GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	An Open-label Study to Assess the Long-term Safety and Efficacy of Tirabrutinib (ONO/GS-4059) in Subjects with Relapsed/Refractory B-cell malignancies	
Sponsor:	Gilead Sciences, Inc.	
IND Number:	This is a non-IND study	
EudraCT Number:	2015-001404-58	
Indication:	Relapsed/Refractory B-cell malignancies	
Protocol ID:	GS-US-401-1787	
Clinical Program Manager:	Name: Telephone:	PPD PPD
Gilead Medical Monitor:	Name: Telephone:	PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5:	19 May 2015 24 January 2017 12 May 2017 30 November 2017 23 January 2019 29 October 2019

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PROTOCOL SYNOPSIS

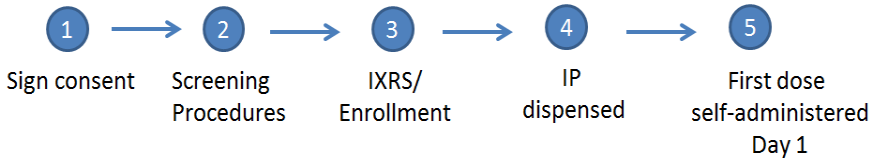
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	An Open-label Study to Assess the Long-term Safety and Efficacy of Tirabrutinib in Subjects with Relapsed/Refractory B-cell malignancies
IND Number: **EudraCT Number:**	This is a non-IND study 2015-001404-58
Study Centers Planned:	Initially, 6 sites in the EU will participate in this study; the number of sites and countries will be expanded as additional tirabrutinib studies are initiated
Objectives:	The primary objective of this study is: • To determine the long-term safety and tolerability of tirabrutinib in subjects in a prior tirabrutinib study and whose disease had not progressed on the parent study The secondary objective of this study is: • To determine the long term efficacy of tirabrutinib
Study Design:	An open-label study for subjects who have tolerated and achieved stable disease or have improved with tirabrutinib treatment while enrolled in a prior tirabrutinib study
Number of Subjects Planned:	The number of subjects enrolled will be determined by the number of subjects who complete a prior tirabrutinib study without disease progression, wish to continue therapy with tirabrutinib and meet the study entry criteria
Target Population:	Subjects who complete a prior tirabrutinib study without disease progression
Duration of Treatment:	Subjects will continue on tirabrutinib for a maximum duration of 5 years from the start of this study.

Diagnosis and Eligibility Criteria:	**Inclusion Criteria:** 1) Currently enrolled in a prior tirabrutinib Study 2) Did not discontinue treatment with tirabrutinib for any reason other than to enroll in this study 3) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at enrollment in this study 4) Any Grade 3 or 4 non-hematologic toxicity that the investigator considers related to previous tirabrutinib use must have resolved, reverted to Grade 1, or reverted to the baseline of the prior study prior to Day 1 of this study 5) Negative serum and urine pregnancy test is required for female subjects (unless surgically sterile or greater than 2 years post-menopausal) 6) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 8. 7) Lactating females must agree to discontinue nursing before the study drug is administered 8) Ability and agreement to attend protocol-specified visits at the study site 9) Able to comprehend and willing to sign the informed consent form **Exclusion Criteria:** 1) Known hypersensitivity to tirabrutinib, its metabolites, or formulation excipients
Study Procedures/ Frequency:	Procedures performed at a regular follow-up visit on subject's previous tirabrutinib study may be used to fulfill screening criteria and to establish any new medical history on this study. At Day 1, the starting dose of tirabrutinib capsules/tablets will be identical to the dose administered in the prior tirabrutinib study. All subjects will self-administer tirabrutinib capsules/tablets.

The initial study procedures to be conducted for each subject enrolled in this study are presented in the following figure:

Initial Study Procedures



- Steps 1 through 5 may occur on the same or different days, but must occur sequentially
- The maximum amount of time allowed from Step 1 to Step 5 is 30 days
- Results from laboratory assessments and procedures performed up to 30 days prior to Step 5 (eg, results from procedures performed during the previous study or as part of the subject's routine care [if documentation is available] may be utilized for determining eligibility)

Study visits consisting of clinical, laboratory, and disease assessments will be completed every 28 days up to Cycle 22, then every 12 weeks. All study required laboratory assessments will be performed by a laboratory and ECG assessments will be performed and interpreted by local departments. Following treatment, subjects will be followed for safety and disease status for a period of 30 days.

Test Product, Dose, and Mode of Administration:	Tirabrutinib oral capsules are brown, opaque, hard capsules and contain 10 mg, 25 mg, or 100 mg of tirabrutinib per capsule. Tirabrutinib oral tablets are supplied as either 20 mg blue, plain-faced, round, film-coated tablets, 80-mg yellow, plain-faced, modified capsule-shaped, film-coated tablets or 100 mg white, plain-faced, round, film-coated tablets. The dosing regimen will be once or twice daily based on the prior dosing regimen from the parent study. The capsules/tablets are packaged in blister packs; the capsule blister packs are also within an aluminum foil pouch. The tirabrutinib tablets are also packaged in white, high density polyethylene (HDPE) bottles.
Reference Therapy, Dose, and Mode of Administration:	n/a

Criteria for Evaluation:	**Safety:** The primary endpoint for this study is safety. Safety will be evaluated by the incidence and severity of adverse events (AEs) and clinical laboratory abnormalities. **Efficacy:** Efficacy endpoints are considered secondary and will include: • Overall response rate (ORR): defined as the proportion of subjects who achieve partial response (PR) or complete response (CR) • Duration of response (DOR): defined as the interval from first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause • Progression-free survival (PFS): defined as the interval from date of the first dose of tirabrutinib on the parent study to the earlier of the first documentation of definitive disease progression or death from any cause • Overall survival (OS): defined as the interval from date of the first dose of tirabrutinib on the parent study until death from any cause. **Pharmacokinetics:** The pharmacokinetic (PK) Analysis Set will consist of all enrolled subjects who have at least 1 evaluable PK sample.
Statistical Methods:	**Analysis Methods** The Rollover Study Analysis Set consists of all subjects who are enrolled into this study. This analysis set will be used for the summary of subject characteristics, disposition, and study drug treatment administration. The Full Analysis Set (FAS) consists of all subjects who are enrolled and treated in the parent study. This analysis set will be used for the summary of safety and efficacy endpoints. Subject characteristics and disposition will be summarized using descriptive statistics. In general, continuous variables will be summarized by sample size, mean, standard deviation (StD), median, minimum, and maximum and categorical variables by counts and percentages. Baseline data are defined as the data collected prior to dosing on the parent study.

Tumor response will be based on investigator assessment. ORR will be estimated and its associated 95% confidence interval will be calculated using the exact method. All time-to-event endpoints (DOR, PFS, and OS) will be analyzed using the Kaplan-Meier method. The medians and associated 95% confidence intervals for these endpoints will be provided if the medians can be estimated.

AEs will be summarized by system organ class, high level term, and preferred term and by severity and relationship to study treatment. Clinical laboratory tests, vital signs, and their changes from baseline will be summarized descriptively.

Sample Size

No formal hypothesis testing is planned for this study. The number of subjects enrolled will be determined by the number of subjects who rollover from prior tirabrutinib studies.

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

°C	degrees Celsius
°F	degrees Fahrenheit
ADME	absorption, distribution, metabolism, elimination
AE	adverse event
ALT	alanine transaminase
AM	morning
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin
AST	aspartate transaminase
AUC	area under the plasma/serum/peripheral mononuclear cell concentration versus time curve
$AUC_{0\text{-last}}$	area under the concentration verses time curve from time 0 to the last quantifiable concentrations
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-last}} + (C_{last}/\lambda_z)$
AUC_{τ}	area under the concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
BSC	best supportive care
BSEP	bile salt export pump
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last observed quantifiable plasma concentration of drug
CLL	chronic lymphocytic leukemia
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$ where "dose" is the dose of the drug
C_{max}	maximum observed serum/plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
Conmed	concomitant medication
CR	complete response
CrCL	creatinine clearance
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRP	c-reactive protein

CSR	clinical study report
CT	computed tomography/ computed axial tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
DMC	data monitoring committee
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EOT	end of treatment
eSAE	electronic serious adverse event
ET	essential thrombocythemia
EudraCT	European clinical trials database
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
5-FU	5-fluorouracil
FL	follicular lymphoma
GCP	Good Clinical Practice (Guidelines)
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GSI	Gilead Sciences, Inc.
H	hour
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
IC50	inhibitory concentration 50
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
INR	international normalized ratio
IMP	investigational medicinal product
IRB	Institutional Review Board

