



## CLINICAL STUDY PROTOCOL

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<b>Study Title:</b>	A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Entospletinib with and without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia	
<b>Sponsor:</b>	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
<b>IND Number:</b>	This is a non-IND study	
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<b>Clinical Trials.gov Identifier:</b>	NCT02983617	
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<b>GCLLSG Protocol ID:</b>	CLLRUmbrella2	
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## PROTOCOL SYNOPSIS

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

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

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**IND Number:** This is a non-IND study  
**EudraCT Number:** 2016-002768-15  
**Clinical Trials.gov Identifier:** NCT02983617

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**Study Centers Planned:** Approximately 25 centers in Germany

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**Objectives:**

**Primary Objective:**

- To determine the preliminary efficacy of finite therapy with the combination of tirabrutinib, entospletinib 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 entospletinib with and without obinutuzumab

**Exploratory Objectives:**

█ [REDACTED]

█ [REDACTED]

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**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 25 including 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)

**Exploratory Endpoints:**

- █ [REDACTED]

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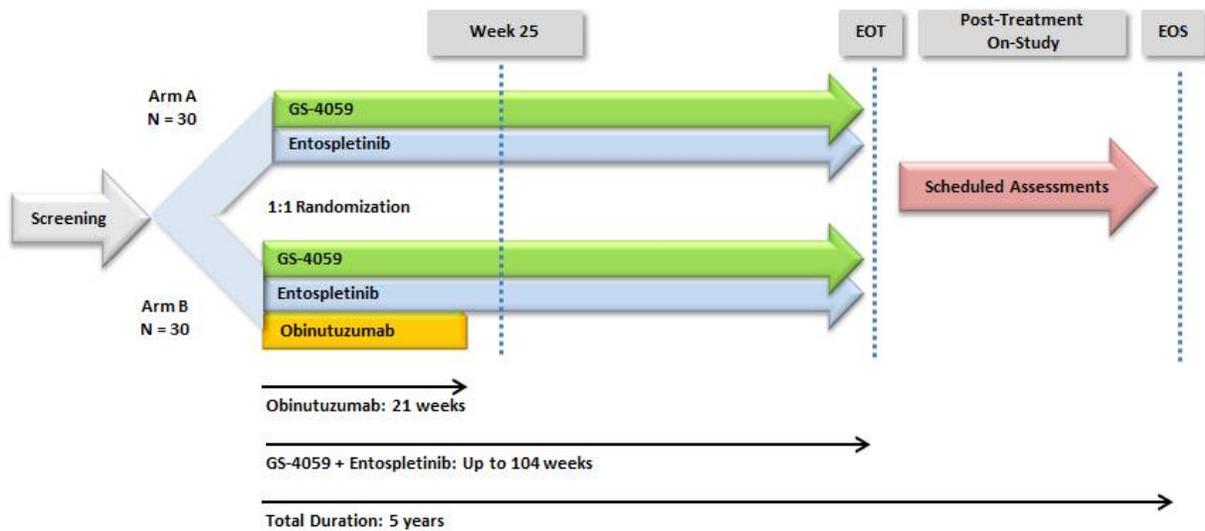
**Study Design:**

This is a Phase 2, prospective, open-label, multicenter trial to evaluate the safety and efficacy of the combination of tirabrutinib (GS-4059) and entospletinib with and without obinutuzumab in subjects with relapsed or refractory CLL.

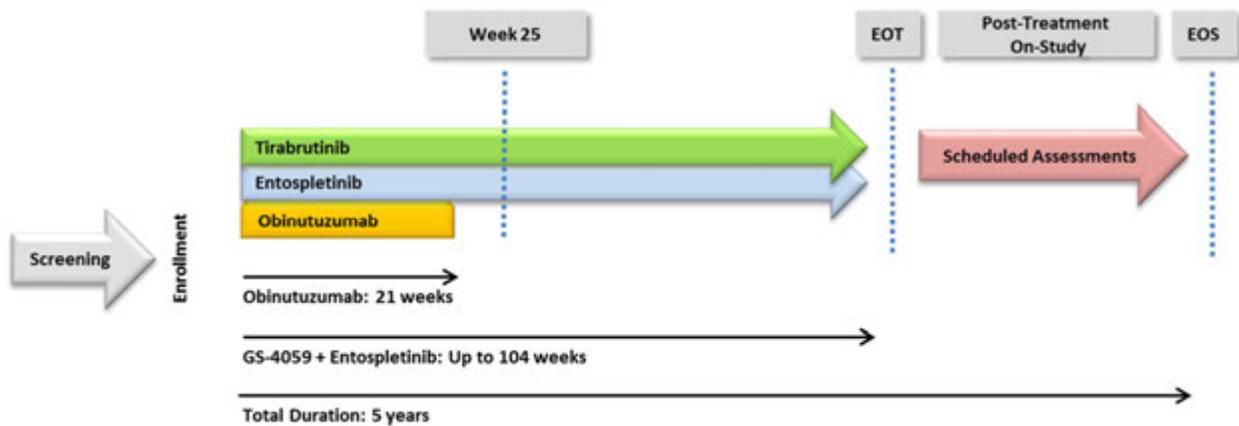
Eligible subjects will be treated with the combination of tirabrutinib and entospletinib and stratified by the presence of 17p deletion/TP53 mutation (del17p/TP53mut) in CLL cells. Following stratification, subjects will be randomized 1:1 to treatment with the combination of tirabrutinib and entospletinib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

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

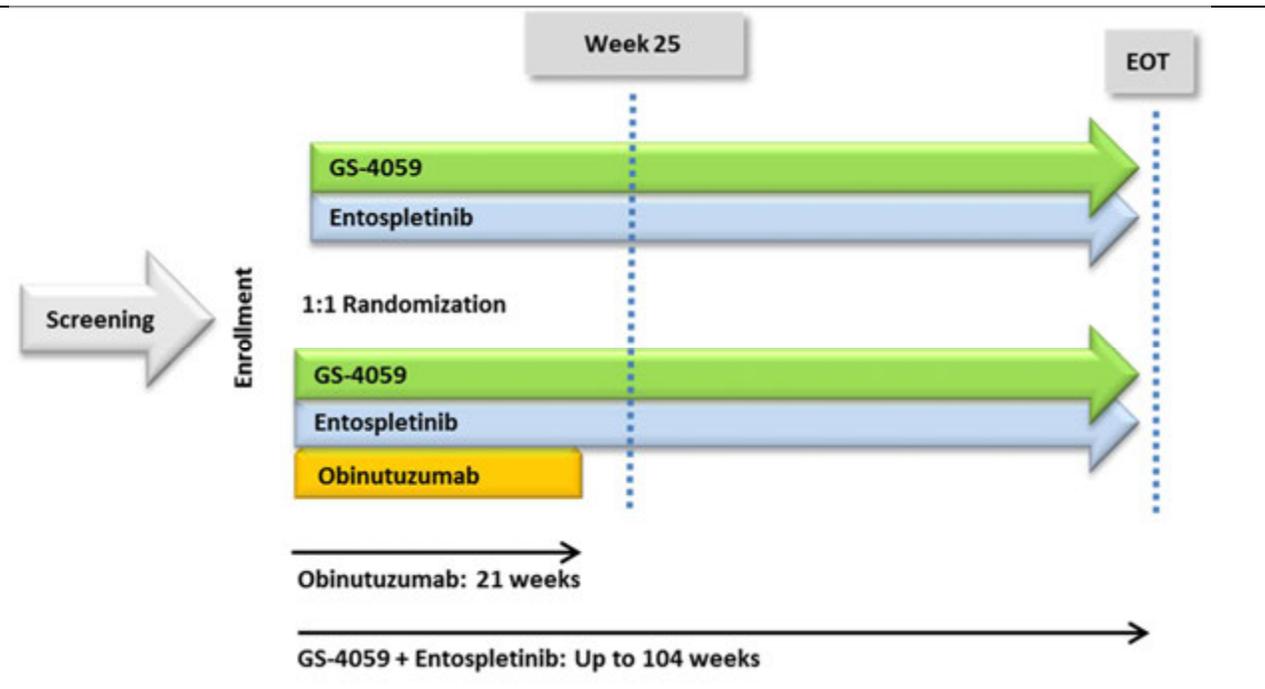
### Study Design Schema



With Amendment 3, randomization was discontinued. All subsequently enrolled subjects will enter Arm B (tirabrutinib + entospletinib + 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 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  $\geq$  4 hematological toxicities persisting for  $>$  7 days
- Grade  $\geq$  4 non-hematologic laboratory abnormalities except for asymptomatic AST/ALT elevation, LDH, or uric acid
- Grade  $\geq$  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  $\geq$  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 shortly after the assessment.

