CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Dose Escalation and Dose Expansion Study of Tirabrutinib (ONO/GS-4059) in Combination with other Targeted Anti-cancer Therapies in Subjects with B-cell Malignancies
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	125473 2015-000834-30 NCT02457598
Indication:	B-cell malignancies
Protocol ID:	GS-US-401-1757
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PROTOCOL SYNOPSIS

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Study Title:	A Phase 1b Dose Escalation and Dose Expansion Study of Tirabrutinib (ONO/GS-4059) in Combination with other Targeted Anti-cancer Therapies in Subjects with B-cell Malignancies
IND Number:	125473
EudraCT Number:	2015-000834-30
Clinical Trials.gov Identifier:	NCT02457598
Study Centers Planned:	Approximately 25 centers worldwide

As of Amendment 9, all subjects currently on the study will transition into long-term safety monitoring. Subjects from the ongoing Study GS-US-401-1787 and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use will be enrolled into Group VI in this study to participate in long-term safety monitoring.

Objectives:

The primary objectives of the study are:

For the dose escalation phase:

- To characterize the safety and tolerability of tirabrutinib combined with idelalisib or entospletinib (also known as ENTO, and GS-9973) in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To characterize the safety and tolerability of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies

For the dose expansion phase:

- To evaluate the preliminary efficacy of tirabrutinib combined with idelalisib or entospletinib in B-cell lymphoproliferative malignancies (subtype[s] to be determined based on the dose escalation phase)

- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the preliminary efficacy of tirabrutinib alone administered at 80 mg once daily in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL)

For long-term safety monitoring phase:

- To evaluate the long-term safety of tirabrutinib as a monotherapy, and in combination with idelalisib or entospletinib, with or without obinutuzumab, in subjects with relapsed or refractory B-cell lymphoproliferative malignancies.

The secondary objectives of the study are:

For the dose escalation phase:

- To evaluate the preliminary efficacy of tirabrutinib combined with idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the pharmacokinetics (PK) of tirabrutinib administered alone and in combination with idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies

For the dose expansion phase:

- To further characterize the safety and tolerability of tirabrutinib combined with idelalisib or entospletinib in subjects with a specific tumor subtype (to be determined)
- To further characterize the safety and tolerability of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with a specific tumor subtype (to be determined)
- To characterize the safety and tolerability and evaluate the preliminary efficacy of single-agent tirabrutinib in subjects with relapsed or refractory CLL

CCI [redacted]

Study Design:

This is a Phase 1b, open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, pharmacodynamics, and efficacy of tirabrutinib in combination with idelalisib or entospletinib, with or without obinutuzumab, in subjects with relapsed or refractory B-cell lymphoproliferative malignancies. Tirabrutinib may also be evaluated as a single-agent to obtain additional safety, tolerability, and efficacy data at the maximum tolerated dose (MTD) equivalent dose.

The study will consist of 3 parts. The first part is a dose-escalation phase to evaluate safety, tolerability, PK, and pharmacodynamics of tirabrutinib combination therapies. Subjects with B-cell lymphoproliferative malignancies who have refractory or relapsed disease will be enrolled in a standard 3 + 3 dose escalation study design, to receive oral tirabrutinib combined with idelalisib or entospletinib.

Once a dose level of tirabrutinib combined with idelalisib or entospletinib has been deemed safe and tolerable, additional cohorts of subjects will be enrolled to receive the triplet combination of obinutuzumab, tirabrutinib and idelalisib or entospletinib. Up to 2 dose levels for each triplet combination may be evaluated.

The second part of the study is an expansion phase to evaluate the preliminary efficacy of tirabrutinib combined with idelalisib or entospletinib in a specific B-cell malignancy subtype (eg, CLL) and non-germinal center B-cell-like diffuse large B cell lymphoma (non-GCB-DLBCL). The iNHL expansion may be grouped into one expansion cohort or divided into more specific subgroups such as mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM) and marginal zone lymphoma (MZL). The expansion phase may also include subjects who receive the triplet combination of obinutuzumab, tirabrutinib, and idelalisib or entospletinib in specific B-cell malignancies (eg, CLL). An expansion arm of single-agent tirabrutinib 80 mg once daily in subjects with relapsed or refractory CLL may also be included.

Each expansion arm will enroll up to approximately 30 subjects.

The choice of enrolling a subject into a specific cohort will be based on the treatment slots open at the time of screening, inclusion/exclusion enrollment criteria and at the discretion of the investigator.

The third part of the study is long-term safety monitoring to evaluate the long-term safety of tirabrutinib both as a monotherapy and in combination with other anti-cancer therapies. As of Amendment 9, all subjects currently on the study who have no clinical evidence of disease progression will transition into long-term safety monitoring. Subjects from the ongoing Study GS-US-401-1787 and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use (or individual expanded use) will be enrolled into Group VI to participate in long-term safety monitoring.

Combination I: Tirabrutinib and Idelalisib

Initially, 3 subjects will enroll in Cohort 1A of Combination I; the starting dose will be 20 mg once daily of tirabrutinib and 50 mg twice daily of idelalisib (Table 1). If a dose-limiting toxicity (DLT) occurs within 28 days from Cycle 1, Day 1 in Cohort 1A, this cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Cohort 1A, (ie, ≥ 2 subjects experience DLTs) development of the combination of tirabrutinib and idelalisib will discontinue.

If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 1A, then Cohort 2A will open. Cohort 2A will enroll 3 subjects with tirabrutinib dosed at 40 mg once daily and idelalisib 50 mg twice daily. Once enrollment is complete in Cohort 2A, Cohort 2B will enroll 3 subjects with tirabrutinib dosed at 20 mg twice daily and idelalisib 50 mg twice daily. Cohorts 2A and 2B will dose escalate independently; if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2A and Cohort 2B has completed enrollment, then the next 3 subjects will be enrolled in Cohort 3A with tirabrutinib dosed at 80 mg once daily and idelalisib 50 mg twice daily. Similarly, if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2B, Cohort 3B will enroll 3 subjects with tirabrutinib dosed 40 mg twice daily and idelalisib 50 mg twice daily. Subsequent cohorts will enroll if no DLTs in 3 subjects or < 2 DLTs occur in up to 6 subjects are observed. If a second DLT is observed in any cohort, the MTD of tirabrutinib combined with idelalisib will have been exceeded and the prior cohort will be the MTD. The MTD for tirabrutinib once-daily will be determined separately from the MTD for tirabrutinib twice-daily.