ITT	intent-to-treat
IUD	intrauterine device(s)
Kg	kilogram
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
µM	micromole
msec	millisecond
MRD	maximum recommended dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	number enrolled
NOAEL	no observed adverse effect level
NHL	non-Hodgkin's lymphoma
OAT	organic anion transporter
OCT	organic cation transporter
OS	overall survival
ORR	overall response rate
PD	progressive disease
PE	physical exam
PFS	progression-free survival
P-gp	permeability glycoprotein
PK	pharmacokinetic
PP	per-protocol
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
PVE	Pharmacovigilance and Epidemiology
QTc	corrected QT interval
RAF	rapidly accelerated fibrosarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumor
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SADR	serious adverse drug reaction(s)

SAE	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SOP	standard operating procedure
STAT	Signal Transducer and Activator of Transcription
StD	standard deviation
SUSAR	suspected unexpected serious adverse reaction(s)
$T_{1/2}$	an estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
T_{last}	the time (observed time point) of Clast
T_{max}	the time (observed time point) of Cmax
TBK1	TANK-binding kinase 1
TTR	time to response
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WBC	white blood cell
WM	Waldenstrom's macroglobulinemia
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biological features. In 2008, there were an estimated 356,000 new cases of NHL and 192,000 deaths from NHL worldwide {Ferlay 2010}. NHL is the eighth most commonly diagnosed cancer in men and the 11th in women. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30% to 40% of all new patients {Sweetenham 2007}, whereas follicular lymphoma (FL) and mantle cell lymphoma (MCL) account for approximately 20% to25% and 6% to10% of new lymphomas, respectively {Dreyling 2007}. B-cell chronic lymphocytic leukemia (CLL) is the most common of the chronic leukemias in adults with approximately 8500 new cases per year in the European Union and the United States (US) {Kristinsson 2009}. Approximately 90% of lymphomas are NHL and nearly 95% of NHLs are of B-cell origin; > 90% of CLL is of B-cell origin {Morton 2006}.

B-cell NHL and CLL arise from the accumulation of monoclonal B lymphocytes in lymph nodes and often in organs such as blood, bone marrow, spleen, and liver. This group includes histopathologic varieties such as FL, MZL, MCL, CLL, small lymphocytic lymphoma (SLL), Waldenstrom's macroglobulinemia (WM), and DLBCL. These disorders are characterized by lymphadenopathy, cytopenias, and sometimes induce life-threatening organ dysfunction. Patients may also have constitutional symptoms (fevers, night sweats, and/or weight loss) and fatigue {Diehl 2004, Dighiero 2008, Salles 2007, Williams 2010}.

Few patients with B-cell malignancies are cured with available therapies. The 3-year progression-free survival (PFS) is only 40% with activated B-cell (ABC) DLBCL compared to 74% with GCB-DLBLC. For patients who are refractory to primary therapy or progress and are not transplant candidates, few therapeutic options exist {Roschewski 2014}. For patients with the indolent B-cell malignancies, such as iNHL (FL and MZL), MCL, CLL, SLL, and WM, the goal of first and subsequent line therapies is to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents {Eichhorst 2010, Friedberg 2011, Gribben 2011, Hoppe 2008, Jost 2007, Zelenetz 2011}. Although patients with iNHL and CLL can achieve durable remissions with front-line combination therapies, most patients will eventually experience disease relapse {Hallek 2010, Lenz 2005, Recher 2011, Santoro 1987, Schulz 2007}. Despite use of agents with differing mechanisms of action, progressive resistance to treatment develops. {Di Bella 2010, Friedberg 2011, Goy 2009, Hess 2009, Keating 2002, Moskowitz 2009, Wierda 2010}.

1.2. Tirabrutinib

1.2.1. General Information

Tirabrutinib (also known as GS-4059, ONO/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.

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

BTK plays a crucial role in the development and activation of B cells through its activation via the B-cell receptor (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}.

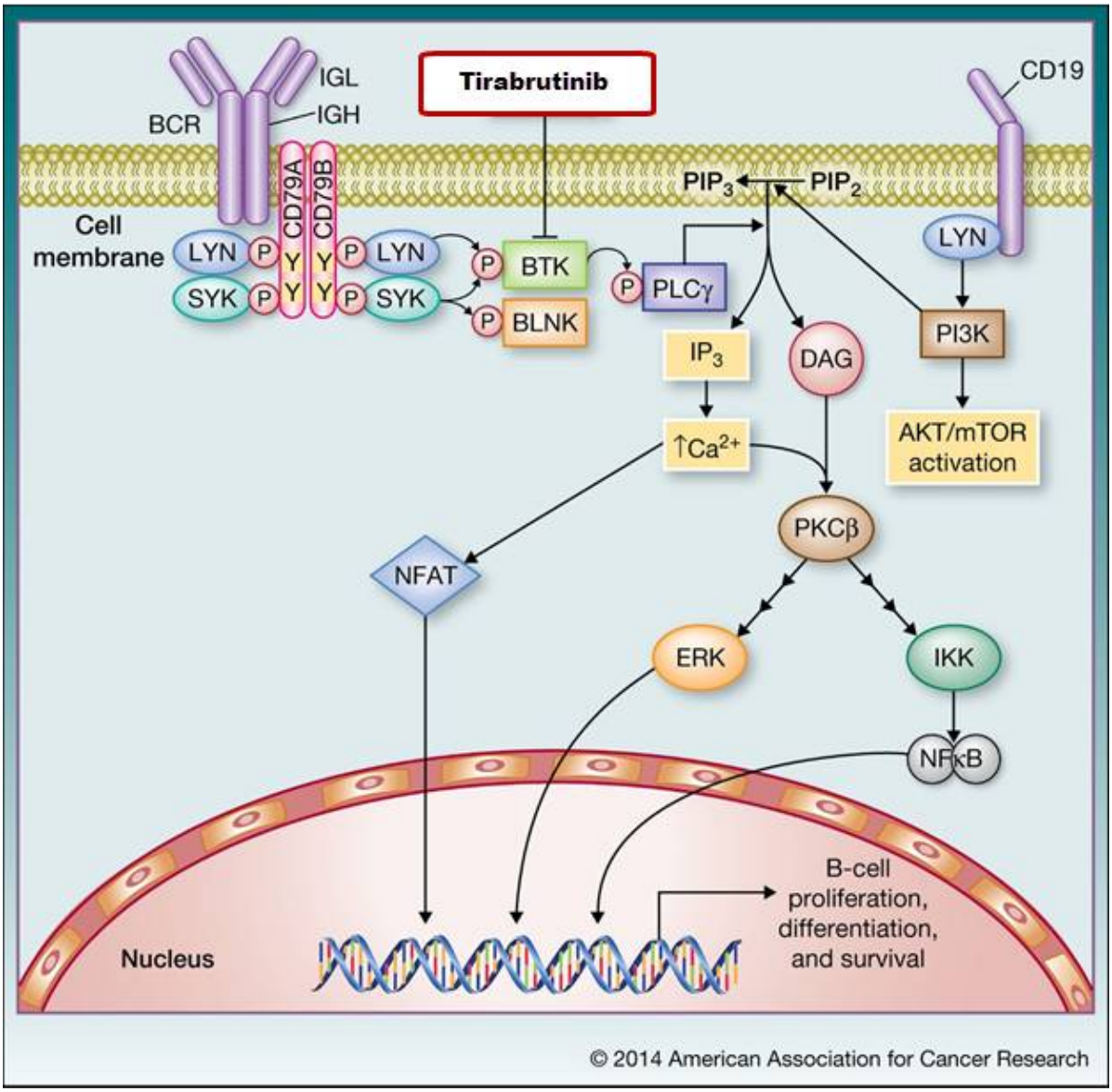
Signaling through the BCR has been established as a key oncogenic driver in many B-cell malignancies, including (CLL, SLL, ABC-DLBCL, MCL, and WM). A first in class BTK inhibitor, ibrutinib (Imbruvica®), has demonstrated clinical benefit to patients with CLL, MCL and WM {Pharmacyclics Inc. 2015}. Additionally, transient clinical responses were observed in a pilot study of relapsed DLBCL, primarily in the non-GCB subtype {Wilson 2012}.

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. This study is completed and has 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.

Additional adverse events (AEs) have been observed during Study ONO-4059POE001, including: hematological disorders such as neutropenia, anemia, and thrombocytopenia; bleeding disorders such as petechiae, purpura, and hemorrhage; pyrexia and concomitant infections; gastrointestinal disturbances such as nausea, diarrhea, and abdominal pain; rash and irritation such as acne, urticarial, petechial or purpuric rash, dry skin, pruritus, and eye pruritus; asthenia; and fatigue. The most commonly reported serious adverse events (SAEs) were infections. Please refer to the current edition of the tirabrutinib Investigator's Brochure (IB) for additional safety information.