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:	<p>Obinutuzumab will be administered for up to 8 doses over 21 weeks to subjects randomized or enrolled to treatment with tirabrutinib + entospletinib + obinutuzumab (Arm B). Combination treatment with the oral agents 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:</p> <ol style="list-style-type: none"><li>1) an additional 3 months of therapy or</li><li>2) 104 weeks of total treatment.</li></ol>
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:	<p><b>Inclusion Criteria</b></p> <p>Subjects must meet all the following criteria to be eligible for participation in this study:</p> <ol style="list-style-type: none"><li>1) Documentation of relapsed or refractory CLL</li><li>2) Have an indication for treatment per modified IWCLL 2008 criteria; subjects without radiographically measureable disease (defined as <math>\geq 1</math> lesion <math>&gt; 1.5</math>cm in diameter as assessed by computer tomography (CT) or magnetic resonance imaging [MRI]) must have bone marrow evaluation at screening</li><li>3) Adequate hematologic function as indicated by a platelet count <math>\geq 50 \times 10^9/L</math>, a neutrophil count <math>\geq 1 \times 10^9/L</math> and a hemoglobin <math>\geq 8g/dL</math> unless lower values are directly attributable to documented bone marrow burden of CLL</li><li>4) Adequate renal function as indicated by a CrCl <math>\geq 50</math> mL/min calculated by the modified Cockcroft-Gault formula or from a 24h urine collection</li></ol>

- 5) Adequate liver function as indicated by total bilirubin  $\leq 1.5$ x institutional upper limit of normal (ULN) unless attributed to Gilbert's syndrome and AST/ALT  $\leq 2.5$ ×ULN
- 6) Male or female  $\geq 18$  years of age
- 7) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)  $\leq 2$
- 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

### **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 in 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  $\geq 1$  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) 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.
- 13) Legal incapacity, prisoners or subjects institutionalized by regulatory or court order, or any individual in dependence to study sponsor or any investigator
- 14) Anticipated chronic use of strong CYP3A4/CYP2C9 inducers, moderate CYP2C9 inducers, or strong P-gp inducers while on study; use within 2 weeks of first dose of study treatment should be avoided.
- 15) Requirement for proton pump inhibitor (PPI) therapy
- 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, entospletinib, tirabrutinib, or any of the excipients

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**Test Product, Dose,  
and Mode of  
Administration:**

**Tirabrutinib and Entospletinib:**

Tirabrutinib 80 mg will be self-administered orally once daily and entospletinib 400 mg will be self-administered orally once daily. Dosing of both agents will begin on Week 1 Day 1 of the study and thereafter 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 x 20 mg) tablets, 40 mg (2 x 40 mg) tablets, or as 80 mg tablets. Entospletinib is supplied as 200 mg (2 x 200 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 may be subsequently 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.

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**Reference Therapy,  
Dose, and Mode of  
Administration:**

Not applicable

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**Criteria for  
Evaluation:**

Safety: Safety will be evaluated by the documentation of 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

Pharmacokinetics: Plasma drug concentrations of tirabrutinib and entospletinib as assessed by validated bioanalytical methods

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**Sample Size Determination**

The primary goal of this study is to evaluate the efficacy of the combination of tirabrutinib and entospletinib with obinutuzumab in relapsed and refractory CLL. The primary endpoint for this study is the rate of CR at Week 25. The corresponding single-agent CR rate with BTK and SYK inhibitors in subjects with relapsed or refractory CLL is  $\leq 5\%$ . The 90% CI corresponding to different CR rates ranging from 20% to 60% for a sample size of 30 is provided in the table below. With a sample size of 30, the lower bound of the 90% CI of an observed CR rate of 20% or above will exclude 5%.

**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 Clopper-Pearson method.

Time-to-event endpoints (DOR, PFS, TTNT, and OS) will be analyzed using the Kaplan-Meier method. The median and quartiles and their associated 90% confidence intervals for these endpoints will be provided if estimable.

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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.

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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

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC <sub>0-24h</sub>	mean exposure
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BHCG	Beta-human chorionic gonadotropin
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 <sub>max</sub>	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 <sup>-4</sup> CLL cells present)
CR/PB MRD-	complete response with peripheral minimal residual disease negativity (<10 <sup>-4</sup> CLL cells present)
CrCl	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
C <sub>tau</sub>	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
DDI	drug-drug interaction
del17p	deletion of short arm of chromosome 17
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response

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
hCG	human chorionic gonadotropin
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
IRC	independent review committee
IWCLL	International Workshop on CLL
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
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

MZL	marginal zone lymphoma
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
PI3K	phosphatidylinositol 3-kinase
PK	Pharmacokinetics
PP	per protocol
PPI	proton pump inhibitor
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
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SPD	sum of the products of greatest perpendicular diameters
SRT	safety review team
StD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
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  $\geq 65$  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.

## **1.2. Entospletinib**

### **1.2.1. General Information**

Entospletinib is a potent and highly selective inhibitor of spleen tyrosine kinase (SYK) that is being developed by Gilead for oral administration in the treatment of hematologic malignancies and chronic graft versus host disease.

### **1.2.2. Spleen Tyrosine Kinase in Hematologic Malignancies**

Spleen tyrosine kinase (SYK) is a non-receptor cytoplasmic tyrosine kinase that is primarily expressed in cells of hematopoietic lineage. It is an important mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells. SYK contains 2 adjacent SH2 domains that bind to immunoreceptor tyrosine-based activation motifs (ITAMs) to autophosphorylate and activate the enzyme. This allows SYK to phosphorylate its specific substrates including other enzymes and adaptor proteins, orchestrating a complex series of cellular responses such as cell proliferation, differentiation, survival, and phagocytosis.

Recent studies have suggested a role for the dysregulation of the tyrosine kinase SYK in B-cell malignancies. SYK is expressed in B cells and is essentially involved in multiple signal transduction pathways downstream of the B-cell receptor (BCR). In this process, SYK trans-autophosphorylates, and activates effector molecules such as PLC $\gamma$ , PI3K, and mitogen-activated protein kinase (MAPK) and their associated signaling pathways, to induce a variety of responses including: proliferation, survival, differentiation, anergy, and apoptosis (Figure 1-1). In B cells, entospletinib effectively blocks BCR-mediated activation and proliferation (data on file). Additionally, the BCR can deliver antigen-independent signals that have also been postulated to require SYK activity. Both antigen-dependent and independent signals have been implicated in the pathogenesis of several common B-cell malignancies, including CLL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and B-lineage acute lymphoblastic leukemia (B-ALL) {Efremov 2011}. As a result, inhibitors of SYK activity are an attractive therapeutic option for hematopoietic B-cell lymphomas and other NHL varieties where SYK inhibition would prevent B-cell receptor-mediated signaling and therefore the uncontrolled growth of lymphoma cells.

### **1.2.3. Nonclinical Pharmacology and Toxicology of Entospletinib**

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

### **1.2.4. Clinical Trials of Entospletinib**

To date, 16 clinical studies have been initiated with entospletinib including treatment of over 300 healthy subjects, 75 subjects with CLL and 150 with NHL. For complete details on the completed and ongoing studies with entospletinib, please refer to the entospletinib IB.

The spray-dried dispersion formulation of the entospletinib tablet will be used in the current study and its superiority to prior tablet formulations in bioavailability and drug-drug interactions was established by Study GS-US-339-0111: A Phase 1 Open-Label, Adaptive Study of Novel Entospletinib Tablets Formulations to Evaluate the Effect of Acid Reducing Agents and Food on Entospletinib PK and Relative Bioavailability of the Novel Entospletinib Tablet Formulations. The PK and PD of this formulation were further evaluated in healthy volunteers in Study GS-US-245-1222. A less-than-proportional increase in exposure was seen with repeated dosing of 400 mg entospletinib in comparison with 200 mg entospletinib. While there was no clinically meaningful effect of coadministration of a PPI (omeprazole) on entospletinib PK with entospletinib 200 mg once daily, entospletinib exposure ( $AUC_{tau}$ ) was significantly reduced (59%) at a dose of entospletinib 400 mg twice daily.