A new cohort will not open for enrollment until the last subject has completed the 28-day safety period for the prior cohort. All available safety, tolerability, and PK data will be reviewed prior to proceeding to the next cohort. The design will be adaptive, with cohorts for reduced or intermediate doses added based on emerging safety, PK, pharmacodynamics, and efficacy results. Additionally, either tirabrutinib once daily or tirabrutinib twice daily cohorts may be discontinued based on emerging safety and efficacy data. If there is no evidence of clear benefit of twice daily dosing of tirabrutinib compared with once daily dosing based on available tolerability, efficacy, PK and pharmacodynamic data, dose escalation in the twice daily dosing arm may be terminated prior to identifying an MTD. Accordingly, as of 25 March 2016, enrollment in the cohorts evaluating twice daily dosing of tirabrutinib combined with idelalisib was discontinued due to 2 of 5 subjects reporting Grade 4 neutropenia (1 DLT with associated fever and infection and 1 DLT without) within the first 28 days of dosing in Cohort 2B.

Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2.

The doses for each cohort are shown in the following Table 1.

Table 1. Dose Escalation for Combination I (Tirabrutinib + Idelalisib)

Dose Level	Combination I-A		Combination I-B	
	Tirabrutinib	Idelalisib	Tirabrutinib	Idelalisib
	A		B	
1	20 mg QD	50 mg BID	—	—
2	40 mg QD	50 mg BID	20 mg BID	50 mg BID
3	80 mg QD	50 mg BID	—	—
4	80 mg QD	100 mg QD	—	—
5	160 mg QD	100 mg QD*	—	—

QD = Once daily dosing, BID = Twice daily dosing * Dose Level 5 (Combination I-A) will be limited to DLBCL only

Once the MTD of the combination of tirabrutinib of idelalisib twice daily has been determined, based on safety and efficacy, additional cohorts may be enrolled at up to the MTD of tirabrutinib combined with 100 mg of idelalisib once daily

Combination II: Tirabrutinib and Entospletinib

Initially 3 subjects will enroll in Cohort 1A of Combination II; the starting dose will be 40 mg once daily of tirabrutinib and 200 mg once daily of entospletinib (Table 2). If 1 DLT occurs within 28 days from Cycle 1, Day 1 in Cohort 1A of Combination II, this cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Cohort 1A of Combination II, (ie, ≥ 2 subjects experience DLTs), development of the combination of tirabrutinib and entospletinib will discontinue. If no DLTs in 3 subjects or < 2 DLTs in up to 6 subjects are observed, then the dose will be escalated to dose Level 2.

Table 2. Dose Escalation for Combination II (Tirabrutinib + Entospletinib)

Dose Level	Combination II-A		Combination II-B	
	Tirabrutinib	Entospletinib	Tirabrutinib	Entospletinib
1	40 mg QD	200 mg QD	—	—
2	80 mg QD	200 mg QD	40 mg QD	400 mg QD
3	150 mg QD	200 mg QD	80 mg QD	400 mg QD
4	—	—	160 mg QD	400 mg QD*

QD = Once daily dosing BID = Twice daily dosing * Dose Level 4 (Combination II-B) will be limited to DLBCL only

Dose Level 2 will consist of 2 cohorts: Cohort 2A with tirabrutinib 80 mg once daily and entospletinib 200 mg once daily and Cohort 2B with tirabrutinib 40 mg once daily and entospletinib 400 mg once daily. The first 3 subjects enrolled in Dose Level 2 will be assigned to Cohort 2A; the next 3 subjects will be assigned to Cohort 2B.

Cohorts 2A and 2B will dose escalate independently; if 1 DLT occurs in Cohort 2A, then Cohort 2A will be expanded to enroll 3 additional subjects. Similarly, if 1 DLT occurs in Cohort 2B, then Cohort 2B will be expanded to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2A then Cohort 3A may begin enrollment. Similarly, if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2B then Cohort 3B may begin enrollment.

If ≥ 2 DLTs are observed in Cohort 2A and < 2 DLTs occur in up to 6 subjects in Cohort 2B, then the MTD of tirabrutinib combined with entospletinib is 40 mg once daily. Cohort 3A will not be enrolled, however, Cohort 3B may continue with enrollment.

Similarly, if ≥ 2 DLTs are observed in Cohort 2B and < 2 DLTs occur in up to 6 subjects in Cohort 2A, then the MTD of entospletinib combined with tirabrutinib is 200 mg once daily. Cohort 3B will not be enrolled, however, Cohort 3A may continue with enrollment.

A new cohort within arm A and arm B will not open for enrollment until the last subject has completed the 28-day safety period for the prior cohort, (ie only one entospletinib/GS-4059 cohort will be open at any time in the A and B groups. All available safety, tolerability, and PK data will be reviewed prior to proceeding to the next cohort.

The maximum dose to be tested will be 160 mg total daily dose of tirabrutinib and 400 mg total daily dose of entospletinib, however, the dose escalation will be adaptive, with cohorts for reduced dosing, intermediate dosing, or different schedule (QD vs BID) added based on emerging safety, PK, pharmacodynamics, and efficacy results. Dose level 5 (Combination I-A) and Dose level 4 (Combination II-B) are limited to subjects with non-GCB DLBCL only.