Another BTK inhibitor, ibrutinib, which is approved in the US for CLL, MCL, and WM, has identified warnings and precautions for hemorrhagic events, infections, cytopenias, atrial fibrillation, second primary malignancies including skin cancers and other carcinomas, tumor lysis syndrome, and embryo-fetal toxicity. The most common AEs observed with ibrutinib in patients with B-cell malignancies were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. As these reported events may be related to target BTK inhibition, clinical trial subjects will be monitored for these events

Figure 1-1. Inhibition of the BCR Pathway by Tirabrutinib



Adapted from Herrera and Jacobsen (2014) {Herrera 2014}

Chronic Lymphocytic Leukemia

Signaling through BTK plays a key role in the maintenance of CLL as demonstrated by the efficacy achieved in CLL by ibrutinib, a first in class BTK inhibitor {Byrd 2014}. In a Phase 3 trial in relapsed or refractory CLL or SLL, ibrutinib-treated patients experienced a rapid and sustained decrease in lymphadenopathy accompanied by lymphocytosis, suggesting that CLL cells are mobilized from lymphoid tissue to blood. CLL cells from the blood, bone marrow, and lymph nodes of patients treated with ibrutinib show reduced proliferation and expression of NF-κB regulated genes and surface activation markers such as CD69 and CD86 {Herman 2014}. Ibrutinib (Imbruvica®) is approved in the US for the treatment of CLL in patients who have

received at least one prior therapy and for patients with 17p deletion based on an overall response rate (ORR) of 42.6% and improved PFS and overall survival (OS) compared to ofatumumab {Pharmacyclics Inc. 2015}. In Study ONO-4059POE001, with a median follow-up of 26.4 months, tirabrutinib demonstrated an ORR of 85.7% (n 28); 7 subjects (25.0%) had a complete response (CR), and 17 subjects (60.7%) had a partial response (PR). The Kaplan Meier (KM) estimate of median duration of response (DOR), median progression-free survival (PFS) and median overall survival (OS) was not reached.

Diffuse Large B-Cell Lymphoma

At present there are no approved drugs for relapsed refractory DLBCL in patients who are not candidates for high dose combination chemotherapy and stem cell transplant. National Comprehensive Cancer Network (NCCN) Guidelines recommend either a clinical trial, palliative radiation therapy or 1 of the following options with or without rituximab: bendamustine, CEPP (cyclophosphamide, etoposide, procarbazine, prednisone), CEOP (cyclophosphamide, etoposide, vincristine, prednisone), DA-EPOCH (dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), GDP (gemcitabine, dexamethasone, cisplatin), Gem-Ox (gemcitabine, oxaliplatin), or lenalidomide {National Comprehensive Cancer Network (NCCN) 2015}. ORRs with these regimens in this patient population range from 28% to 63%, with median PFS of 3 to 7 months. The activated B-cell (ABC) -DLBCL subtype, identified by gene expression profiling has been identified retrospectively as a poor prognostic indicator for PFS and OS for patients treated with first line rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) chemotherapy, although not at the time of relapse, when all patients have a poor prognosis {Lenz 2008}.

ABC-DLBCL cells are dependent on NF-κB signaling for survival and proliferation {Davis 2010}. The sensitivity of ABC-DLBCL to NF-κB inhibition can be explained by the chronic activation of BCR and/or TLR signaling mediated in 50% of cases by activating mutations in components of the BCR such as CD79B (18% of ABC-DLBCL) or myeloid differentiation primary response 88 (MYD88) (29% of ABC-DLBCL) and caspase recruitment domain family, member 11 (CARD11) (10% of ABC-DLBCL). Inhibition of BTK inhibits proliferation and induces apoptosis in a subset of ABC-DLBCL; tirabrutinib and ibrutinib have demonstrated evidence of short-term efficacy in the relapsed setting in the non-GCB DLBCL subgroup (41% ORR [12/29] with ibrutinib and ORR 41% [7/17] with tirabrutinib). Median PFS was short with both inhibitors, at approximately 4 months.

Mantle Cell Lymphoma

MCL is a rare type of B-cell non-Hodgkin's lymphoma (approximately 6% of NHL) which, at presentation, can be indolent or aggressive. Cure is uncommon and there is no standard front-line regimen, although common therapies are rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone (R-HyperCVAD), variations on R-CHOP, rituximab-bendamustine, and the Nordic regimen {Geisler 2008}. Consolidation with autologous transplant in first remission may prolong PFS. If and when patients relapse, the goal of therapy is similar to the other relapsed B cell malignancies; to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Options at relapse include ibrutinib,

bortezomib, rituximab-bendamustine, and lenalidomide. Similar to CLL, a large proportion of cells from patients with MCL, harbor a stereotypic BCR repertoire, indicating a crucial role for BCR stimulation in this disease {Hadzidimitriou 2011}. In addition, constitutive activation of NF-κB and the PI3K pathways is observed in MCL, reflecting chronic activation of BCR, TLR, and/or tumor necrosis factor receptors (TNFR) in this disease {Colomer 2014, Jares 2012}. Ibrutinib is approved for use in patients with MCL who have received at least 1 prior therapy, based on an ORR of 65.8% (complete responses [CR] 17.1%) and median PFS of 13.9 months {Wang 2013}. In Study ONO-4059POE001, tirabrutinib demonstrated a similar ORR in a small number of subjects; (60% [6/10]).

Waldenstrom's Macroglobulinemia

In WM, activating mutations in MYD88 are prevalent (67% to 100% of cases), leading to constitutive activation of BTK and NF-κB downstream of TLR {Treon 2012, Yang 2013}. In WM cell lines and primary cells, ibrutinib, reduced NF-κB activation and triggered apoptosis. Ibrutinib is approved for use in WM with a reported ORR of 61.9% (39/63) without any CRs, and duration of response (DOR) ranging from 2.8 to 18.8 months {Pharmacyclics Inc. 2015}. In Study ONO-4059POE001, 1 of 2 subjects with WM responded to tirabrutinib.

For further information on tirabrutinib, refer to the current edition of the tirabrutinib IB.

1.2.2. Tirabrutinib Preclinical Pharmacology and Toxicology

1.2.2.1. Nonclinical Pharmacology

Primary pharmacology studies in enzyme-based and cell-based systems indicate that tirabrutinib is a potent inhibitor of BTK. BTK inhibition by tirabrutinib resulted in inhibition of proliferation and survival in ABC-DLBCL and MCL-derived cell lines, and in primary cells from CLL subjects.

Tirabrutinib is a potent and selective inhibitor of BTK relative to 3 other non-receptor tyrosine kinases which function in B-cell and T-cell activation: human FYN, LCK, and LYNa. The IC_{50} values of tirabrutinib against recombinant human BTK, FYN, LCK, and LYNa were 2.10, 2220, 788, and 3490 nM, respectively, demonstrating tirabrutinib to be 1060-, 375-, and 1660-fold more selective for BTK relative to FYN, LCK, and LYNa, respectively. Selectivity was also demonstrated by evaluating the binding affinity (K_d) of tirabrutinib for BTK, BLK, BMX, CSK, ERBB2, HUNK, LCK, MAP2K5, RIPK2, TEC, and TXK. tirabrutinib was demonstrated to be 21- to > 3500-fold more selective for BTK than for other kinases that are structurally or functionally related, with the exception of similar binding affinity to the tyrosine-protein kinase TEC.

Tirabrutinib demonstrated in vitro cellular activity on BTK autophosphorylation in human B lymphocytes from peripheral blood monocyte cells and whole blood in ABC-DLBCL-derived cell lines. The maximum inhibitory activity and potency of tirabrutinib increased with length of exposure and decreased after 24 hours following washout of tirabrutinib from the media. The in vitro inhibitory activity of tirabrutinib on 2 ABC-DLBCL lymphoma cell lines, TMD-8 and U-2932 demonstrated inhibition of P-BTK in a dose dependent manner.

These data collectively demonstrate that tirabrutinib is a potent inhibitor of BTK tyrosine kinase activity in primary human B lymphocytes from peripheral blood mononuclear cells and in ABC-DLBCL-derived cell lines.

For further information on tirabrutinib, refer to the current edition of the IB.