The single agent entospletinib treatment experience in the ongoing Phase 2 GS-US-339-0102 study showed a benefit in relapsed and refractory CLL. The primary efficacy endpoint for a CLL specific cohort with 41 subjects was PFS rate at 24 weeks and was assessed by the independent review committee (IRC) to be 69% (95% CI: 51.3, 82.7). With a median exposure of 36 weeks (range of 1 to 131 weeks), the safety data for the 41 subjects in the CLL cohort showed entospletinib treatment to be generally well tolerated. Treatment emergent AEs with an incidence over 15% in the study overall were as follows: fatigue, nausea, diarrhea, decreased appetite, constipation, cough, headache, dizziness, pyrexia, anemia, vomiting, dyspnea, and insomnia. The most frequently reported SAEs included dyspnea (4%), pneumonia (4%), febrile neutropenia (3%), dehydration (3%), and pyrexia (2%).

The ongoing Phase 1b GS-US-401-1757 study is evaluating the safety and tolerability of the combination of entospletinib with tirabrutinib and provides the primary supportive data for this Phase 2 study. The preliminary safety results from this study are summarized in the dose rationale Section 1.5.1.

### **1.3. Tirabrutinib**

#### **1.3.1. General Information**

Tirabrutinib (also known as GS-4059, ONO-4059HCL, ONO-1973, and ONO-WG-307) is a potent 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**

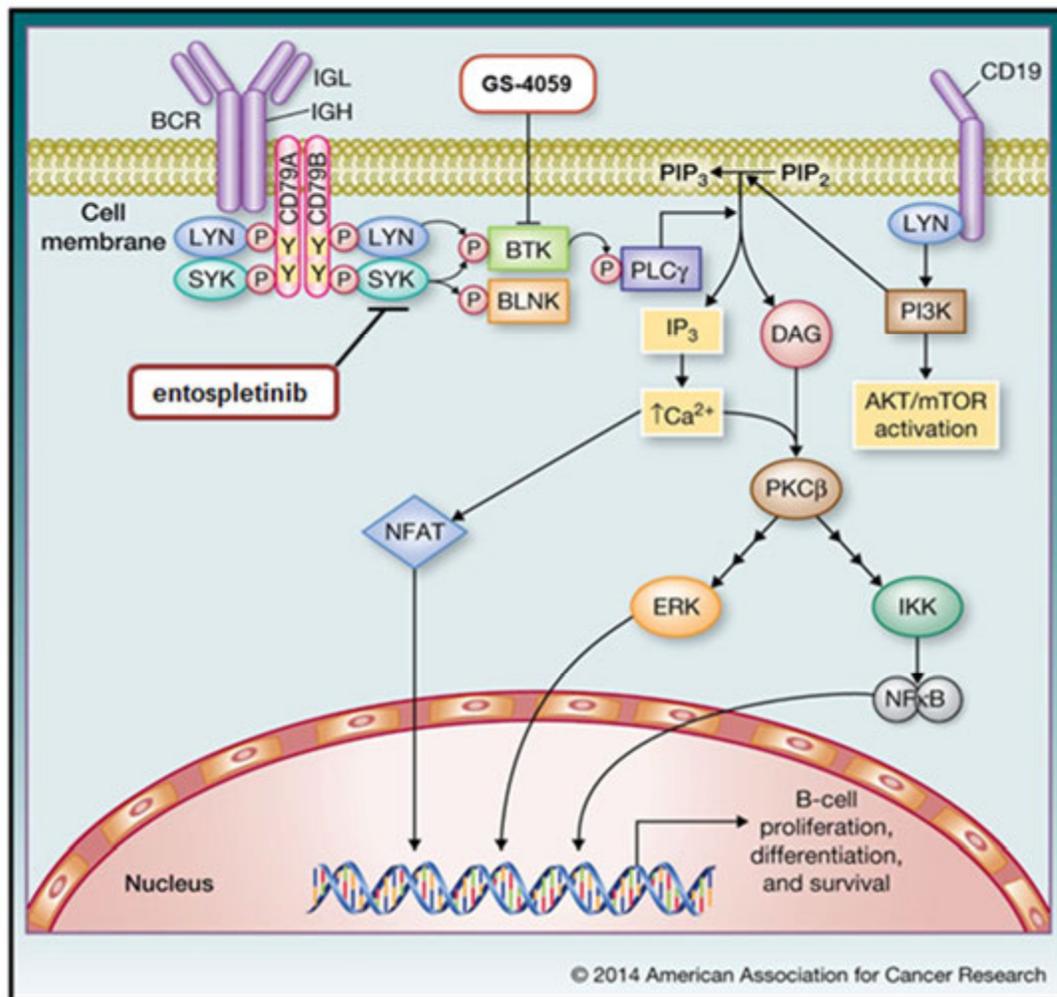
BTK was originally identified in 1993 as a non-receptor intracellular protein tyrosine kinase that is defective in the inherited immunodeficiency disease X-linked agammaglobulinaemia (XLA) {Tsukada 1993, Vetrie 1993}. XLA is characterized by low levels of immunoglobulin production and the absence of 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, Geneviev 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 as a key oncogenic driver 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<sup>®</sup>), has demonstrated clinical benefit to subjects with CLL, MCL, and WM {[Pharmacyclics Inc. 2015](#)}. Additionally, transient clinical responses were observed in a pilot study of relapsed DLBCL, primarily in the non-GCB subtype {[Wilson 2012](#)}.

Figure 1-1. Inhibition of the BCR Pathway



Adapted from {Herrera 2014}

### 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 were demonstrated in subjects with CLL at doses ranging from 40 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  $\geq$  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 doses ranging from 80 to 600 mg once daily.

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 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 and 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  $^{14}\text{C}$ -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 entospletinib. Tirabrutinib administered at doses up to 160 mg once daily combined with entospletinib administered at doses up to 400 mg once daily has been well tolerated with no DLTs. Further safety results are discussed in the dose rationale Section 1.5.1.

For additional information, 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 CLL11 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.

Obinutuzumab (Gazyva<sup>®</sup>/Gazyvaro<sup>®</sup>) 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 entospletinib 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 entospletinib, 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 entospletinib *in vitro* had striking efficacy, supporting the possibility of improving efficacy with low toxicity.

As of June 7, 2017 10 subjects with CLL have been treated on Phase 1b Study GS-US-401-1757 with the combination of tirabrutinib and entospletinib with a median exposure of 43 weeks (range: 18-55). All 10 subjects continue on study and treatment at this time; however no CLL subjects have achieved a CR. Given the lack of CRs in the ongoing treatment experience with the combination of tirabrutinib and entospletinib, enrollment into the doublet combination of tirabrutinib and entospletinib 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 tirabrutinib and entospletinib with and without obinutuzumab in subjects with relapsed or refractory CLL.

In the combination proposed for this study, the doses of both tirabrutinib and entospletinib have been reduced from the maximal safe doses previously used as single agent therapy. Prior single-agent dose-ranging with tirabrutinib in the ONO-4059POE001/GS-US-401-1787 study

did not identify a MTD in subjects with CLL at doses up to tirabrutinib 600 mg daily. Similarly, there was no MTD identified for entospletinib as monotherapy in subjects with CLL at doses up to 400 mg twice daily. The tirabrutinib dose of 80 mg once daily used in this study is approximately 13% of highest safe single-agent dose in ONO-4059POE001; the entospletinib dose of 400 mg once daily represents a 50% reduction from that used in Phase 2 monotherapy treatment for CLL in the GS-US-339-0102 study. The combination of tirabrutinib 80 mg once daily and entospletinib 400 mg once daily was shown to be safe and tolerable in the Phase 1b GS-US-401-1757 study.

Based on data as of 22 July 2016, the median time on treatment with tirabrutinib and entospletinib in the GS-US-401-1757 study was 114 days (range: 29-239) in 17 subjects with lymphoid malignancies, of whom 3 had CLL. Two subjects reported a Grade 3 or 4 AE that was attributed by the investigator to be related to treatment. One subject with DLBCL at the tirabrutinib 150 mg/entospletinib 200 mg dose level experienced Grade 4 hyperglycemia; the subject remained on therapy throughout with standard-of-care management. One subject with WM at the tirabrutinib 40 mg/entospletinib 400 mg dose level developed Grade 3 neutropenia that resolved with conservative management within 2 weeks while remaining on treatment. Three subjects reported an SAE on study. One subject with WM at the tirabrutinib 40 mg/entospletinib 200 mg dose level reported an SAE of pneumonia that did not necessitate interruption of treatment. One subject with FL at the tirabrutinib 80 mg/entospletinib 200 mg dose level had pyrexia and atrial fibrillation in the context of a pneumonia requiring hospitalization for management. One subject with DLBCL at the tirabrutinib 80 mg/entospletinib 400 mg dose level reported hematemesis in the 30-day window following treatment discontinuation due to progressive disease.