Combination III and Combination IV: The addition of obinutuzumab to Combination I or II

Once a dose escalation cohort in Combination I or II has completed a 28-day safety review, an additional cohort of 3 (+3) subjects may be enrolled at this Dose Level with the addition of obinutuzumab. Up to 2 dose levels for each triplet combination may be evaluated. Initially 3 subjects each will enroll at the chosen dose level(s) in Combination III and Combination IV in parallel (see Table 3). If 1 DLT occurs within 28 days from Cycle 1 in Combination III, the Combination III cohort will be expanded to enroll 3 additional subjects. Similarly, if 1 DLT occurs within 28 days from Cycle 1 in Combination IV, the Combination IV cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Combination III or IV, (ie, ≥ 2 subjects experience DLTs), development of the specific Combination (III or IV) will be discontinued.

Based on the results for Combination I and Combination II, the dose levels for each triplet combination (III and IV) will be determined.

If multiple dose levels of tirabrutinib plus idelalisib or entospletinib are chosen in Combination III or IV, they will be conducted in a staggered manner (lowest dose level first), similar to the dose levels in Combination I and II, with the same stopping rules applied.

Table 3. Dose Evaluation for Triplet Combinations (Combination III and IV)

	Combination III		Combination IV	
Dose Level	**Tirabrutinib + idelalisib**	**Obinutuzumab**	**Tirabrutinib + Entospletinib**	**Obinutuzumab**
A Triplet Dose Level 1	Dose determined by results of Combination I Dose Escalation (Table 1)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 2)	1000 mg IV infusion x 8 doses
B Triplet Dose Level 2	Dose determined by results of Combination I Dose Escalation (Table 1)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 2)	1000 mg IV infusion x 8 doses

A DLT is a toxicity (defined below) which occurs during the DLT assessment window (Cycle 1, Day 1 through Cycle 1, Day 28) in each cohort:

1) All Grade ≥ 4 hematological toxicities persisting for > 7 days
2) All Grade ≥ 3 non-hematological toxicities (except for tumor lysis syndrome or alopecia, or Grade 3 nausea, vomiting, diarrhea, or constipation that resolves within 72 hours with medical intervention)
3) All Grade ≥ 4 non hematologic laboratory abnormalities
4) Febrile Neutropenia (defined as ANC < 1.0 x 10^9/L with a single temperature > 38.3ºC [101 ºF] or sustained temperature ≥ 38ºC [100.4 ºF] for more than 1 hour)
5) Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk

All adverse events (AEs) should be considered relevant in determining DLTs and to reporting unless the event can clearly be determined to be unrelated to tirabrutinib and/or idelalisib or entospletinib. Lymphocytosis will not be considered a DLT.

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and medical monitor, may take place to determine if this AE should be assessed as a DLT and necessitate dose interruption or dose reduction.

During the DLT assessment window, subjects who fail to complete at least 21 total days of tirabrutinib and idelalisib or entospletinib for reasons other than DLT will not be evaluable for DLT assessment and additional subjects may be enrolled to that cohort in order to provide adequate safety data for dose escalation decisions.

Expansion phase cohort(s) and dose selection will be based on emerging safety, PK, pharmacodynamics, and efficacy results from the dose escalation. Dose expansion may occur after the next higher dose cohort has opened in the dose escalation. Dose expansion may proceed at a lower dose than the MTD.

Group V: Tirabrutinib single agent

Additionally, a cohort of up to approximately 30 subjects with relapsed or refractory CLL may be enrolled to receive single-agent tirabrutinib 80 mg once daily to provide preliminary safety and efficacy data at this recommended Phase 2 combination dose level.

	Long-Term Safety Monitoring As of Amendment 9, all subjects currently on the study will transition into long-term safety monitoring. Subjects from the ongoing Study GS-US-401-1787 and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use will be enrolled into Group VI to participate in long-term safety monitoring. Subjects enrolled in Group VI will continue the same treatment regimen in Study GS-US-401-1787 or named patient use starting from Long-Term Safety Monitoring Cycle 1 Day 1. Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 end of treatment (EOT) visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI in this study should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. All active subjects who have no clinical evidence of disease progression will transition to long-term safety monitoring and will continue the same treatment regimen. Study visits will be completed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase.
Number of Subjects Planned:	Up to 98 subjects in the dose escalation phase and up to 270 subjects in the dose expansion phase will be enrolled. As of Amendment 9, all subjects currently on this study will transition into long-term safety monitoring. Up to 6 additional subjects in the United Kingdom (UK) from the ongoing Study GS-US-401-1787 and up to 2 additional subjects in total in the United States (US) and UK who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use will be enrolled into Group VI to participate in long-term safety monitoring. Therefore, up to 376 subjects may be enrolled in the study.
Target Population:	Adults with relapsed or refractory FL, marginal zone lymphoma (MZL), CLL, small lymphocytic lymphoma (SLL), MCL, Waldenstrom's macroglobulinemia (WM), or non-GCB DLBCL who have measurable disease per standard criteria and require therapy for their cancers.

	As of Amendment 9, subjects previously enrolled in the ongoing Study GS-US-401-1787, and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use who are clinically deriving benefit from their therapy and have not experienced progression of disease.
Duration of Treatment:	Treatment will continue in the absence of disease progression (clinical or radiographic), unacceptable toxicity, pregnancy, and substantial noncompliance with study procedures or study drug, initiation of another anti-cancer or experimental therapy, study discontinuation, or withdrawal from study. As of Protocol Amendment 8, the maximum participation in the treatment period for any subject is an additional 6 years from the date of that amendment (ie, until November 2025). As of Amendment 9, entospletinib will be provided until 31 December 2020 to subjects enrolled in Combination II and IV who are currently receiving entospletinib. Subjects treated with entospletinib as part of a combination regimen with tirabrutinib will stop receiving entospletinib by 31 December 2020 but may continue to be treated with tirabrutinib monotherapy. Tirabrutinib is supplied as 40 mg, 80 mg, and 100 mg until study completion. Idelalisib is supplied as 50 mg tablets until 31 December 2020 and 100 mg tablets until study completion. Subjects assigned to the 50 mg once daily idelalisib dose will be given the option, at the investigator's discretion, to switch to 100 mg once daily idelalisib dose leading to an increase in total daily dose from 50 mg to 100 mg idelalisib, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment. Subjects receiving 50 mg once daily of idelalisib must not experience any ≥ Grade 3 AEs related to idelalisib to be eligible for this dose increase. Following the dose increase, if the subjects experience any ≥ Grade 3 toxicity, they will discontinue idelalisib and be given the option to continue tirabrutinib monotherapy, at the investigator's discretion. Subjects assigned to the 50 mg twice daily idelalisib dose will be given the option, at the investigator's discretion, to switch to the 100 mg once daily idelalisib dose with no change to the total daily dose, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