1.2.2.2. Absorption, Distribution, Metabolism and Elimination (ADME)

The bioavailability of tirabrutinib was 15.5% following a single oral administration of tirabrutinib at 5 mg/kg to fasted male rats. Following repeated oral daily administration of tirabrutinib for 28 days to non-fasted male rats, the maximum observed concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 h (AUC_{24h}) increased proportionally with doses ranging from 3 to 100 mg/kg/day. There was no obvious accumulation of tirabrutinib after 28 days repeated dosing.

Following a single oral administration of [^{14}C]-ONO-4059HCL at 5 mg/kg to fasted male rats, the radioactivity concentrations in several tissues were 2.1 to 26 fold that found in plasma at 0.5 h post-dose with radioactivity concentrations decreasing in all tissues to 7.0% of C_{max} or lower by 168 h post-dose. The elimination half-life ($t_{1/2}$) of the radioactivity in the eyeball in pigmented rats (130 h) was longer than that in albino rats (79 h), suggesting that tirabrutinib or its metabolites binds to melanin. The primary binding protein of tirabrutinib in human serum is albumin; protein binding of [^{14}C]-ONO-4059HCL at 0.5µg/mL in rat, monkey, and human serum was 98.2%, 90.7%, and 92.3%, respectively.

Species differences were observed in the main metabolites in *in vitro* metabolism analysis; however, all metabolite peaks detected in cultured human hepatocytes were also detected in cultured hepatocytes of rat or monkey. The primary cytochrome P450 (CYP) iso-form responsible for tirabrutinib metabolism is CYP3A4/5, but CYP2D6 also metabolizes tirabrutinib though to a lesser degree. Tirabrutinib is not a CYP inducer. Tirabrutinib inhibited CYP2C8, 2C9 and 2C19, the respective inhibition constant (Ki) values were 7.02, 8.31, and 14.4µmol/L. Tirabrutinib resulted in mechanism based inhibition of CYP3A4/5 at 10µmol/L. Tirabrutinib is a P-glycoprotein (P-gp) substrate, whereas tirabrutinib inhibited human P-gp with an IC_{50} value of 26.8µmol/L. In addition, tirabrutinib showed inhibitory potential for several other transporters including OAT3, OATP1B1, MATE1, OCT1, and OCT2.

Refer to the tirabrutinib IB for additional information.

1.2.2.3. Nonclinical Toxicology

In the single dose toxicity studies in rats and monkeys, doses of tirabrutinib ranged from 1 to 2000 mg/kg and 1 to 1000 mg/kg, respectively. The lethal dose was 2000 mg/kg in rats and 1000 mg/kg in monkeys. In the 4-week repeated oral dose toxicity studies, 8/44 mortalities at 1000 mg/kg/day were observed in rats. These 8 rats showed spontaneous activity decrease along with bradypnea, stool volume decrease, lacrimation and a severe body weight decrease. At 100 mg/kg/day in monkey, one animal was moribund. This single monkey exhibited somnolence, ataxia and prone position before showing moribund condition. The primary target organs of tirabrutinib were pancreas islets at doses of 10 mg/kg/day or higher in rats and CNS

effects at 100 mg/kg/day in monkeys. In the 4-week repeated oral dose toxicity study in rats, fibrosis of the centre/periphery of the pancreatic islets was observed at doses at 10 mg/kg/day or higher as well as eosinophilic changes and hypertrophy of the hepatocytes, hypertrophy of the zona fasciculate and glomerulosa cells accompanied with an increase in lipid in the adrenal at doses 100 mg/kg/day or higher.

In the 4-week repeated oral dose toxicity study in monkeys, Berlin blue staining positive pigment-laden macrophages in the medullary sinus were observed at 3 mg/kg/day or higher as well as angiectasis and/or haemorrhage in pancreatic islets and lobules at 10 mg/kg/day or higher. Surviving animals at 100 mg/kg/day showed CNS effects which were weaker than that of moribund animal. The no observed-adverse-effect-levels (NOAEL) in rats and monkeys are estimated to be 3 mg/kg/day and less than 3 mg/kg/day, respectively. The severe toxic dose in 10% (STD 10) in rats and the highest non-severe toxic dose (HNSTD) in monkeys were determined to be 600 mg/kg/day and 30 mg/kg/day, respectively.

A more detailed summary of findings from studies in rats and dogs is available in the IB for tirabrutinib.

1.2.3. Clinical Trials of Tirabrutinib

As of 1 October 2017, 6 clinical studies of tirabrutinib are ongoing.

Updated clinical information regarding completed and ongoing clinical studies may be found in the tirabrutinib IB.

1.3. Rationale for This Study

Based on the analysis of Study ONO-4059POE001, subjects obtained a clinical benefit from treatment with tirabrutinib as demonstrated by response rate. As of the completion of the study, 86% of CLL subjects and 39% of NHL subjects demonstrated an objective response.

Tirabrutinib appears to have been well tolerated overall and with prolonged administration in Study ONO-4059POE001.

1.4. 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 long-term safety and tolerability of tirabrutinib in subjects in a prior tirabrutinib study and whose disease had not progressed on the parent study

The secondary objective of this study is:

- To determine the long term efficacy of tirabrutinib

3. STUDY DESIGN

3.1. Endpoints

The endpoints of this study are described in Section 8.

3.2. Study Design

This study is an open-label rollover study for subjects who have tolerated and achieved stable disease or improved with tirabrutinib treatment while enrolled in a prior tirabrutinib study.

3.3. Study Treatments

Subjects who meet eligibility criteria will receive a single dose of tirabrutinib on Study Day 1 (Cycle 1, Day 1). Each cycle will consist of 28 days of therapy. If there is no evidence of disease progression by clinical assessment or by CT (or MRI), a subject may continue receiving tirabrutinib until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

In subjects who have a tumor flare after the discontinuation of therapy or are at a high risk of such an event, treatment may be reinstituted or continued following progression until initiation of subsequent therapy.

3.4. Duration of Treatment

Subjects will continue on tirabrutinib for a maximum duration of 5 years from the start of this study. After discontinuation of treatment, subjects will be followed for safety for 30 days.

3.5. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Pregnancy
- Investigator discretion
- Non-compliance with study drug
- Initiation of other anti-cancer or experimental therapy
- Protocol violation
- Withdrawal of consent

- Lost to follow-up
- 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 7.6), 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

3.6. Source Data

The subject identification numbers assigned by the Sponsor or captured by the interactive voice/web response system (IXRS) will be considered source data.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

All subjects enrolled in a prior tirabrutinib study who are still alive and have not had disease progression may be eligible to participate in this extension study.

4.2. Inclusion Criteria

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

1) Currently enrolled in a prior tirabrutinib study

2) Did not discontinue treatment with tirabrutinib for any reason other than to enroll in this study

3) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at enrollment

4) Any Grade 3 or 4 non-hematologic toxicity that the investigator considers related to previous tirabrutinib use must have resolved, reverted to Grade 1 or reverted to the baseline of the prior study prior to Day 1 of this study

5) Negative serum and urine pregnancy test is required for female subjects (unless surgically sterile or greater than 2 years post-menopausal)

6) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 8.

7) Lactating females must agree to discontinue nursing before the study drug is administered

8) Ability and agreement to attend protocol-specified visits at the study site

9) Able to comprehend and willing to sign the informed consent form

4.3. Exclusion Criteria

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

1) Known hypersensitivity to tirabrutinib, the metabolites, or formulation excipient

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for the study prior to enrollment. Subjects will be assigned a unique screening number at the time of consent.

An interactive web response system (IWRS) will be employed to manage the conduct of the trial. The IWRS will be used to maintain a central log documenting screening and enrollment, to manage dose modifications, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of treatment.

Once eligibility is confirmed subjects will be assigned a unique subject number. This is an open-label study.

All baseline tests and procedures must be completed prior to the administration of the first dose of tirabrutinib on Day 1. Once a subject number is assigned to a subject, it will not be reassigned to another subject.

5.2. Description and Handling of Tirabrutinib

5.2.1. Tirabrutinib

5.2.1.1. Formulation

Tirabrutinib capsules are brown, opaque hard HPMC capsules. Each capsule contains the equivalent of 10 mg, 25 mg, or 100 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The capsules contain the following inactive ingredients: microcrystalline cellulose, and magnesium stearate. Each capsule shell contains carrageenan, potassium chloride, titanium dioxide, red iron oxide, and hypromellose.

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, 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.

Tirabrutinib film-coated tablets, 100 mg, contain the equivalent of 100 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The 33% drug load formulation tablet is a white, plain-faced, round, film-coated tablet. The tirabrutinib film-coated tablets, 100 mg, contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

5.2.1.2. Packaging and Labeling

Tirabrutinib (ONO/GS-4059) capsules, 10 mg, 25 mg, and 100 mg are packaged in polyvinyl chloride (PVC) blisters with aluminum foil lidding and placed within an aluminum foil pouch.