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 entospletinib 400 mg once daily.

Preliminary BTK occupancy data in peripheral blood mononuclear cells demonstrates no detectable free BTK at tirabrutinib doses of 40 mg once daily and higher. At doses of tirabrutinib  $\geq 80$  mg daily in the ONO-4059POE001 single-agent dose escalation study with tirabrutinib, 20 of 21 evaluable subjects with CLL had at least a PR; at a tirabrutinib dose of 20 mg or 40 mg, 2/3 subjects at each dose level had a PR or better. Entospletinib demonstrates 40% inhibition of B-cell receptor pathway activation with a dose of 400 mg daily. In the combination Phase 1b GS-US-401-1757 study, 8 subjects treated with tirabrutinib and entospletinib are evaluable for response across dose levels, of whom, 4 have had a best response of a PR.

Obinutuzumab will be used at the approved 1000 mg dose and schedule. The safety of the addition of obinutuzumab to the combination of tirabrutinib 80 mg daily and entospletinib 400 mg once daily will be initially evaluated in the safety run-in before additional subjects are enrolled.

## 1.6. Risk/Benefit Assessment for the Study

### Tirabrutinib

In the completed single-agent Phase 1 study ONO-4059POE001, 28 subjects with relapsed/refractory CLL were treated with 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 has been reported as of October 2015. 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  $\geq$  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%).

### Entospletinib

Entospletinib has been well tolerated across the 16 clinical studies in which it has been evaluated. Treatment-emergent AEs commonly reported across the studies involving healthy volunteer subjects include headache, somnolence, and GI symptoms (nausea and abdominal pain), all of which were mild and reversible. Increased transaminases were noted in some subjects and were reversible. The safety profile for subjects with CLL treated with entospletinib is described in Section 1.2.4.

Entospletinib is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. Administration of drugs such as entospletinib that inhibit UGT1A1 are expected to increase total bilirubin due to decreased conjugation rather than liver dysfunction. The elevations in indirect bilirubin observed in clinical trials with entospletinib were generally self-limited and did not result in discontinuation of entospletinib.

### Obinutuzumab

Obinutuzumab (Gazyva<sup>®</sup>/Gazyvaro<sup>®</sup>) 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  $\geq 10\%$ ) 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  $\geq 10\%$ ) observed in patients with CLL in the GAZYVARO containing arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

The most common adverse reactions (incidence  $\geq 10\%$ ) observed in patients with CLL in the GAZYVARO containing arm were infusion related 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 mandated unless medically contraindicated.

To mitigate the risk of HBV reactivation in subjects treated with an anti-CD20 antibody, hepatitis B virus 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 CD20 therapy and every 3 months thereafter for 1 year from the last dose of CD20 during study participation. 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 ( $>25 \times 10^9/L$ ) or renal impairment ( $CrCl < 70 mL/min$ ).

### **Combination therapy**

Although new toxicities due to the combination of agents remains a possibility, the safety and tolerability of tirabrutinib combined with entospletinib has been previously evaluated in Study GS-US-401-1757. Entospletinib 400 mg once daily does not increase the exposure of tirabrutinib significantly based on preliminary PK data from this study.

The safety of the combination of tirabrutinib 80 mg once daily and entospletinib 400 mg once daily will be further evaluated in this Phase 2 study through a review of the safety data for the initial 6 subjects treated with the combination through 28 days of therapy prior to the enrollment of additional subjects. Similarly, the safety of the addition of obinutuzumab to the combination of tirabrutinib and entospletinib will be evaluated through a review of the safety data for the initial 6 subjects treated through 28 days of therapy prior to the enrollment of additional subjects on this treatment arm. 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.

### **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 entospletinib 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 entospletinib with and without obinutuzumab

The exploratory objectives of this study are:

█ [REDACTED]

█ [REDACTED]

### 3. STUDY DESIGN

#### 3.1. Study Design

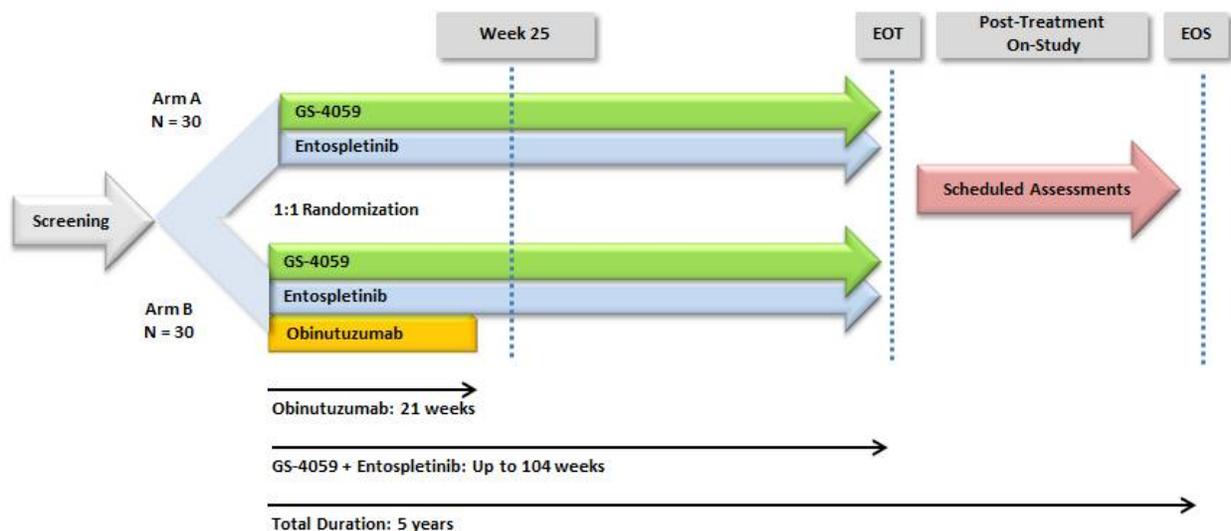
This is a Phase 2, prospective, open-label, multicenter trial to evaluate the safety and efficacy of the combination of tirabrutinib (GS-4059) and entospletinib with and without obinutuzumab in subjects with relapsed or refractory CLL.

#### 3.2. Study Treatments

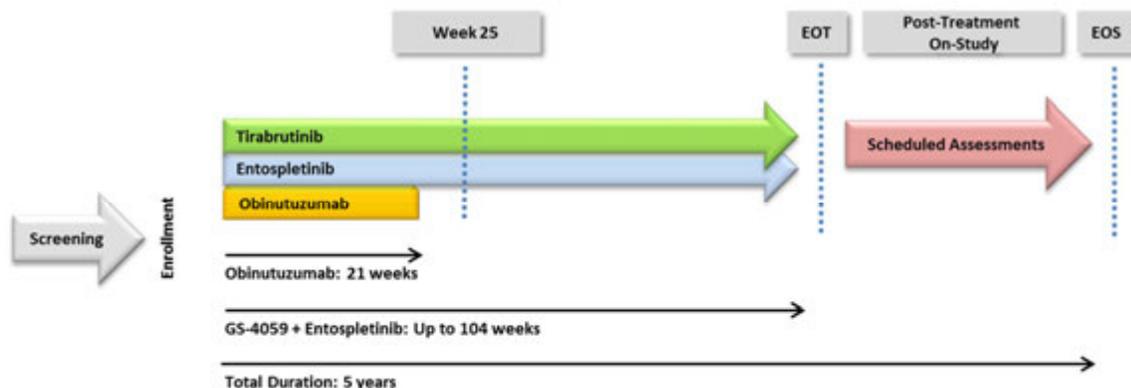
Combination therapy of tirabrutinib (BTK inhibitor) 80 mg once daily and entospletinib (SYK inhibitor) 400 mg once daily with and without obinutuzumab will be evaluated for efficacy, safety, and tolerability.

Eligible subjects will be treated with the combination of tirabrutinib and entospletinib 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 entospletinib with or without obinutuzumab.