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

1) Male or female ≥18 years of age
2) Diagnosis of FL, MZL, SLL, CLL (meeting IWCLL Criteria 2008), MCL, WM, or non-GCB DLBCL as documented by medical records and with histology based on criteria established by the World Health Organization (WHO).
   a) FL Grades 1, 2, or 3a
   b) SLL with absolute lymphocyte count of $< 5 \times 10^9$/L at initial diagnosis
   c) MZL (splenic, nodal, or extra-nodal)
   d) WM, measurable disease defined as serum monoclonal IgM > 0.5 g/dL or meeting at least 1 of the recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia for requiring treatment (Appendix 4)
3) Prior treatment for FL, MZL, SLL, MCL or WM with ≥ 2 or for CLL or non-GCB DLBCL with ≥1 chemotherapy-based or immunotherapy-based regimen who are not transplant eligible and have had either documented disease progression or no response (stable disease) to the most recent treatment regimen.
4) For diseases other than WM, presence of radiographically measurable lymphadenopathy or extra-nodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥2.0 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).
5) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or bone marrow parameters [any of Grade 1 or 2 permitted]).
6) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2
7) Adequate organ function defined as follows:
   a) Hematologic: Platelets ≥ 50 x 109/L; Hemoglobin ≥ 8.0 g/dL; ANC ≥ 1.0 x 109/L (without platelet transfusion or any growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)

b) Hepatic: Aspartate transaminase (AST) / Alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) Total or conjugated bilirubin ≤ 1.5 x ULN

c) Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockcroft-Gault method

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol specified method of contraception as described in Appendix 8.

9) Male subjects of reproductive potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 8

10) Able and willing to provide written informed consent to participate in the study

11) Willingness and ability to comply with protocol-specified Pneumocystis jirovecii pneumonia (PJP) prophylaxis

Group VI only (Numbers 12-18):

12) Currently enrolled in Study GS-US-401-1787 or previously enrolled in Study GS-US-401-1757 or Study GS-US-401-1787 and currently receiving continued treatment via named patient use

13) Continuing to benefit from the current treatment regimen in the opinion of the investigator/treating physician

14) Negative urine pregnancy test is required for female subjects of childbearing potential as described in Appendix 8

15) 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.

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

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

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

Exclusion Criteria:

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

1) History of lymphoid malignancy other than those allowed per the inclusion criteria.
2) Known active central nervous system or leptomeningeal lymphoma. Imaging documentation of the absence or presence of central disease is not required.
3) History of myelodysplastic syndrome.
4) History of or current Richter's transformation.
5) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to start of study therapy, or any other cancer that has been in complete remission for ≥ 5 years.
6) Less than 21 days since receiving treatment with biologic, small molecule, immunotherapy, chemotherapy, radiation, or other agent for lymphoid malignancy including other investigational products.
7) Ongoing liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
8) Hepatitis B surface antigen (HBsAG) positive or hepatitis B core antibody positive
9) Hepatitis C virus (HCV) antibody positive
10) Known human immunodeficiency virus (HIV) infection
11) Ongoing CMV infection, treatment, or prophylaxis within the past 28 days prior to the screening test for active CMV (subjects may receive CMV prophylaxis on study)
12) Ongoing symptomatic pneumonitis
13) Ongoing inflammatory bowel disease
14) Pregnancy or breastfeeding

15) History of prior therapy with any inhibitor of serine/threonine protein kinase (AKT), Bruton tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K) (including idelalisib, GS-9820, GS-9901), Janus Kinase (JAK), mammalian target of rapamycin (mTOR), or spleen tyrosine kinase (SYK) except for Group V (single-agent tirabrutinib), for which only prior BTK treatment is excluded.

16) Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of lymphoid malignancy. Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (≤5 mg/day of methylprednisolone or equivalent) is permitted. During study participation, subjects may receive systemic or other corticosteroids as needed for treatment-emergent comorbid conditions

17) Life expectancy < 4 months as per investigator assessment.

18) Concurrent participation in another therapeutic clinical trial.

19) History of long QT syndrome or whose correct QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 450 ms).

20) History of stroke or intracranial hemorrhage within 12 months prior to enrollment.

21) Use of strong CYP3A4 and P-gp inducers within 2 weeks prior to the first dose of study drug

22) For subjects enrolling in the entospletinib combination arms only:

    a) Use of strong CYP3A4 or CYP2C9 inducers or moderate CYP2C9 inducers within 2 weeks prior to the first dose of study drug.

    b) Use of a proton pump inhibitor during the screening window. H2 receptor antagonists are allowed.

23) History of sensitivity or intolerance to any of the excipients of the drug to be administered based on the study arm (tirabrutinib, idelalisib, entospletinib, or obinutuzumab)

24) For subjects enrolling in the idelalisib combination arms only: History of serious allergic reaction including anaphylaxis and toxic epidermal necrolysis

25) For subjects enrolling in the obinutuzumab arms: prior treatment with obinutuzumab and/or the presence of any active infection

Group VI only (Numbers 26-27):

26) History of sensitivity or intolerance to any of the excipients of the drug to be administered based on the study arm (tirabrutinib, idelalisib, or entospletinib)

27) Evidence of clinical or radiological disease progression

Study Procedures/ Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dosing of study drug on Cycle 1, Day 1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead electrocardiogram (ECG), ECOG Performance Status, prior/concomitant medication review, chemistry, hematology and coagulation, AE assessment, and CT or MRI (scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to Cycle 1, Day 1 are acceptable) and for WM, serum evaluation for IgM. Baseline tumor assessment according to disease type will be measured and characterized prior to Cycle 1, Day 1 to assess the subject's disease status prior to beginning treatment.