Tirabrutinib (ONO/GS-4059) tablets 20 mg and 100 mg are packaged in blister strips made of polyvinyl chloride/ polychlorotrifluoroethylene (Aclar) film and have aluminum foil lidding materials that are then placed in a blister card.

Tirabrutinib (GS-4059) tablets 80 mg and 100 mg are also 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.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products, Feb. 2010), and/or other local regulations.

5.2.1.3. Storage and Handling

Tirabrutinib packaged drug product should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling tirabrutinib.

5.3. Dosage and Administration of Tirabrutinib

Tirabrutinib capsules/tablets will be provided by Gilead and will be taken orally. Initiation of treatment with the study drug will take place after enrollment and cohort assignment. Subjects will self-administer tirabrutinib capsules 10 mg, 25 mg, or 100 mg capsules or tirabrutinib tablets 20 mg, 80 mg or 100 mg orally once or twice daily from prior dosing regimen on parent study. To reduce variability in drug absorption, subjects will be instructed to take tirabrutinib at least 1 hour before or 2 hours after a meal.

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 8 hours has elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time.

5.4. Prior and Concomitant Medications

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

Examples of strong CYP3A4/P-gp inducers are provided in Table 5-1.

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

	Strong
CYP3A4/P-gp **Inducer**	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide rifabutin, phenobarbital, mitotane, avasimibe

5.5. Accountability for Tirabrutinib

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

Tirabrutinib accountability records will be provided to each study site to:

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

The methods of tirabrutinib return and destruction are described in Section 9.1.7.

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. Additional information is provided in the study procedures manual.

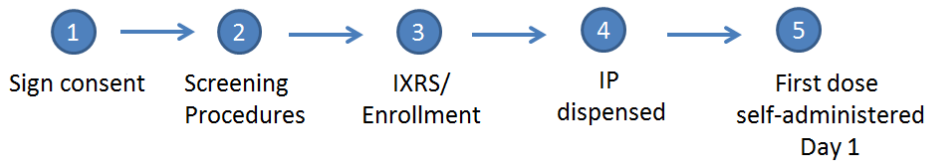
The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

Procedures performed at a regular follow-up visit on subject's previous tirabrutinib study may be used to fulfill screening criteria and to establish any new medical history on this study.

At Day 1, the starting dose of tirabrutinib capsules/tablets will be identical to the dose administered in the prior tirabrutinib study. All subjects will self-administer tirabrutinib capsules/tablets.

The initial study procedures to be conducted for each subject enrolled in the study are presented in Figure 6-1.

Figure 6-1. Initial Study Procedures



- Steps 1 through 5 may occur on the same or different days, but must occur sequentially
- The maximum amount of time allowed from Step 1 to Step 5 is 30 days
- Results from laboratory assessments and procedures performed up to 30 days prior to Step 5 (eg, results from procedures performed during the previous study or as part of the subject's routine care [if documentation is available] may be utilized for determining eligibility)

Study visits consisting of clinical, laboratory, and disease assessments will be completed every 28 days up to Cycle 22, then every 12 weeks. All study required laboratory assessments will be performed by a local laboratory and ECG assessments will be performed and interpreted by local departments. Following treatment, subjects will be followed for safety and disease status for a period of 30 days.

6.1. Subject Enrollment and Treatment Assignment

A subject will be considered enrolled once enrolled in IXRS. It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment. Details regarding treatment assignment and dosing are provided in Section 5.3.

6.2. Description of Study Procedures

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

6.2.1. Written Informed Consent

All subjects must personally sign and date the institutional review board / independent ethics committee (IRB/IEC) approved informed consent form before any study procedures are performed (Section 9.1.3).

6.2.2. Recording Medical History

Medical history from the previous study will not be reported in the electronic case report form (eCRF) for this study. Any ongoing AE from the previous study at the time of enrollment in this study will be considered medical history on this study and should be reported in the eCRFs and followed to resolution.

6.2.3. Medication History

A current list of ongoing medications will be obtained prior to enrollment and recorded on the eCRF.

6.2.4. 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 will be a complete physical examination. Beginning at Cycle 1 Day 1, a modified physical examination will be a performed to monitor for any changes (eg, lymph nodes, lung, cardiac, abdomen, skin, neurologic, and any systems, as clinically indicated). Abnormal findings prior to first dose of study treatment will be reported on the medical history page of the eCRF. Any changes from the prior to first dose of study treatment baseline physical examination which represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Weight (without shoes) should be measured with each physical examination.

Height (without shoes) should be measured at Screening only.

6.2.5. Vital Signs

Vital signs will include pulse, systolic and diastolic blood pressure, and body temperature. They should be collected per institutional guidelines.

6.2.6. Electrocardiogram

Twelve (12) lead ECGs will be obtained at the time points outlined in the Study Procedures Tables (Appendix 2). Subjects should be resting quietly for 5 minutes prior to ECG collection.

The Investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.2.7. Laboratory Assessments

All samples collected in this study for laboratory assessments will be sent to local laboratories with the exception of urine pregnancy test which may be completed at the site. Screening laboratory samples should be obtained within 30 days prior to the first dose of tirabrutinib taken on this study.

The local laboratory will be responsible for chemistry, CBC, coagulation, urinalysis, and serum pregnancy testing per Table 6-1. Any samples collected per the Schedule of Assessments (Appendix 2) may be analyzed for any tests necessary to ensure subject safety. The date and time of sample collection will be reported to the local laboratory.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology and Coagulation	Other Analytes
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate BUN Calcium Chloride Creatinine[a] GGT Glucose LDH Lipase Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Ketones Nitrite Urobilinogen Microscopic[c] Urine beta hCG[b]	Hematology RBC Hemoglobin Hematocrit Platelets WBC Differential Neutrophils Bands Eosinophils Basophils Lymphocytes Monocytes % blasts ANC Coagulation PT (INR) PTT	Serum beta hCG[b] Total IgA, IgG, IgM Immunoglobulin electrophoresis

ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen; GGT gamma glutamyl transpeptidase; LDH lactate dehydrogenase; PT prothrombin time; PTT partial thromboplastin time; RBC red blood cell; WBC white blood cell; hCG human chorionic gonadotropin
Note: Additional components, abnormal, and/or atypical cells will also be reported if present
a Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockroft Gault formula
b If applicable, serum and urine pregnancy test should be obtained
c Reflex testing based on other abnormalities

6.2.8. Pharmacokinetic Samples

Plasma samples for pharmacokinetics (PK) will be collected pre-dose (Cycles 2 and 3 only) and concentrations of tirabrutinib will be determined. Plasma concentrations of tirabrutinib metabolites may be determined.

6.2.9. Bone Marrow Examination

Bone marrow examination (core biopsy and/or aspirate as per local standard of care) will be performed for follow-up only (for both NHL and CLL subjects) if previously positive and/or to confirm CR, if physical examination and CT-scans demonstrate a CR.

6.2.10. Treatment Response Assessment

The determination of disease response and progression will be based on standardized criteria {Cheson 2007, Hallek 2008, Owen 2013}. During the course of the study, investigators will periodically assess the status of each subject's disease. Treatment decisions by the investigator in this study will be based on these assessments. All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification.

6.2.11. ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG will be scored using the scale index in Appendix 6.

6.2.12. Tumor Imaging (CT)

CT with contrast or MRI (for subjects who cannot tolerate CT contrast) will be obtained to document disease, in accordance with the NHL and CLL response assessment guidelines {Cheson 1999, Hallek 2008}. If not performed in the previous 90 days prior to Cycle Day 1 on this study, imaging of the neck, chest, abdomen and pelvis by CT scan with contrast or MRI will be performed between C1D1 and C1D28, and at approximately week 12 and then every 24 weeks. The timing of all scan should be regardless of cycle number or dose interruption.

Scans taken as part of procedures performed at a regular follow-up visit on subject's previous tirabrutinib study may be used to fulfill the screening criteria up to 90 days prior to first dose of tirabrutinib. During the treatment, scans may be performed at time points other than specified, as clinically indicated to assess tumor progression. For subjects who stop study treatment in the absence of disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 24 weeks until disease progression or initiation of systemic anti-tumor therapy other than the study treatment (whichever is earlier). Assessment of progression will be as determined by the investigator.

As this is an extension protocol from ONOPOE001 [EudraCT Number: 2011-005033-39], the same imaging procedure and specifications (eg, contrast agent, scanner, slice thickness, etc.) used to define measurable target and non-target lesions from the time of initiation of treatment should be used throughout the study for each subject.