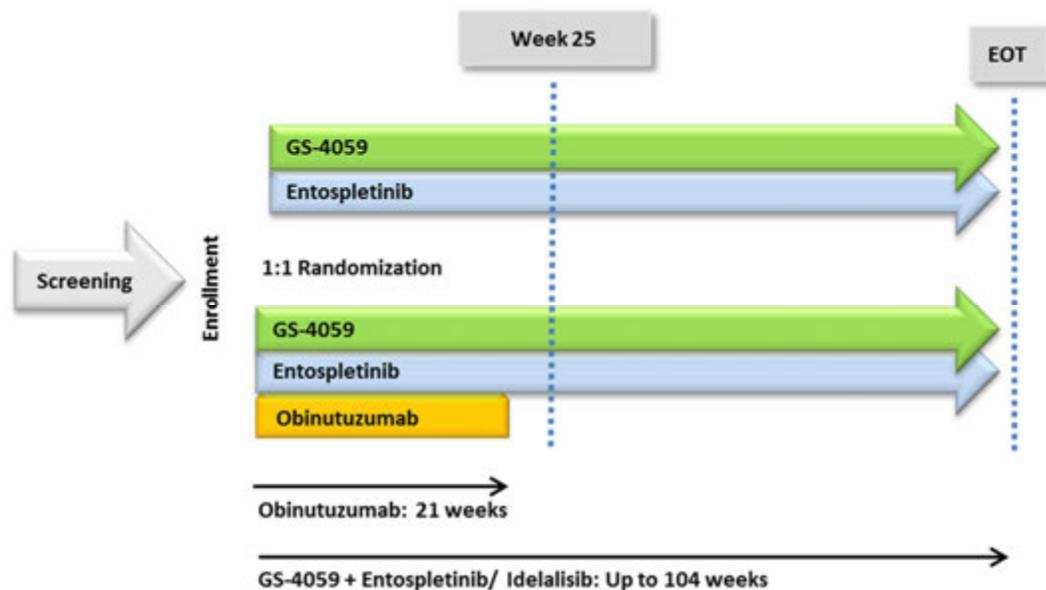
#### Study Design Schema



With Amendment 3, randomization was discontinued. All subsequently enrolled subjects entered Arm B (tirabrutinib + entospletinib + 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 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 SRT will consist of at least one investigator from the GCLLSG and Gilead Sciences, Inc. (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  $\geq 4$  hematological toxicities persisting for  $> 7$  days
- Grade  $\geq 4$  non-hematologic laboratory abnormalities except for asymptomatic AST/ALT elevation, LDH, or uric acid
- Grade  $\geq 3$  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  $\geq 2$  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), 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 shortly after the assessment.

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 + entospletinib + obinutuzumab). Combination treatment with the oral agents (tirabrutinib and entospletinib) 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:

- 1) an additional 3 months of therapy or
- 2) 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 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 for treatment per modified IWCLL 2008 criteria; subjects without radiographically measureable disease (defined as  $\geq 1$  lesion  $> 1.5$ cm 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  $\geq 50 \times 10^9/L$ , a neutrophil count  $\geq 1 \times 10^9/L$  and a hemoglobin  $\geq 8$ g/dL unless lower values are directly attributable to documented bone marrow burden of CLL
- 4) Adequate renal function as indicated by a CrCL  $\geq 50$  mL/min calculated by the modified Cockcroft-Gault formula or from a 24h urine collection
- 5) Adequate liver function as indicated by total bilirubin  $\leq 1.5$ x institutional upper limit of normal (ULN) unless attributed to Gilbert's syndrome and AST/ALT  $\leq 2.5$ xULN
- 6) Male or female  $\geq 18$  years of age
- 7) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)  $\leq 2$
- 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

#### 4.3. 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 in 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  $\geq 1$  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) 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
- 13) Legal incapacity, prisoners or subjects institutionalized by regulatory or court order, or any individual in dependence to study sponsor or any investigator
- 14) Anticipated chronic use of strong CYP3A4/CYP2C9 inducers, moderate CYP2C9 inducers, or a strong P-gp inducers while on study; use within 2 weeks of first dose of study treatment should be avoided.
- 15) Requirement for PPI therapy
- 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, entospletinib, 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 entospletinib 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, Entospletinib, 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). The 10% drug load formulation tablet is a blue, plain-faced, round, film-coated tablet. The tirabrutinib film-coated tablets, 20 mg, contain 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, 40 mg, 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). The 33% drug load formulation tablet is a yellow, plain-faced, modified capsule-shaped, film-coated tablet. The tirabrutinib film-coated tablets, 80 mg, contain 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, 20 mg, 40 mg, and 80 mg, are packaged in white, high density polyethylene (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. Tirabrutinib 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

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. Keep the bottle tightly closed to protect from moisture.

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. Entospletinib

#### 5.2.2.1. Formulation

Entospletinib tablets, 200 mg strength, are available as blue, capsule-shaped film-coated tablets that are plain-faced. In addition to the active ingredient, entospletinib tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

Entospletinib tablets, 200 mg strength, are also available as beige, capsule-shaped film-coated tablets debossed with “GSI” on one side and “9973” on the other side. In addition to the active ingredient, entospletinib tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, ferrosferric oxide/black iron oxide, iron oxide red, and iron oxide yellow.

#### 5.2.2.2. Packaging and Labeling

Entospletinib tablets are packaged in white, high-density polyethylene bottles with silica gel desiccant, and polyester packing material in each bottle. Each bottle contains 60 tablets and is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Entospletinib 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

Entospletinib tablets should be stored at a 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. Keep the bottle tightly closed to protect from moisture.

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.

### 5.2.3. 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, Entospletinib, and Obinutuzumab**

#### **5.3.1. Tirabrutinib and Entospletinib**

Tirabrutinib and entospletinib will be provided by Gilead Sciences, Inc. Tirabrutinib tablets (4 x 20 mg, 2 x 40 mg, or 1 x 80 mg) and entospletinib tablets (2 x 200 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 may be administered without regard to food. Subjects will be instructed to take entospletinib at least 1 hour before and at least 2 hours after a meal.

For patients assigned to the 20 mg tirabrutinib dose, 40 mg tirabrutinib tablets may be exchanged for 20 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. 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  $\geq$  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.  $\geq$  30 min before starting the obinutuzumab infusion
- Antihistamines including a H1-antagonist (eg, dimetindene 4 mg IV) and a H2-antagonist (eg, ranitidine 50 mg IV)  $\geq$  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.  $\geq$  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/ $\mu$ l 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  $\geq$  25 x 10<sup>9</sup>/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*<sup>®</sup>).

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 this infusion should be started 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  $\geq 100$  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.

	<b>Dose of Obinutuzumab</b>	<b>Rate of Infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)</b>
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
<b>Grade 1-2</b>	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
<b>Grade 3</b>	Discontinue infusion immediately Administer supportive treatment (as described in Section 8.5.1) 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.
<b>Grade 4</b>	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.

*Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is mandated unless medically contraindicated throughout the course of active treatment.

Strong CYP3A4/CYP2C9/P-gp inducers or moderate CYP2C9 inducers should be avoided within 2 weeks of study treatment initiation; if administration of such an agent is medically needed after study initiation, this situation should be immediately discussed with the study medical monitor.

Subjects should not receive PPI therapy within 2 weeks of study treatment initiation; if administration of such an agent is required after study initiation, this situation should be immediately discussed with the study medical monitor.

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

#### **5.4.1. IVIg and G-CSF**

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

#### **5.4.2. 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. Preliminary PK data from study GS-US-401-1757 indicates 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/P-gp inducer, rifampin, resulted in a significant decrease in tirabrutinib exposure (~70%). As such, potent CYP3A4/P-gp inducers are prohibited while subjects are on study drug and should be avoided within 2 weeks prior to study drug administration. Examples of strong CYP3A4/P-gp inducers are provided in [Table 5-1](#).

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.

#### **5.4.3. Prior and Concomitant Medications with Entospletinib**

In vitro and in vivo data indicates that entospletinib is a substrate of CYP2C9 and CYP3A. In a study in healthy subjects, co-administration of the strong CYP3A4 / CYP2C9 inducer rifampin resulted in a significant decrease in entospletinib exposure (~70%). As such, co-administration of strong CYP3A and CYP2C9 inducers, and moderate CYP2C9 inducers are prohibited in this study. In addition, administration of strong CYP3A and CYP2C9 inducers and moderate CYP2C9 inducers should be avoided for 2 weeks prior to study drug administration. Caution should be exercised when co-administering drugs that are moderate/strong inhibitors of CYP2C9 (eg. fluconazole, voriconazole or amiodarone) as they may increase entospletinib exposure.

Studies in healthy volunteers have demonstrated a significant reduction in entospletinib exposure when proton pump inhibitors are co-administered. Therefore, proton pump inhibitors are prohibited in combination with entospletinib. Use of a proton pump inhibitor should be avoided for 1 week prior to study drug administration. H2 blockers and antacids will be allowed for use during the protocol.