For Group VI, urine pregnancy testing performed up to 30 days and imaging performed up to 90 days prior to enrollment may be used to fulfill eligibility criteria.

Dose Escalation Arms:

Subjects who meet eligibility criteria will receive a single dose of tirabrutinib on Cycle 1, Day 1 and then initiate idelalisib or entospletinib in combination with tirabrutinib on Cycle 1, Day 2. The first cycle will consist of 28 days (1 day of single agent tirabrutinib and 27 days of combination treatment), and each subsequent cycle will be 28 days of combination treatment. The assigned combination drug will remain consistent throughout the subject's study participation, there will be no dose escalation or crossover permitted on study. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, tirabrutinib and idelalisib or entospletinib PK, pharmacodynamics, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT (or MRI) scan every 12 weeks, except DLBCL and CLL. Subjects with

DLBCL will have an additional scan at week 6. Subjects with CLL will only undergo scans at baseline, 24 weeks, and at the time of progression. As of Amendment 7, CT/MRI scans will no longer be performed and will only be performed at the time of disease progression or at study discontinuation.

Obinutuzumab will be initiated on Study Day 1 with a test dose of 100 mg. If this dose is tolerated well, the remainder of the full dose may be subsequently administered on Study Day 1. Alternatively, the remaining 900 mg will be administered on Study Day 2. Subsequent infusions of obinutuzumab will be administered on Cycle 1, Day 6 (+/- 2 days), Cycle 1, Day 13 (+/- 2 days), Cycle 2, Day 1 (+/- 3 days) and then every 28 days (+/- 3 days) until Cycle 6, Day 1 (+/- 3 days) for up to 8 intravenous infusions of 1000 mg each.

Treatment with the combination of tirabrutinib with idelalisib or entospletinib will be administered in combination with obinutuzumab 1-2 days after Study Day 1. The first day of dosing these oral agents is considered Cycle 1, Day 1. The combination of oral targeted agents will continue to be taken daily on a schedule (once daily or twice daily) as determined by the results of the Combination I and II dose escalations. The 28-day window for DLT evaluation will start with the initiation of the oral agent combination. Subjects who withdraw or discontinue study after only receiving obinutuzumab will not be considered evaluable for the purposes of DLT determination and will be replaced.

A subject who does not show evidence of disease progression by clinical assessment or by CT (or MRI) may continue receiving study drugs until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.6.

Dose Expansion Arms:

Subjects enrolling in expansion arms will follow the same treatment and evaluation schedule with sparse PK sampling.

After discontinuation of treatment, subjects will be followed for safety for 30 days.

Long-Term Safety Monitoring:

As of Amendment 9, all subjects currently on the study will transition into long-term safety monitoring and will continue the same treatment regimen. Subjects enrolled in Group VI will receive the same treatment regimen administered in Study GS-US-401-1787 or named patient use. Only study

procedures for the long-term safety monitoring phase are to be conducted for each subject enrolled, as presented in Appendix 3. Screening procedures will only apply to Group VI. Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 EOT visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI in this study should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Clinical evaluations and laboratory assessments will be performed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care.

PK and Pharmacodynamics Sampling (As of Amendment 7, Pharmacodynamics samples will no longer be collected)

Dose Escalation (Combination I and II):

PK samples will be collected on Cycle 1, Day 1 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and CCI [redacted] post-dose of tirabrutinib and Cycle 1, Days 2 and 8 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, CCI [redacted] and 24 hours post-dose of tirabrutinib and idelalisib or entospletinib. CCI [redacted] and the 24-hour sample should be collected 24 hours post-dose relative to the morning dose. PK samples will be collected in all cohorts at pre-dose and between 1-6 hours post-dose on Cycle 1 Day 15. A sparse PK sample will also be collected anytime on the first day of Cycles 2 to 6.

Blood samples for pharmacodynamics will be collected on Cycle 1, Day 1 at pre-dose, 2, and 6 hours post-dose; on Cycle 1, Days 2 and 8 at pre-dose, 2, 6, and 24 hours post-dose; and at the end of treatment or disease progression. When study drug is administered twice daily, the 24 hour sample will be collected 24-hours postdose relative to the morning dose. The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling time points may be eliminated or modified based upon emerging data.

Dose Expansion (Combinations I and II):

A PK sample will be collected on Cycle 1, Day 1 between 1.5and 4 hours (inclusive) post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

Pharmacodynamic samples will be collected on Cycle 1, Day 1 at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a pharmacodynamic sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib and at the end of treatment or disease progression.

Dose Escalation and Dose Expansion Combinations III and IV:

A PK sample will be collected on Cycle 1, Day 1 between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib. A PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

Pharmacodynamic samples will be collected on Cycle 1, Day 1 at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a pharmacodynamics sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib and at the end of treatment or disease progression.

Dose Expansion Group V:

A PK sample will be collected on Cycle 1, Day 1 between 1.5 and 4 hours post dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

Pharmacodynamic samples in these same subjects will be collected at Cycle 1, Day 1 pre-dose and between 1.5-4 hours post-dose of tirabrutinib. Cycle 1, Day 8 at pre-dose and 4 hours and at the end of treatment or disease progression.