CT scans may not be performed at sites or in countries where additional radiology approval is required, unless that approval is sought and granted.

CCI [redacted]

CCI [redacted]

6.4. Unscheduled visits

Unscheduled procedures, including, but not limited to, vital signs, 12-lead ECG, and CT or MRI, will be recorded on the applicable eCRFs.

6.5. 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 3.5, Criteria for Discontinuation of Study Drug). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.6. End of Study

End of study for a subject is defined as the date of the last study-related procedures or the date of death for an on-study subject or when a subject has reached the end of the study duration. See Section 9.3.4.

Subjects will be contacted by phone 30 days (± 7 days) after the last dose of tirabrutinib to assess for AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

All treatment-emergent AEs and laboratory abnormalities present at the end of study are to be followed until resolution or the event is determined to be irreversible by the investigator.

6.7 Tirabrutinib Dose interruption and adjustment

The following are the guidelines for tirabrutinib dose interruption.

Interruption of tirabrutinib administration of up to 28 days will be acceptable to allow for any reversal of toxicity. If the toxicity does not resolve to CTC Grade ≤ 2 or to baseline within 2 weeks, tirabrutinib will be permanently discontinued. Additionally, tirabrutinib should be permanently discontinued if any Grade 4 study drug- related adverse event is observed. No dose reductions will be allowed.

If, in the opinion of the investigator, a subject who has been tolerating therapy well demonstrates a loss of clinical response, the dose of tirabrutinib may be increased to the MTD (600 mg for CLL and 480 mg for NHL). To be considered for a dose increase, the subject must not ever have had a previous dose reduction of tirabrutinib due to a drug related adverse event or any Grade 3 or higher drug related adverse event. It must be noted, that no data is available to inform whether a higher dose of tirabrutinib will overcome resistance to tirabrutinib and therefore an increased dose is allowed if thought to be in the best interest of the patient by the investigator, but not recommended.

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, lack of efficacy, 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 AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the first dose of study drug on the previous study, are considered medical history. If they occurred during the previous study, prior to the first dose of tirabrutinib on this study, but have not resolved, they are considered medical history on this study
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- 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 CRF.

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.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

Protocol-specific SAEs, in this study, is to be considered medically important and therefore "serious." To maintain the integrity of the study, the following events that are assessed as unrelated to IMP will not be considered as SAEs:

- Progression of malignancy being studied
- Death due to malignancy being studied

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression and death should be captured on the eCRF.

These events will be reported, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

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 (eg, 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 (eg, 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).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

- **No**: Evidence exists that the AE has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, 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 AE reporting.

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

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE Version 4.03. For each episode, the highest severity grade attained should be reported.

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 eCRF: all SAEs and AEs related to protocol-mandated procedures.

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 AE is stable, if possible. Gilead 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 occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, 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.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. 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 AE reporting form and submit within 24 hours to:

Gilead PVE	Fax:	PPD
	E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the tirabrutinib IB.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or 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. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to tirabrutinib interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Version 4.03.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

Dosing requirements for certain toxicities are specified in Section 5.3. The investigator may contact the medical monitor to review toxicities that are not directly discussed in the protocol. Laboratory abnormalities identified at Screening/Baseline and during study participation should be treated at the investigator's discretion.

7.6.1. Warnings and Precautions

7.6.1.1. Hemorrhage

Bleeding events have occurred in subjects with relapsed/refractory CLL and relapsed/refractory NHL who received tirabrutinib as monotherapy. These include minor hemorrhagic events such as contusion, hematoma, purpura, and petechiae, and major hemorrhagic events such as small intestinal hemorrhage and subdural hematoma. Subjects should be monitored for signs of bleeding and treated appropriately. 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.

7.6.1.2. Infections

Infections, some with fatal outcome, have occurred in subjects with CLL and NHL who received tirabrutinib as monotherapy. Monitor subjects for fever and infections and treat appropriately.

7.6.1.3. Hypersensitivity Reaction

Hypersensitivity reactions (including an allergic reaction) have been observed in a small number of subjects who received tirabrutinib. If a subject experiences a hypersensitivity reaction, consider interruption or discontinuation of tirabrutinib.

7.6.1.4. Embryo-Fetal Toxicity

Based on findings in animals, tirabrutinib may cause fetal harm when administered to a pregnant woman. Reproductive failure and embryo-fetal toxicity have been observed in rats and rabbits. In rabbits, post-implantation loss was observed at systemic exposures approximately 63 times greater than the expected exposure in rheumatoid arthritis (RA) subjects receiving 20 mg tirabrutinib once daily and approximately 4 times the mean exposure in CLL subjects receiving 320 mg tirabrutinib once daily.

Women of childbearing potential should be advised of the risk of fetal harm during exposure to tirabrutinib. They should use highly effective contraception and have pregnancy testing during exposure to tirabrutinib. Women of childbearing potential should be advised to contact their physician immediately if they become pregnant or suspect they may be pregnant.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs 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.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. 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 section 7.3 and 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 described in Section 7.3. 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 contact information is as follows: Fax number PPD or email PPD

Refer to Appendix 8 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. 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 does 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 long-term safety and tolerability of tirabrutinib in subjects who received tirabrutinib in the prior tirabrutinib study and whose disease had not progressed on the parent study.

The secondary objective of this study is to determine the long-term efficacy of tirabrutinib.

8.1.2. Primary Endpoint

The primary endpoint is safety. Safety will be evaluated by the incidence and severity of AEs and clinical laboratory abnormalities, as defined by Common Terminology Criteria for CTCAE v4.03.

8.1.3. Secondary Endpoint

Secondary endpoints will include:

- ORR: defined as the proportion of subjects who achieve PR or CR
- DOR: defined as the interval from first documentation of CR or PR to the earlier of the first documentation of definitive disease progression as assessed by the investigator, or death from any cause
- PFS: defined as the interval from date of the first dose of tirabrutinib on the parent study to the earlier of the first documentation of definitive disease progression as assessed by the investigator, or death from any cause
- OS: defined as the interval from date of the first dose of tirabrutinib on the parent study until death from any cause.

8.2. Analysis Sets

8.2.1. Rollover Analysis Set

The Rollover Study Analysis Set consists of all subjects who are enrolled into this study. This analysis set will be used for the summary of subject characteristics, disposition, and study drug treatment administration.

8.2.2. Full Analysis Set

The Full Analysis Set consists of all subjects who are enrolled and treated in the parent study. This analysis set will be used for the summary of safety and efficacy endpoints.

8.2.3. Pharmacokinetics Analysis Set

The Pharmacokinetic Analysis Set consists of all enrolled subjects who have at least 1 evaluable PK sample.

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8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method). Data will be described and summarized by phase and dose level, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value on the parent study. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Subject Disposition

The number and percentage of subjects who received study drug, completed each parent study, entered this study and discontinued from this study will be summarized. A summary of the reasons of the discontinuation from the study treatment will be provided separately for each study.

8.5. Subject Characteristics

Demographic and baseline measurements will be captured from parent study and summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of baseline ECOG performance status and selected patient and disease characteristics.

8.6. Efficacy Analysis

Subjects' efficacy data will be integrated with the parent study. The efficacy analysis will be based on full analysis set defined based on the parent study.

Tumor response will be based on investigator assessment. ORR will be estimated and its associated 95% confidence interval will be calculated using the exact method. Subjects who do not have sufficient baseline or on study tumor assessment to characterize response will be counted as non-responders.

DOR, PFS, and OS will be analyzed using Kaplan-Meier (KM) methods. The median will be provided along with the corresponding 95% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided.

The data for DOR and PFS will be censored on the date of the last available disease assessment for subjects who are not known to have relapsed or died by the end of the study follow-up. The data for OS will be censored on the date of last known alive for subjects who are not known to have died by the end of the study follow-up.

8.7. Safety Analysis

All safety data collected on or after the date tirabrutinib was first dispensed up to the date of last dose of tirabrutinib will be summarized by patient cohort and dose levels.

8.7.1. Extent of Exposure and Compliance

Descriptive information will be provided by phase and dose level regarding the number of doses of study treatment prescribed, the total number of doses taken, duration of treatment, and the number and timing of prescribed dose reductions and interruptions.

Tirabrutinib compliance will be described in terms of the proportion of study treatment actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

8.7.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of study treatment in the parent study to 30 days after the last dose of study treatment in the rollover study.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddramsso.com) with descriptions by System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT). The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe

the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study treatment will be categorized as related or unrelated.