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

	<b>Strong</b>	<b>Moderate</b>
<b>CYP3A/P-gp Inducer</b>	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide, rifabutin, phenobarbital, mitotane, avasimibe	Not prohibited
<b>CYP2C9 Inducer</b>		carbamazepine, rifampin, ritonavir, enzalutamide
<b>Proton Pump Inhibitors</b>	omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole	

In vitro data indicates that entospletinib has the potential to inhibit several drug transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, MATE1, P-gp and BCRP or metabolized by UGT1A1; dose adjustment or switching to an alternative medication may be necessary if clinically indicated.

In a study in healthy subjects, entospletinib 400 mg twice daily increased rosuvastatin exposure by approximately 3.8-fold. In reviewing the safety of subjects whom have received a statin with entospletinib there have been no reports of rhabdomyolysis or a different adverse event profile, but in the interest of caution, restrictions apply to the use of HMG-CoA reductase inhibitors with entospletinib in this study ([Table 5-2](#)).

**Table 5-2. Recommended dose limits for HMG-CoA reductase inhibitors**

<b>Concomitant Medication</b>	<b>Restriction</b>
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 40 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg BID or 40 mg QD
Pitavastatin	Maximum dose 1 mg QD

#### **5.4.4. 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.

##### **5.4.4.1. 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 ( $CrCl < 70\text{mL}/\text{min}$ ) 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 ( $\geq 300$  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.

##### **5.4.4.2. 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, Entospletinib, and Obinutuzumab**

The investigator is responsible for ensuring adequate accountability of all used and unused study drug bottles and vials. 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, entospletinib, 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 randomization or enrollment. 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. Optional procedures may require separate subject consent, either within the main informed consent form or on a separate informed consent form, per IEC requirements.

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. History of smoking in the past 30 days and 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 other 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 geriatric screening tool ([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 National Cancer Institute (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.

### **6.2.11. 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 as 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 date and time of blood and urine collection will be recorded in the subject's source documentation. The volume of blood phlebotomized will be roughly 100 mL at Screening and subsequently is not to exceed 200 mL every 3 months. The date and time of previous tirabrutinib and entospletinib administration, and whether the dose was taken with or

without food, will be recorded in the subject's source documentation on days when blood for PK analysis is collected. 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.

### **6.2.14. Laboratory Samples to Address the Study Objectives**

The biological specimens described herein will be collected in this study and will be used to evaluate the association of systemic and/or tissue specific biomarkers with study drug response including efficacy and/or AEs, as well as to increase knowledge and understanding of the biology of these and related diseases and possible companion diagnostics development. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of the art knowledge. Biomarker samples may also be used for potential assay development of companion diagnostics.

Specimens will be collected from all subjects. These samples will be destroyed and tested no later than the end of study, unless a subject consents to the optional future storage samples.

Biomarker testing will include but not limited to the following:

#### **6.2.14.1. Laboratory Samples**

- Assessment by fluorescence in situ hybridization (FISH) and mutation analysis of TP53 and IGHV will be performed from peripheral blood at Screening at the GCLLSG molecular cytogenetics reference laboratory in Ulm.

- Immunophenotyping for confirmation of diagnosis as well as assessment of CD38 and ZAP70 and karyotyping will be performed from peripheral blood at Screening at the GCLLSG reference laboratory in Cologne.
- MRD assessments of peripheral blood and bone marrow are to be performed at Week 1 Day 1 and at intervals specified in Study Procedures Table ([Appendix 2](#)) on samples sent to the Durchflußzytometrisches Labor at the Hämatologielabor Kiel.
- Pharmacodynamic activity of tirabrutinib and entospletinib may be assessed through proteomic analysis and rare cell analysis may be performed to detect resistant CLL clones.

[REDACTED]

- Immune cell phenotyping may be performed to monitor changes in immune cell subsets over time.

#### **6.2.15. Samples for Optional Future Research**

CCI [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.

#### **6.2.17. Pharmacokinetic Samples**

A PK sample will be collected on Week 1 Day 1 at 2 ( $\pm$ 1) hours (inclusive) post-dose of tirabrutinib and entospletinib. At the visits on Week 5, 13, and 21, a PK sample will be collected at pre-dose (within 2 hours prior to dosing) and 1 sample will be collected at 2 ( $\pm$ 1) hours (inclusive) post-dose of tirabrutinib and entospletinib. Subjects should be instructed to hold their dose of tirabrutinib and entospletinib on the morning of the visit at Weeks 5, 13, and 21 until after collection of the pre-dose PK sample.

Plasma concentrations of tirabrutinib and entospletinib will be determined. Plasma concentrations of metabolites may be determined. Plasma protein binding of each analyte may be evaluated.

**Table 6-1. Blood and Urine Samples Collected During the Course of the Study**

Serum Chemistry	Hematology	Other
Sodium	WBC	Tirabrutinib, entospletinib, plasma concentrations Other metabolites of tirabrutinib and entospletinib may be measured FISH/Karyotyping TP53 Status IGHV status MRD Immunophenotyping Serum Beta2- Microglobulin Serum Thymidine kinase Blood Pharmacodynamic Biomarkers CLL mutational and phenotypic analysis HBsAG Hepatitis B core antibody HBV DNA if HBVcAb+ Hepatitis C antibody HCV PCR if HCVAbs+ CMV IgG, IgM HIV serology Serum quantitative immunoglobulins
Potassium	RBC	
Chloride	Hemoglobin	
Glucose	Hematocrit	
Blood urea nitrogen or urea	Platelet Count	
Creatinine <sup>a</sup>	Neutrophils (ANC)	
ALT	Lymphocytes	
AST	Monocytes	
GGT	Basophils	
Cholesterol	Eosinophils	
Triglycerides	Reticulocytes	
Uric Acid	<b>Coagulation</b>	
Alkaline phosphatase	PT/INR	
Total and direct bilirubin	aPTT	
Total protein		
Albumin		
Calcium		
Magnesium		
Phosphate		
LDH		
Amylase		
Lipase		
<b>Pregnancy Testing</b>	<b>Urinalysis<sup>b</sup></b>	
Serum Qualitative β-HCG (females)	pH	
Urine Pregnancy (females)	Occult blood	
	Protein	
	Glucose	
	Ketones	
	Bilirubin	
	Urobilinogen	
	Nitrite	
	Leukocyte esterase	
	<b>Microscopic<sup>b</sup></b>	
	WBC/High Power Field	
	RBC/High Power Field	

a Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula (see [Appendix 8](#) for formula)

b Dipstick will be used for Screening urinalysis: Microscopic evaluation to be performed only if the dipstick results are abnormal Note: Additional components, abnormal, and/or atypical cells should also be reported if present  
 ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

### **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 3.6 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.

An interruption of tirabrutinib and/or entospletinib administration will be acceptable to allow for any reversal of toxicity of tirabrutinib and/or entospletinib. Unless the toxicity is deemed related to the subject's underlying disease in the opinion of the investigator, subsequent treatment with the suspected offending agent should only be undertaken after reevaluation of the potential risk. If the toxicity is deemed to be related to one agent, resuming single-agent therapy with the other drug should be considered.

A subject who discontinues obinutuzumab for any reason other than progression should remain on study and may continue receiving the combination of tirabrutinib and entospletinib in accordance with the guidelines in Table 6-2 and Table 6-3.

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 entospletinib, a subject may continue to receive tirabrutinib and/or entospletinib at their assigned dose or at a lower dose (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.