	CCI [redacted] **Long-Term Safety Monitoring:** No PK or pharmacodynamics samples will be collected.
Test Product, Dose, and Mode of Administration:	Tirabrutinib will be self-administered orally once or twice daily depending on cohort, beginning on Cycle 1, Day 1 of the study and thereafter at approximately the same time each day until end of treatment. In the tirabrutinib and idelalisib arm, idelalisib will be self-administered orally twice daily, beginning on Cycle 1, Day 2 and at approximately the same time as tirabrutinib. In the tirabrutinib and entospletinib arm, entospletinib will be self-administered orally as per assigned treatment group, beginning on Cycle 1, Day 2. Tirabrutinib is supplied as 10 mg and 25 mg capsules or as 20 mg, 40 mg, 75 mg, 80 mg, or 100 mg tablets. Idelalisib is supplied as 50 mg and 100 mg tablets. Entospletinib is supplied as 200 mg tablets. As of Amendment 9, tirabrutinib is supplied as 40 mg, 80 mg, and 100 mg until study completion. Idelalisib is supplied as 50 mg tablets until 31 December 2020 and 100 mg tablets until study completion. Entospletinib is supplied as 200 mg tablets until 31 December 2020. Obinutuzumab: Obinutuzumab will be administered as 8 intravenous infusions of 1000 mg each over approximately 21 weeks. A test dose of 100 mg will be administered on Study Day 1. If the dose is tolerated well, the remaining 900 mg may be administered. Alternatively, the remaining 900 mg may be given the next day, on Study Day 2. Subsequent infusions of obinutuzumab will be administered on Cycle 1 Day 6, Cycle 1 Day 13 Cycle 2, Day 1 and then every 4 weeks until Cycle 6, Day 1.
Reference Therapy, Dose, and Mode of Administration:	Not applicable

Criteria for Evaluation	
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements, and the documentation of AEs As of Amendment 9, long-term safety will be evaluated by the assessment of AE/serious adverse events (SAEs).
Efficacy:	In subjects who do not have CLL, overall response rate (ORR) defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) at Week 12 and at any time point. In subjects with CLL, the endpoint will be evaluated at Week 24. (Proportion of subjects with CLL achieving CR and negative minimal residual disease (MRD) will also be evaluated). Progression free survival (PFS) defined as the interval from the start of the study therapy to the earlier of the first documentation of definite disease progression or death from any cause. Duration of response (DOR) defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definite disease progression or death from any cause. Time to response (TTR) defined as the interval from start of treatment to the first documentation of CR or PR. Response criteria for each disease is included in Appendix 4, Appendix 5, and Appendix 6.
Pharmacokinetics:	In the dose escalation phase, PK parameters for tirabrutinib, idelalisib, idelalisib metabolite GS-563117, and entospletinib will be calculated, as applicable: C_{max}, AUC_{tau}, C_{tau}, T_{max}, and $t_{1/2}$. PK of other tirabrutinib, idelalisib or entospletinib metabolites may be explored.
Statistical Methods:	The All Enrolled Analysis Set will include all subjects who are enrolled in the study. The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. The Pharmacokinetic Analysis Set will include subjects who receive at least 1 dose of study treatment and have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

Subject characteristics and study results will be described and summarized by phase (escalation and expansion) and dose level for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% exact CIs on the percentage for categorical variables.

Based on the Safety Analysis Set, information regarding study treatment administration, study drug compliance, safety variables, and post-study therapies will be described and summarized. Study drug plasma concentrations will also be described and summarized using the Pharmacokinetics Set.

Tumor response will be based on investigator's assessment. ORR and CR will be estimated for each dose level or expansion arm where appropriate and their associated 95% confidence intervals will be calculated using the exact method. Duration of response and PFS will be analyzed using the Kaplan-Meier method. The median and quartiles and their associated 95% confidence intervals for these endpoints will be provided if estimable.

Adverse events will be coded using the current MedDRA and graded using the NCI-CTCAE criteria and will be summarized by system organ class 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 Calculation

The trial employs the standard National Cancer Institute (NCI) definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window) to determine dose escalation. The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next cohort of the study if the true underlying probability of DLT is low. For example, if the true underlying probability of DLT is low (eg, < 10%) at the current dose level, there is a high probability (> 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, > 60%) at the current dose level, there is a low probability (< 0.08) of escalation to the next dose level.

It is estimated that approximately 90 evaluable subjects will be needed for the planned dose-escalation phase of the study. Under the assumption that ~10% of enrolled subjects may not be evaluable for DLT, approximately 98 subjects will be enrolled during the 2 dose escalation phases. During the dose expansion phase, up to 270 subjects will be enrolled under the assumption that up to 4 disease types and/or dose levels will be evaluated in the idelalisib combination, and up to 4 disease types and/or dose levels in the entospletinib combination.

The sample size of the expansion cohort is determined based on Simon's 2-stage optimal design. If 3 or fewer out of the first 11 subjects achieve response, then the expansion of the cohort will be stopped; otherwise the enrollment will continue to 30 subjects. The design will have approximately 83% power to rule out that ORR is below 25% based on a 1-sided binomial test at 0.05 significance level with assumed response rate of 50%.

In addition, as of Amendment 9, up to 8 additional subjects from Study GS-US-401-1787 or previously enrolled in Study GS-US-401-1757 or Study GS-US-401-1787 who are currently receiving continued treatment via named patient use may be enrolled for long-term safety monitoring.

Therefore, up to 376 subjects may be enrolled in the study.

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

ABC-DLBCL	activated B cell-like diffuse large B cell lymphoma
ADME	absorption, distribution, metabolism, and excretion
ADP	adenosine 5'-diphosphate sodium salt
AE	adverse event
Akt	serine/threonine protein kinase
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ANC	absolute neutrophil count
AST	aspartate transaminase
$AUC_{0\text{-}24h}$	mean exposure
AUC_{24h}	area under the concentration-time curve from time 0 to 24 h
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/serum concentration versus time curve over the dosing interval
BA	Bioavailability
BCR	B-cell receptor
BHCG	Beta-human chorionic gonadotropin
BID	twice daily
BTK	Bruton tyrosine kinase
BUN	Blood urea nitrogen
CARD11	caspase recruitment domain family, member 11
CBC	complete blood count
CH50	50% hemolytic complement activity
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma/serum concentration of drug
CMV	cyotmegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
C_{tau}	observed drug concentration at the end of the dosing interval
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	cytochrome P450 enzyme

