukocytes [0.01 %], ie, $<10^4$ and patients are defined as MRD negative if their disease burden is below this threshold MRD in the bone marrow will be assessed after the completion of 24 weeks of treatment and MRD in the peripheral blood will be assessed in the schedule outlined in Appendix 2 in the event that peripheral blood ALC<4K/µL.

Appendix 7. Cumulative Illness Rating Scale (CIRS)

The CIRS used in this protocol is designed to provide an assessment of recurrent or ongoing chronic comorbid conditions. For each condition selected from the CIRS List of Comorbid Conditions, please rate the severity of that condition. For the severity rating, please use the scoring guidelines shown in the table below, considering the magnitude of symptoms, how manageable the condition is, and the extent of intervention required.

Please take into account that CLL induced illness or organ damage are not included in this rating scale. The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are two or more illnesses/impairments of one organ system, the illness/impairment with the highest severity should be evaluated.

CIRS Rating Strategy of Comorbidity

Score	Severity	Findings
0	No problem	Organ system not compromised
1	Mild	Illness/impairment with/without requirement of therapy, excellent prognosis, patient with normal activity
2	Moderate	Illness/impairment requiring therapy, good prognosis, compromised activity of patient
3	Severe	Illness/impairment with urgent requirement of therapy, prognosis unclear, marked restriction in activity
4	Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis

CIRS List of Comorbid Conditions

Organ System	If illness/impairment present, please specify	Score[1]
Heart		
Blood Pressure		
Vascular		
Respiratory		
Eye/ear/nose/throat/larynx		
Upper gastrointestinal		
Lower gastrointestinal		
Liver		
Renal		
Genitourinary		
Musculoskeletal		
Endocrine/metabolic		
Neurological		
Psychiatric		
Total Score		

Appendix 8. Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided in the table below. The formula appropriate to the units in which serum creatinine was measured and the subject's gender should be used.

Serum Creatinine Units	Gender	Formula
mg/dL	Males	$eC_{cr}\ [mL/min] = \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1}{72 \times \text{subject serum creatinine [mg/dL]}}$
	Females	$eC_{cr}\ [mL/min] = \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dL]}}$
µmol/dL	Males	$eC_{cr}\ [mL/min] = \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.23}{\text{Subject serum creatinine [µmol /L]}}$
	Females	$eC_{cr}\ [mL/min] = \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.04}{\text{Subject serum creatinine [µmol /L]}}$

Abbreviation: eC_{cr} estimated creatinine clearance

Appendix 9. Binet and Rai Staging Systems for the Classification of CLL

Binet

Stage	Lymph Node Areas	Hemoglobin < 10 g/dL	Platelet < 100 × 10^9/L
A	< 3	No	No
B	≥ 3	No	No
C	±	Either present	

Rai

Stage	Lymphocytosis	Lymph Node Enlargement	Spleen/Liver Enlargement	Hemoglobin < 11 g/dL	Platelet < 100 × 10^9/L
0	Yes	No	No	No	No
I	Yes	Yes	No	No	No
II	Yes	±	Yes	No	No
III	Yes	±	±	Yes	No
IV	Yes	±	±	±	Yes

Appendix 10. The G8 Screening Questionnaire

- **8 questions**
- **Nurse administered**
- **Takes 5-10 minutes to perform**
  - —Appetite, weight loss, BMI
  - —Mobility
  - —Mood and cognition
  - —Number of medications
  - —Patient related health
  - —Age categories
- **Abnormal if score ≤ 14**
  - —Preliminary analysis
  - —Sensitivity: 89.6%
  - —Specificity: 60.4%

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, or chewing or swallowing difficulties?	0: severe decrease in food intake
		1: moderate decrease in food intake
		2: no decrease in food intake
B	Weight loss during the last 3 months	0: weight loss > 3 kg
		1: does not know
		2: weight loss between 1 and 3 kg
		3: no weight loss
C	Mobility	0: bed or chair bound
		1: able to get out of bed/chair but does not go out
		2: goes out
E	Neuropsychological problems	0: severe dementia or depression
		1: mild dementia or depression
		2: no psychological problems
F	Body mass index (BMI weight in kg) / (height in m)^2	0: BMI < 18.5
		1: BMI = 18.5 to BMI < 21
		2: BMI = 21 to BMI < 23
		3: BMI = 23 and > 23
H	Takes more than 3 prescription drugs per day	0: yes
		1: no
P	In comparison with other people of the same age, how do they consider their health status?	0: not as good
		0.5: does not know
		1: as good
		2: better
	Age	0: > 85 yr
		1: 80 85 yr
		2: < 80 yr
	Total Score	**0-17**