Treatment-emergent AEs will be summarized by cohort. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AEs within the same PT (or SOC) is counted only once for that PT (or SOC) using the worst severity grade. AE descriptions will be presented in alphabetical order of System Organ Class, then by decreasing frequency in the "overall" column for a given Preferred Term. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study treatment interruption and/or dose modification
- AEs leading to study treatment discontinuation
- SAEs

8.7.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the period from the first dose of study treatment on the parent study to 30 days after the last dose of study treatment on the rollover study. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ in severity) will be considered treatment emergent. Laboratory abnormalities that occur before the first dose of study treatment or > 30 days after the last dose of study treatment will be included in data listings.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE grade does not exist, reference ranges from the local laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE grade does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE grade does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal] to each visit (normal, low and high [or abnormal]). Tables will be prepared to show frequencies adjusted for baseline values; for this frequency, subjects with the same or worse toxicity grade at baseline are not considered.

8.8. Pharmacokinetic Analysis

The concentration of tirabrutinib and, if applicable, metabolite(s) will be summarized by nominal sampling time using descriptive statistics. Population PK and exposure-response may be explored.

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8.10. Sample Size

No formal hypothesis testing is planned for this study. The number of subjects enrolled will be determined by the number of subjects who completed a prior tirabrutinib study. .

8.11. Data Monitoring Committee

A Data Monitoring Committee will not be 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 European Union 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 subinvestigators 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 subinvestigator's) participation in the study. The investigator and subinvestigator 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. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/EC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/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 IRB or 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 IRB or IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic 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, IRB or 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, CRF and query forms, 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 AEs 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. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. 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, to IRBs or IECs, 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 IRB or IEC in accordance with local requirements and receive documented IRB or 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), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

An Open-label Study to Assess the Long-term Safety and Efficacy of Tirabrutinib (ONO/GS-4059) in Subjects with Relapsed/Refractory B-cell Malignancies

GS-US-401-1787, Protocol Amendment 5, 29 October 2019

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

PPD

Name (Printed)
Author

Oct 30, 2019
Date

PPD

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

Study Phase	Screening/ Enrollment[a]	C1D1 [a] (Baseline)	Day 1 of Each Cycle up to and including Cycle 22 (28 days)	Every 12 weeks starting with Cycle 22 until EOT	60 Month Visit/ EOT/Early Withdrawal	30-Day Safety Follow-up Visit
Window (Days)	**- 30**	**± 3**	**± 7**	**± 14**		**± 7**
Informed Consent	X					
General and Safety Assessments						
Medication History	X					
Physical Examination[b]	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
12-lead ECG		X			X	
AE/Concomitant Medication	X	X	X	X	X	X
Disease Assessments						
Response Assessment	X	X	X	X	X	
ECOG	X	X	X	X	X	
CT scan (neck, chest, abdomen, Pelvis) & Tumor Measurements[c]		X		X[c]	X	
Bone Marrow Examination[d]		X		X[d]	X	
Laboratory Assessments						
Serum / Urine Pregnancy Test[e]	X		X	X	X	
Chemistry	X	X	X	X	X	
CBC and Differential	X	X	X	X	X	
Coagulation		X			X	

Study Phase	Screening/ Enrollment[a]	C1D1 [a] (Baseline)	Day 1 of Each Cycle up to and including Cycle 22 (28 days)	Every 12 weeks starting with Cycle 22 until EOT	60 Month Visit/ EOT/Early Withdrawal	30-Day Safety Follow-up Visit
Window (Days)	**- 30**	**± 3**	**± 7**	**± 14**		**± 7**
Total IgA, IgG, IgM Immunoglobulin electrophoresis		X	X[f]	X		
Urinalysis		X	X[f]	X	X	
Sparse PK[g]			X[g]			
CCI						
Investigational Product						
Tirabrutinib Accountability and Dispensing	X[h]	X	X	X	X[i]	

a Results from laboratory assessments and procedures performed up to 30 days prior may be utilized to determine eligibility and serve as study baseline
b A complete physical examination will be performed at Screening and End of Treatment visit. Starting C1D1 a modified physical examination may be performed
c For subjects who have not had tumor imaging in the 90 days prior to C1D1, a scan should be performed at baseline (between day 1 and day 28), at approximately 12 weeks and then every 24 weeks (± 2 weeks). For subjects who have undergone tumor imaging within 90 days prior to C1D1, scan should be performed at approximately 12 weeks then every 24 weeks (± 2 weeks)
d To confirm clinical response if physical exam and CT scan demonstrate possible CR
e Pregnancy testing only in women per Appendix 8
f Total IgA, IgG, IgM Immunoglobulin electrophoresis and Urinalysis every 3 cycles
g PK samples collected pre dose on C2D1 and C3D1 only
h Dispensing only
i Accountability only

Appendix 3. Definitions of Response for Waldenstrom's Macroglobulinemia

- Complete response (CR): Absence of serum monoclonal IgM protein by immunofixation, Normal serum IgM level and complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline. Morphologically normal bone marrow aspirate and trephine biopsy.

- Very good partial response: Monoclonal IgM protein is detectable. ≥ 90% reduction in serum IgM level from baseline. Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline. No new signs or symptoms of active disease.

- Partial response (PR): Monoclonal IgM protein is detectable. ≥ 50% but < 90% reduction in serum IgM level from baseline. Reduction of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline. No new signs or symptoms of active disease.

- Minor response: Monoclonal IgM protein is detectable. ≥ 25% but < 50% reduction in serum IgM level from baseline. No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly. No new signs or symptoms of active disease.

- Stable disease: Monoclonal IgM protein is detectable. < 25% reduction and < 25% increase in serum IgM level from baseline. No new signs or symptoms of active disease.

- Progressive disease: ≥ 25% increase in serum IgM level from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease.

Appendix 4. Modified International Workshop on Chronic Lymphocytic Lymphoma Leukemia (IWCLL) Criteria for Response Assessment

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) Criteria {Hallek 2008}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of tirabrutinib, and similar drugs.

Note: As this is an extension protocol from ONO-POE001 (EudraCT Number: 2011-005033-39), please monitor the same index and nodal index lesions that were previously identified at the initiation of treatment.

1. Identification and Measurement of Tumor Lesions and Organomegaly

1.1 Index Lesions

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

Index lesions will be measured and recorded at baseline and at the stipulated intervals during treatment. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter (LD) × the longest perpendicular diameter (LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) for each index lesion and the sum of greatest perpendicular diameters (SPD) for all index lesions will be calculated and recorded. The baseline SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Index lesions measuring > 1.5 cm in the LD and > 1.0 cm in the LPD, will be prioritized during baseline index lesion selection.

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

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

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

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

1.2 Spleen and Liver

Both the spleen and liver will be should be assessed by CT/MRI scan at baseline and at the stipulated intervals during treatment. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL during treatment.

The spleen will be considered enlarged if it is > 12 cm in LVD {Asghar 2011, Bezerra 2005}, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (eg, if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

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

A 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or decrease to ≤ 12 cm in the LVD is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir is required for declaration of splenic progression.

The liver will be considered enlarged if it is > 18 cm in LVD {Erturk 2006}.

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

1.3 Non-Index Lesions

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

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

1.4 Definitions of Disease Response and Progression

Responses will be categorized by the Investigator as CR, PR, SD, or PD. In addition, a response category of non-evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of ND is included for situations in which there is no evidence of tumor either at baseline or on treatment.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until PD/recurrence (taking as reference for PD the smallest measurements recorded since treatment started). Subjects with a best overall response of NE or ND will be included in the denominator in the analyses of disease response.

1.4.1. Complete Response

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

- No evidence of new disease
- ALC in peripheral blood of $< 4 \times 10^9$/L
- Regression of all index lesions to normal size ≤ 1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as < 30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood counts meeting all of the following criteria:

  ANC $> 1.5 \times 10^9$/L without need for exogenous growth factors (eg, G-CSF)

  Platelet count ≥ 100×10^9/L without need for exogenous growth factors

  Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

1.4.2. Partial Response

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

- No evidence of new disease
- A change in disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; (2) Only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:

  In a subject with baseline lymphocytosis (ALC ≥ 4 x 10^9/L), a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to < 4 x 10^9/L

  A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions

  In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 1.2

  In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 1.2

  A decrease by ≥ 50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules

- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥ 1 of the following criteria:

  ANC ≥ 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (eg, G-CSF)

  Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors

  Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

1.4.3. Stable Disease

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

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

1.4.4. Definitive Progressive Disease

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

- Evidence of any new disease:

  A new node that measures > 1.5 cm in the LD and > 1.0 cm in the LPD

  New or recurrent splenomegaly, with a minimum LVD of 14 cm

  New or recurrent hepatomegaly, with a minimum LVD of 20 cm

  Unequivocal reappearance of an extra-nodal lesion that had resolved

  A new unequivocal extra-nodal lesion of any size

  New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:

  Increase from the nadir by ≥ 50% in the SPD of index lesions

  Increase from the nadir by ≥ 50% in the LD of an individual node or extra-nodal mass that now has an LD of > 1.5 cm and an LPD of > 1.0 cm

  Splenic progression, defined as an increase in splenic enlargement by ≥ 50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)

  Hepatic progression, defined as an increase in splenic enlargement by ≥ 50% from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)

  Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

  Transformation to a more aggressive histology (eg, Richter syndrome) as established by lymph node or other tissue biopsy, or fluid cytology (with the biopsy or fluid cytology date being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).

- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells

  The current platelet count is < 100 x 10^9/L and there has been a decrease by > 50% from the highest on-study platelet count

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

1.4.5. Non-Evaluable

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

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

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

1.4.6. No Disease

Subjects have a status of ND if all of the following conditions occur:

- Index disease absent at both baseline and on-treatment.
- Non-index disease absent at both baseline and on-treatment.
- Enlargement of the liver and spleen absent at both baseline and on-treatment
- Abnormalities of peripheral blood counts (elevated ALC and abnormally low ANC, platelet count, and hemoglobin) and evidence of CLL in bone marrow (if available) absent at both baseline and on treatment

1.4.7. Lymphocytosis During Therapy

- tirabrutinib, and other agents in class can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms.

- In the absence of other objective evidence of disease progression, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for a PR if other criteria for PR are met and will not be considered evidence of CLL progression if occurring in isolation.

- Subjects with lymphocytosis should be continued on tirabrutinib until the occurrence of definitive disease progression (ie, disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study treatment as described in Section 3.5.

1.5 Definitive CLL Progression

Assessment of response and progression will be by the investigator. Subjects who progress will be discontinued from the study.

Appendix 5. Follicular Lymphoma, Marginal Zone Lymphoma, and Small Lymphocytic Lymphoma Response Assessment

The determination of FL, MZL, and SLL response and progression will be based on standardized response criteria for malignant lymphoma {Cheson 2007}.

1. Identification and Follow-up of Tumor Lesions and Organomegaly

Note: As this is an extension protocol from ONO-POE001 (EudraCT Number: 2011-005033-39), please monitor the same index and nodal index lesions that were previously identified at the initiation of treatment.

1.1. Index Lesions

Up to 6 lesions (eg, lymph nodes, liver or spleen nodules, and/or other circumscribed extra-nodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions LD × LPD will be recorded (in cm) for each index lesion. Using the LD and LPD, the product of the PPD for each index lesion will be calculated. The SPDs for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which objective tumor response will be characterized during treatment. The nadir LDs of individual lesions and the nadir SPDs will be used as references by which objective tumor progression will be characterized during study. All PPD and SPD measurements will be reported in centimeters squared.

1.2. Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- Large nodal lesions have an LD that is > 1.5 cm and an LPD that is ≥ 1.0 cm.
- Small nodal lesions have an LD that is > 1.0 cm and ≤ 1.5 cm and an LPD that is > 1.0 cm.

Index lesions measuring > 1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

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

New or enlarging nodal lesions that are still ≤ 1.0 cm by ≤ 1.0 cm will not be considered to represent recurrent disease or PD. A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in at least 1 diameter will be considered abnormal and used in calculating the SPD. Components that are ≤ 1.0 cm in the LD are assumed to be normal lymph node structures. PD will not be based on the growth of a lesion sub-component until it meets the criteria for abnormal. Lesion sub-components that are abnormal (> 1.0 cm in ≥ 1 diameter) will have the true PPDs calculated with the result used only for calculating an accurate nadir. Lesion sub-components that are normal (≤ 1.0 cm in the LD) will have the default PPD of 1.0 cm^2 (1.0 cm x 1.0 cm) stored only for the purposes of calculating the nadir value.

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

1.3. Extra-Nodal Index Lesions

An extra-nodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extra-nodal mass of any size is considered abnormal. It is considered measurable at baseline if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

At follow-up time points, the PPD of each single extra-nodal index lesion and the SPD of all extra-nodal index lesions will be considered. Because extra-nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extra-nodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extra-nodal lesion that had resolved (ie, had a PPD of 0 cm^2) subsequently reappears unequivocally, the subject will be considered to have PD. A new unequivocal extra-nodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernible to the radiologist by CT scan will be considered PD.

1.4. Non-Index Lesions

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

If present at baseline, up to 6 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as "present" or "absent".

1.5. Definitions of Tumor Response and Progression

Responses will be categorized as CR, PR, SD, or PD. In addition, a response category of NE is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of ND is included for situations in which there is no evidence of tumor both at baseline and on-treatment.

The best overall response will be determined. The best overall response is the best response recorded from the start of study drug until PD/recurrence (taking as reference for PD the smallest measurements recorded since study drug started). Subjects with a best overall response of NE or ND will be included in the denominators in calculations of tumor response rate.

1.5.1. Complete Response

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

- No evidence of new disease
- Regression of all index nodal lesions to normal size (≤ 1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LD and ≤ 1.0 cm in the LPD for nodes that were considered small at baseline) (see Section 1.2 for definitions of large and small nodes)
- Regression to normal of all nodal non-index disease
- Disappearance of all detectable extra-nodal index and non-index disease

- Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new liver or spleen enlargement

- Morphologically negative bone marrow based on an adequate unilateral core biopsy (> 20 mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry

- If PET performed (not required), no evidence of residual disease

1.5.2. Partial Response

To satisfy criteria for PR, all of the following criteria must be met except for subjects with WM as noted below:

- No evidence of new disease

- A ≥ 50% decrease from baseline in the SPD of the index lesions

- No increase in the size of non-index disease

- No increase in the size of the liver or spleen and no new liver or spleen enlargement

- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extra-nodal masses

- If PET performed (not required):

  Typically FDG-avid lymphoma: if no baseline PET scan or if the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥ 1 previously involved site. If baseline PET was performed and was negative, there is no new PET evidence of disease

  Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during study. If the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥ 1 previously involved site.

1.5.3. Stable Disease

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

- No evidence of new disease

- Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD

1.5.4. Progressive Disease

The occurrence of any of the following events indicates PD:

- Evidence of any new disease that was not present at baseline:

  A new node that measures > 1.5 cm in LD and > 1.0 cm in the LPD

  A new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and > 1.0 cm in the LPD

  Unequivocal reappearance of an extra-nodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)

  A new unequivocal extra-nodal lesion of any size

  New non-index disease (eg, effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma).

  New or recurrent bone marrow involvement with iNHL if the last prior bone marrow biopsy performed as part of the study (baseline or on-study) was negative for iNHL

- Evidence of worsening of nodal or extra-nodal index lesions:

  Increase from the nadir by ≥ 50% in the SPD of index lesions

  Increase from the nadir by ≥ 50% in the LD of an individual node or extra-nodal mass that now has an LD of > 1.5 cm and an LPD of > 1.0 cm

- Unequivocal increase in the size of non-index disease

- Transformation to a more aggressive NHL histology as established by lymph node biopsy or cytology.

- If PET performed (not required):The appearance of any new lesion compatible with lymphoma with confirmation by other radiographic or histological modalities

  The reappearance of any activity in a pre-existent lesion that meets size criteria for a new lesion on CT

1.5.5. Non-Evaluable

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

- There are no images or inadequate or missing images.

1.5.6. No Disease

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

- Index disease absent at both baseline and on-study
- Non-index disease absent at both baseline and on-study
- Enlargement of the liver and spleen absent at both baseline and on-study

Appendix 6. ECOG status

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

{Oken 1982}

Appendix 7. 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 8. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

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

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

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

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered of 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

The risks of treatment with tirabrutinib during pregnancy have not been evaluated. There is no data available at this time to exclude the possibility that tirabrutinib has a drug-drug interaction (DDI) with hormones used for contraception. There is insufficient data to exclude the possibility of a clinically relevant interaction of tirabrutinib 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. Please refer to the latest version of the tirabrutinib IB for additional information.

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. They must also 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 pregnancy test on the Baseline/Day 1 visit prior to randomization. Pregnancy tests will be performed at each visit thereafter. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

- 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

  Essure micro-insert system (provided confirmation of success 3 months after procedure) for countries where it's available

  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 after the end of relevant systemic exposure.

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 after the end of relevant systemic exposure. 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 after the end of relevant systemic exposure.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., 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

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 last study drug dose. 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. Subjects whose 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 7.7.2.1.

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ELECTRONIC SIGNATURES

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PPD	Biostatistics eSigned	29-Oct-2019 17:05:18
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