CYP	cytochrome P
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC_{50}	estimated concentration of drug for a half maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ENTO	Entospletinib, GS-9973
EOT	end of treatment
eSAE	electronic Serious Adverse Event
FAS	full analysis set
FDA	Food and Drug Administration
FL	follicular lymphoma
FSH	follicle stimulating hormone
GCB	germinal center B-cell lymphoma
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HSP	hysterosalpingogram
IB	Investigator's Brochure
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICxx	concentration that results in xx% inhibition
IEC	independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	investigational medicinal product
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
IP	investigational product

IRC	Independent review committee
JAK	Janus kinase
LD	longest dimension
LPD	longest perpendicular dimension
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MZL	marginal zone lymphoma
ND	no disease
NA	not applicable
NCI	National Cancer Institute
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PI3K	phosphatidylinositol 3-kinase
PLCγ	phospholipase C gamma
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
PS	performance status
PR	partial response
PT	prothrombin time
PVE	Pharmacovigilance and Epidemiology
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	stable disease
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SPD	sum of the products of greatest perpendicular diameters
SRT	safety review team
StD	standard deviation

STD10	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (lz)
TEAE	treatment-emergent adverse event
TLR	Toll-like receptor
T_{max}	time (observed time point) of C_{max}
TNFR	tumor necrosis factor receptors
TTR	time to response
ULN	upper limit of normal
US	United States
UK	United Kingdom
WBC	white blood cell
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia

1. INTRODUCTION

1.1. Background

Non-Hodgkin lymphomas (NHL) 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 8th 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% to 25% and 6% to 10% of new lymphomas, respectively {Dreyling 2007}. B-cell chronic lymphocytic leukemia (CLL) is the most common of the chronic leukemias in adults with approximately 20,000 new cases per year in the European Union (EU) 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, SLL, 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 PFS is only 40% with activated B-cell (ABC) DLBCL compared to 74% with GCB-DLBCL. 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 (formerly 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 LLC 2016}. Additionally, transient clinical responses were observed in a pilot study of relapsed DLBCL, primarily in the non-GCB subtype {Wilson 2012}.

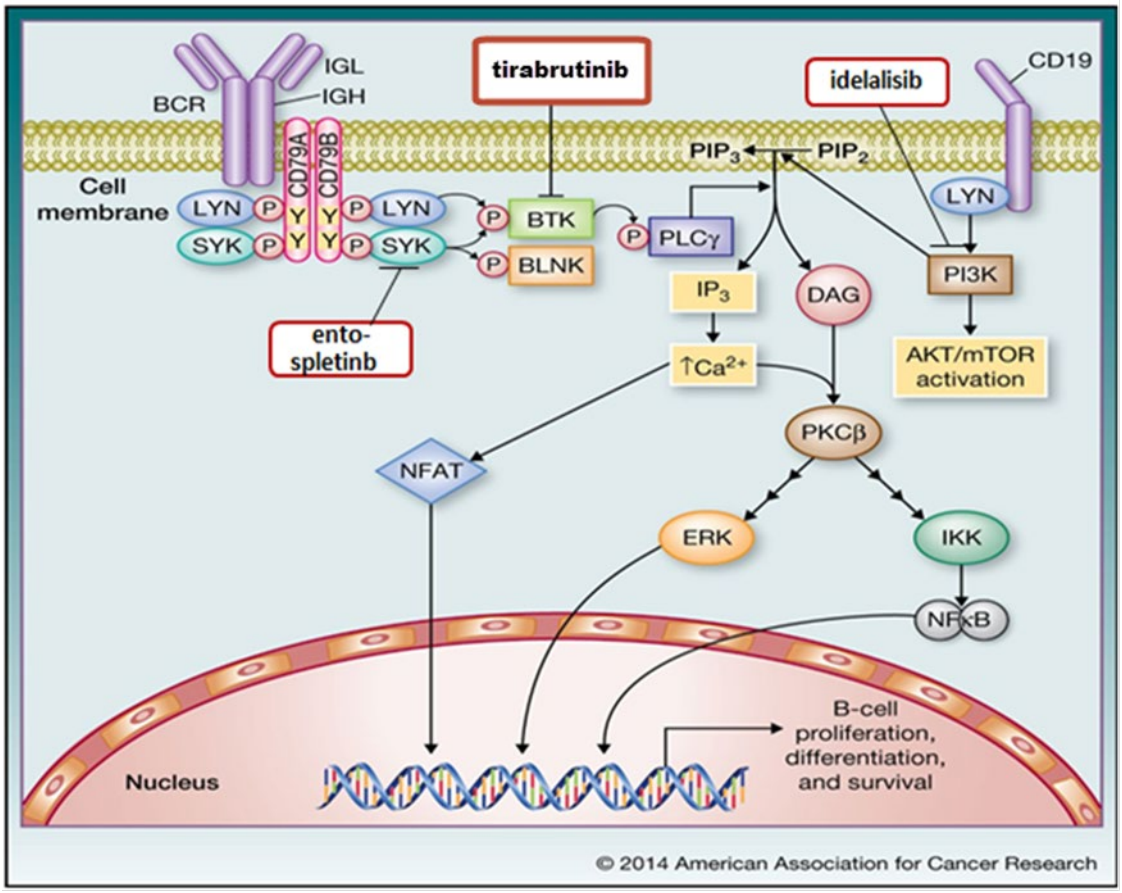
Tirabrutinib is an orally administered, potent and selective inhibitor of BTK initially evaluated in a Phase 1 single agent dose escalation study, ONO-4059POE001, conducted in the United Kingdom (UK) and France. As of January 2015, this study has enrolled and treated 90 subjects with relapsed CLL, non-GCB 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.

Another BTK inhibitor, ibrutinib, which is approved in the US and EU 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, they are considered potential risks for tirabrutinib.

Preliminary in vitro data from ABC-DLBCL, MCL, and CLL samples have shown additive or synergistic growth inhibition when combining the BTK inhibitor tirabrutinib and the phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib, and additive growth inhibition when combining the tirabrutinib with the spleen tyrosine kinase (SYK) inhibitor entospletinib, suggesting the potential for improved and more durable responses with combination treatment. Based on these data, tirabrutinib is being evaluated in combination with idelalisib or entospletinib for the treatment of the B-cell lymphoproliferative malignancies, including CLL, MCL, WM, FL, SLL, MZL, and non-GCB DLBCL.