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

	Entospletinib	Tirabrutinib
Starting dose	400 mg	80 mg
Dose level -1	200 mg	40 mg

NCI CTCAE Grade	Recommendation	
	Entospletinib	Tirabrutinib
<b>HEMATOLOGICAL ADVERSE EVENTS</b>		
<b>Neutropenia</b>		
Grade $\leq$ 3 Neutropenia	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Withhold tirabrutinib and entospletinib until resolved to Grade $\leq$ 3 or baseline; consider G-CSF. Tirabrutinib and entospletinib may be reinitiated at the previous dose. If the toxicity recurs, decrease tirabrutinib or entospletinib by one dose level. If toxicity recurs and persists following a dose reduction in both tirabrutinib and entospletinib, discontinue tirabrutinib and/or entospletinib.	
<b>Thrombocytopenia</b>		
Grade 3 Thrombocytopenia	In the absence of symptomatic bleeding, maintain current dose level and schedule. With bleeding, withhold entospletinib until Grade $\leq$ 2.	In the absence of symptomatic bleeding, maintain current dose level and schedule. With bleeding, withhold tirabrutinib until Grade $\leq$ 2.
Grade 4 Thrombocytopenia	Withhold tirabrutinib and entospletinib until resolved to Grade $\leq$ 2 or baseline. Tirabrutinib and entospletinib may be reinitiated at the previous dose. If the toxicity recurs, decrease tirabrutinib or entospletinib by one dose level. If toxicity persists or recurs following a dose reduction in both tirabrutinib and entospletinib, discontinue tirabrutinib and/or entospletinib.	
<b>NON-HEMATOLOGICAL ADVERSE EVENTS</b>		
<b>Dermatological</b>		
Grade $\leq$ 2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 3 or 4	Withhold study treatment until resolved to Grade 1 or baseline. Tirabrutinib and entospletinib may be reinitiated at the previous dose. If the toxicity recurs, decrease tirabrutinib or entospletinib by one dose level. If toxicity persists or recurs following a dose reduction in both tirabrutinib and entospletinib, discontinue tirabrutinib and/or entospletinib.	
<b>Diarrhea</b>		
Grade $\leq$ 1	Provide anti-diarrheal (eg, loperamide) and maintain current tirabrutinib and entospletinib dose level and schedule	
Grade 2	Withhold tirabrutinib and entospletinib until resolved to Grade 1 or baseline. Tirabrutinib and entospletinib may be reinitiated at the previous dose. If the toxicity recurs, decrease tirabrutinib or entospletinib by one dose level. If toxicity persists or recurs following a dose reduction in both tirabrutinib and entospletinib, discontinue tirabrutinib and/or entospletinib.	

NCI CTCAE Grade	Recommendation	
	Entospletinib	Tirabrutinib
Grade 3 or 4	Withhold all study treatment until Grade $\leq 1$ . Consider anti-diarrheal (eg, loperamide) and/or anti-inflammatory (eg budesonide). Consider resuming with lower dose level of both tirabrutinib and/or entospletinib. If toxicity persists or recurs following dose reduction of both tirabrutinib and entospletinib, discontinue tirabrutinib and/or entospletinib.	
<b>Hepatic Adverse Events (elevations in ALT, AST or bilirubin)</b>		
Grade 1 (ALT/AST $\leq 3$ xULN) (Bilirubin $\leq 1.5$ xULN)	Maintain current dose level and schedule.	
Grade 2 (ALT/AST $> 3$ - $5$ xULN) (Bilirubin $> 1.5$ - $\leq 3$ xULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	
Grade 3 (ALT/AST $> 5$ - $20$ xULN) (Bilirubin $> 3$ - $10$ xULN)	Withhold all study treatment. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade $\leq 1$ or baseline. If bilirubin abnormality was Grade $< 3$ , resume tirabrutinib and entospletinib at previous dose level or at lower dose level per investigator discretion. If bilirubin abnormality was Grade $\geq 3$ , discuss with medical monitor prior to resuming tirabrutinib or entospletinib.	
Grade 4 (ALT/AST $> 20$ xULN) (Bilirubin $> 10$ xULN)	Withhold all study treatment. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade $\leq 1$ or baseline. If bilirubin abnormality was Grade $\leq 3$ , resume tirabrutinib at previous or lower dose level and entospletinib at lower dose level. If bilirubin was Grade 4, discontinue tirabrutinib and entospletinib.	
<b>Pneumonitis</b>		
Grade 1	Maintain current dose level and schedule. Consider Pneumocystis treatment.	
Grade 2	Withhold all study treatment until Grade $\leq 1$ , consider systemic corticosteroids and Pneumocystis treatment. Upon resolution discuss with medical monitor prior to study drug reinitiation.	
Grade 3 or 4	Discontinue all study treatment, consider systemic corticosteroids.	
<b>Progressive Multifocal Leukoencephalopathy (PML)</b>		
Any Grade	Discontinue all study treatment; refer subject to a neurologist for further evaluation (see Section 6.6.6).	
<b>Hypersensitivity</b>		
Any Grade	Consider interrupting or discontinuing tirabrutinib treatment (see Section 6.6.3).	
<b>OTHER NON-HEMATOLOGICAL ADVERSE EVENTS</b>		
Grade 1	Maintain current dose level and schedule	
Grade 2	Withhold tirabrutinib and entospletinib until Grade $\leq 1$ or baseline. May resume tirabrutinib and/or entospletinib at initial or lower dose level or discontinue tirabrutinib and/or entospletinib at investigator discretion.	
Grade 3	Withhold tirabrutinib and entospletinib until Grade $\leq 1$ or baseline. May resume tirabrutinib and/or entospletinib at lower dose level or discontinue tirabrutinib and/or entospletinib at investigator discretion.	
Grade 4	Discontinue all study treatment. Discuss with medical monitor prior to reinitiation of any treatment.	

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

NCI CTCAE Grade	Recommendation
	Toxicity attributable to obinutuzumab
<b>HEMATOLOGICAL ADVERSE EVENTS*</b>	
<b>Neutropenia<sup>a</sup></b>	
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 all study treatment until Grade ≤ 2 (ANC ≥ 1 × 10 <sup>9</sup> /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.
<b>Thrombocytopenia</b>	
Grade ≤3	Maintain current dose level and schedule.
Grade 4	Delay all study treatment until Grade ≤ 2 or baseline; thereafter, resume at full dose. If delay is > 4 weeks, discontinue obinutuzumab, unless the Grade 4 thrombocytopenia occurred after the first 3 weekly doses.
<b>Hemorrhage</b>	
N/A	<p>Hold obinutuzumab in case of platelets &lt; 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.</p> <p>At the discretion of the study investigator, for subjects who are on low molecular weight heparin (LMWH), when thrombocytopenia with platelets &lt;20,000/μL develops, reduce the dose of LMWH or new oral anticoagulants (NOAC) used.</p> <p>Hold all study medication for clinically significant bleeding (irrespective of platelet count) until it resolves.</p>
<b>NON-HEMATOLOGICAL ADVERSE EVENTS</b>	
<b>Cutaneous</b>	
Grade ≤2	Maintain current dose level and schedule.
Grade 3 or 4	Delay all study treatment until Grade ≤ 1; thereafter, may resume at full dose or discontinue obinutuzumab at investigator discretion.
<b>Gastrointestinal Inflammation/Diarrhea</b>	
Grade ≤1	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.
Grade 3	Delay all study treatment until subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade 4	Delay all study treatment until subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue at investigator discretion.
<b>Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)</b>	
Grade ≤1 (ALT/AST≤3×ULN) (Bilirubin≤1.5×ULN)	Maintain current dose level and schedule.

NCI CTCAE Grade	Recommendation
	Toxicity attributable to obinutuzumab
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)	Delay all study treatment until subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade 4 (ALT/AST>20×ULN) (Bilirubin>10×ULN)	Delay all study treatment until subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue at investigator discretion.
<b>Pneumonitis</b>	
Grade ≤1	Maintain current dose level and schedule.
Grade 2	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade ≥3	Discontinue all study treatment, consider systemic corticosteroids.
<b>Progressive Multifocal Leukoencephalopathy (PML)</b>	
Any Grade	Discontinue all study treatment; refer subject to a neurologist for further evaluation (see Section 6.6.6).
<b>Hypersensitivity</b>	
Any Grade	Stop the infusion and discontinue obinutuzumab treatment (see section 6.6.3)
<b>Other Non-hematological Adverse Events</b>	
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.
Grade 4	Delay all study treatment until subject is sufficiently stable to receive further treatment. Discuss with medical monitor prior to reinitiation of treatment or discontinue treatment 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 study treatment if it is believed that the cytopenia is due to CLL, and not to the treatment(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. Infectious Events**

Subjects with lymphoid cancers receiving tirabrutinib or obinutuzumab have developed serious and fatal infections during therapy. Monitor subjects for fever and infections and treat appropriately. Therapy should not be initiated in the context of an active infection.

### **6.6.3. Dermatological and Hypersensitivity Events**

Subjects receiving entospletinib or tirabrutinib with  $\geq$  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 treatment should be interrupted. Resumption of study treatment should be considered once rash resolves.

Hypersensitivity symptoms can occur after previous exposure and very rarely with the first infusion of obinutuzumab. 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.

#### **6.6.4. Hepatic Events**

Transaminase Elevations: Reversible asymptomatic ALT/AST increases have been observed with entospletinib in subjects with hematologic malignancies. Successful rechallenge after resolution at either the same or lower dose level of entospletinib has been achieved in the majority of subjects. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate treatment interruption and reinstatement.

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**

Treatment-emergent Grade 3 or 4 neutropenia events including those accompanied by fever or infection have occurred in subjects treated with entospletinib. 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. Progressive Multifocal Leukoencephalopathy (PML)**

PML has been reported in patients treated with obinutuzumab and should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. Therapy with all medications should be withheld during investigation of potential PML and permanently discontinued in case of confirmed PML. The subject should be referred to a neurologist for the evaluation and treatment of PML with evaluation including, but not limited to, brain MRI and lumbar puncture with cerebrospinal fluid testing (include testing for John Cunningham viral DNA).

#### **6.6.7. Further Safety Information**

Further safety information regarding the study drug may be found in the Investigator's Brochures for entospletinib 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 treatments 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 (i.e., 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 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: PPD

Email: 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 entospletinib IB and local obinutuzumab prescribing information for information related to toxicity management. See Section 6.6 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, including the post study drug follow-up period, 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: PPD

Email: 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 entospletinib 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 entospletinib with and without obinutuzumab

The exploratory objectives of this study are:

[REDACTED]

[REDACTED]

#### 8.1.2. Primary Endpoint

The primary endpoint is the rate of CR per modified IWCLL 2008 {[Hallek 2008](#)} criteria 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

#### 8.1.4. Exploratory Endpoints

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 into each study arm who received at least 1 dose of any study treatment. Following the ITT principle, 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. 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.

#### 8.2.1.3. Pharmacokinetics

The pharmacokinetic (PK) analysis set includes all subjects who received at least 1 dose of study treatment and had at least 1 non-missing post-dose concentration value for the corresponding analyte in plasma.

#### 8.2.1.4. Biomarkers

The biomarker analysis set consists of randomized or enrolled subjects who have at least 1 evaluable biomarker sample in this study.

### 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. For duration of response, PFS, OS and TTNT, if the outcome event is not observed, the data will be right-censored at the date of last adequate assessment. 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.

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For subjects who have not experienced disease progression or death, their data for DOR and PFS will be censored on the date of the last available valid disease assessment. Detailed censoring rules will be described in the SAP.

## **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.

### 8.7. Pharmacokinetic Analysis

Plasma concentrations will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

### 8.8. Biomarker Analysis

Changes from baseline in biomarkers will be summarized descriptively. Data explorations may be performed to evaluate potential associations between biomarkers and subject characteristics or outcome measures.

### 8.9. Sample Size

The primary goal of this study is to evaluate the efficacy of the combination of tirabrutinib and entospletinib with obinutuzumab in relapsed and refractory CLL. The primary endpoint for this study is the rate of CR at Week 25. The corresponding single-agent CR rate with BTK and SYK inhibitors in subjects with relapsed or refractory CLL is  $\leq 5\%$ . The 90% CI corresponding to different CR rates ranging from 20% to 60% for a sample size of 30 is provided in the table below. With a sample size of 30, the lower bound of the 90% CI of an observed CR rate of 20% or above will exclude 5%.

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

Sample Size	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.

### 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.
- 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.
- 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.
- Efremov DG, Laurenti L. The Syk kinase as a therapeutic target in leukemia and lymphoma. *Expert opinion on investigational drugs* 2011;20 (5):623-36.
- 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.
- 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.
- 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, Lounsbury 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:
- 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.
- 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.

## 11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. Study Procedures Table
- Appendix 3. Common Terminology Criteria for Adverse Events (CTCAE) v4.03
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**Appendix 1.**

**Investigator Signature Page**

**GILEAD SCIENCES, INC.  
333 LAKESIDE DRIVE  
FOSTER CITY, CA 94404**

**STUDY ACKNOWLEDGEMENT**

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

**GS-US-401-2076, Amendment 4, 15 January 2019**

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

PPD

\_\_\_\_\_  
Name  
Author

PPD

01/17/19

\_\_\_\_\_  
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**

	Screening	24 Weeks										Week 25 Day 1 <sup>19</sup>	Week 29 Day 1	Every 12 weeks starting Week 33 until Week 105	EOT <sup>17</sup>
	Day -28	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1 <sup>16</sup>	Week 5 Day 1	Week 9 Day 1	Week 13 Day 1	Week 17 Day 1	Week 21 Day 1					
<b>Visit Window (days)</b>		0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7	±7	±7	±7
Informed Consent	X														
Medical and Medication History <sup>1</sup>	X														
Physical Examination <sup>2</sup>	X	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	X
ECOG Performance Status / B-symptoms	X	X				X	X	X	X	X	X	X	X	X	X
Binet/Rai Staging	X														
G8 Geriatric Screening Tool <sup>3</sup>		X										X		X	X
12-lead ECG <sup>4</sup>	X	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
Tirabrutinib + entospletinib Dispensing <sup>5</sup>		X				X	X	X	X	X	X	X	X	X	
Tirabrutinib + entospletinib Accountability						X	X	X	X	X	X	X	X	X	X
Obinutuzumab Administration <sup>6</sup>		X	X	X		X	X	X	X	X					
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	24 Weeks										Week 25 Day 1 <sup>19</sup>	Week 29 Day 1	Every 12 weeks starting Week 33 until Week 105	EOT <sup>17</sup>
	Day -28	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1 <sup>16</sup>	Week 5 Day 1	Week 9 Day 1	Week 13 Day 1	Week 17 Day 1	Week 21 Day 1					
Chemistry <sup>18</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (PT/INR, aPTT)	X														X
Peripheral Blood MRD <sup>7</sup>		X						X				X		X	X
Urinalysis and Urine Chemistry	X														
Pregnancy Testing <sup>8</sup>	X	X				X	X	X	X	X	X	X	X	X	X
Viral Serologies <sup>9</sup>	X														
PK sampling <sup>10</sup>		X				X		X		X					
CCI															
CLL phenotyping <sup>12</sup>	X														X
Radiographic Tumor evaluation <sup>13</sup>	X											X			
Bone marrow evaluation <sup>14</sup>	X											X			
Response Assessment <sup>15</sup>						X	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. History of smoking in the past 30 days and 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 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 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.
- 8 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.
- 9 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 for at least 1 year following the EOT visit. HIV testing and CMV IgG and IgM testing should be performed at screening.
- 10 A PK sample will be collected approximately 2 hours ( $\pm$  1 hour) post-dose on Week 1, Day 1. On Day 1 of Weeks 5, 13, and 21 a PK sample will be drawn at pre-dose (within 2 hours prior to AM dosing) and at 2 hours ( $\pm$  1 hour) post-dose.

CCI

- 12 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.
- 13 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.
- 14 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 complete remission (CR) or complete remission with incomplete bone marrow recovery (CRi) per the modified IWCLL 2008 criteria. MRD should be assessed from bone marrow aspirate at the reference laboratory in Kiel. CCI  
The analysis of the biopsy should be performed at the site's local laboratory. An additional bone marrow biopsy 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.
- 15 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.
- 16 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.
- 17 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  $\pm$  7 day window from all study drug discontinuation.
- 18 Screening results should include creatinine clearance, and serum thymidine kinase, serum beta2-microglobulin and serum quantitative immunoglobulins.
- 19 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  $\geq 54$  years of age with cessation of previously occurring menses for  $\geq 12$  months without an alternative cause. In addition, women of any age with amenorrhea of  $\geq 12$  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**

#### **a) Study Drug Effects on Pregnancy and Hormonal Contraception**

Tirabrutinib is contraindicated in pregnancy as the risks of treatment during pregnancy have not been evaluated. Entospletinib 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.

## **b) 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 entospletinib 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 entospletinib 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 entospletinib 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 entospletinib 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 entospletinib 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**

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

- 1 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.
- 2 Patients with treatment-related lymphocytosis should not be rated PD and remain on study treatment if other criteria for progressive disease are absent.
- 3 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/ $\mu$ L.

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

**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 x 10 <sup>9</sup> /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 x 10 <sup>9</sup> /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)
<b>A</b>	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>B</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
<b>C</b>	Mobility	0: bed or chair bound
		1: able to get out of bed/chair but does not go out
		2: goes out
<b>E</b>	Neuropsychological problems	0: severe dementia or depression
		1: mild dementia or depression
		2: no psychological problems
<b>F</b>	Body mass index (BMI weight in kg) / (height in m) <sup>2</sup>	0: BMI < 18.5
		1: BMI = 18.5 to BMI < 21
		2: BMI = 21 to BMI < 23
		3: BMI = 23 and > 23
<b>H</b>	Takes more than 3 prescription drugs per day	0: yes
		1: no
<b>P</b>	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
	<b>Total Score</b>	<b>0-17</b>