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 and SLL in the EU for adult CLL patients who are previously untreated of have received at least 1 prior therapy. {Pharmacyclics LLC 2016}. 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), 17 subjects (60.7%) had a partial response (PR), and overall response was missing for 1 subject (3.6%). 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}. Overall response rates with these regimens in this patient population range from 28% to 63%, with median PFS of 3 to7 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 progression-free survival. 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 complete responses, and duration of response ranging from 2.8 to 18.8 months {Pharmacyclics LLC 2016}. In Study ONO-4059POE001, 1 of 2 subjects with WM responded to tirabrutinib.

1.2.2. Tirabrutinib Nonclinical 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. Potentiation of tirabrutinib activity was achieved in combination with other BCR inhibitors, idelalisib and entospletinib, and with a BCL-2 inhibitor. tirabrutinib efficacy in an in vivo model of ABC-DLBCL was enhanced when combined with anti-CD20 therapeutic monoclonal antibodies. Thus, evaluation in nonclinical models of B-cell malignancies demonstrated the nonclinical activity of tirabrutinib for inhibiting BCR- induced signaling, and suppressing the growth and survival of malignant B cells in vitro and in vivo.

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 (PBMCs) and in ABC-DLBCL-derived cell lines.

For further information on tirabrutinib, refer to the current edition of the Investigator's Brochure (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]-tirabrutinib 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 (t1/2) 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]-tirabrutinib 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 was found to be a substrate for the hepatic update transporters OATP1B1 and OATP1B3. Tirabrutinib is not a CYP inducer. Tirabrutinib inhibited CYP2C8, 2C9 and 2C19, the respective inhibition constant (Ki) values were 7.02, 8.31 and 14.4 μmol/L. Tirabrutinib resulted in mechanism based inhibition of CYP3A4/5 at 10 μmol/L. Tirabrutinib is a P-glycoprotein (P-gp) substrate, whereas tirabrutinib inhibited human P-gp, with an IC_{50} value of 26.8 μmol/L. In addition, tirabrutinib showed inhibitory potential for several other transporters including OAT3, OATP1B1, MATE1, OCT1 and OCT2.

Refer to the IB for additional information on tirabrutinib.

1.2.2.3. Nonclinical Toxicology

Nonclinical safety pharmacology studies of tirabrutinib showed no significant adverse effects on central nervous, respiratory or cardiovascular system functions at the exposure observed at tirabrutinib 320 mg once daily in humans.

Nonclinical safety pharmacology parameters measured in the single dose and 28-day repeat dose tirabrutinib studies in rats and cynomolgus monkeys showed no significant adverse effects on central nervous, respiratory, or cardiovascular system functions at the projected exposure of the human target dose of 320 mg once daily. In rats, CNS signs prior to death or euthanasia in moribund condition included decreased spontaneous activity, decreased respiratory rate (bradypnea), decreased stool volume, lacrimation and severe body weight decreases at a dose of ≥ 1000 mg/kg/day. In monkeys, morbidity and mortality was seen at doses of 1000mg/kg/day and 1 monkey was euthanized in moribund condition at a dose of 100 mg/kg/day CNS signs

ataxic gait, increased grooming, abnormal posture (sitting or prone position), decreased spontaneous activity, and/or somnolence. No microscopic correlates were identified in central or peripheral nervous system tissues or skeletal muscle. The no-observed-adverse-effect level (NOAEL) for CNS effects was 100 mg/kg in rats and 30 mg/kg in monkeys.

Increased risk of QT prolongation is not expected based on hERG studies, but subjects will be monitored closely for QT changes through frequent ECGs at or around C_{max} throughout this Phase 1 trial.

The following target organs/systems were identified in the nonclinical toxicology studies: pancreas in rats and monkeys, adrenal glands in rats, and lesser effects on the liver and thyroid gland in rats. Lesser effects on the liver and thyroid gland in rats are consistent with induction of metabolic enzymes in hepatocytes and compensatory hypertrophy of the thyroid gland in rats and of limited significance to humans.

In the pancreas, fibrosis in the islets of Langerhans and intra-islet regions and/or lobules, often accompanied by inflammation and hemorrhage were seen in rats after 4 weeks of repeated daily oral administration of doses ≥ 10 mg/kg/day tirabrutinib. The frequency of pancreatic findings increased with increasing dosing duration through 26 weeks of daily dosing. Microscopic findings were at least partially reversible after a 4- or 8-week non-dosing recovery period following up to 26 weeks of repeated daily dosing. There was no effect on exocrine pancreatic function as measured by blood amylase and lipase concentrations. Fasting insulin concentrations were decreased after 12 and 26 weeks of daily oral dosing with 300 mg/kg/day tirabrutinib, but were fully reversible after a 4 to 8 week non-dosing recovery period. In monkeys, focal interstitial hemorrhage in the pancreas and angiectasis in the islets were seen after 4-weeks of repeated daily administration of doses ≥ 10 mg/kg/day and at doses of ≥ 3 mg/kg in males and ≥ 1 mg/kg in females after 13 weeks of repeated daily administration. These findings were unassociated with inflammation or fibrosis in monkeys, unassociated with decreases in fasting insulin levels, reversible after a 4-week non-dosing recovery period.

Tirabrutinib inhibited the production of several pro-inflammatory cytokines by human immune cells ex vivo (eg, IL-6, TNF-α, MCP-1, MIP-1α, IL-1β, IL-8, and IFN-γ) but did not inhibit the production of pro-inflammatory cytokines including by isolated rat pancreatic islet cells in primary culture. In contrast, tirabrutinib increased the production of selected pro-inflammatory cytokines IL-1β and IFN-γ in rats and TNF-α and IL-8 monkey immune cells ex vivo. For this reason, it is considered unlikely that tirabrutinib administration will produce inflammatory changes in the human pancreas as compared with changes seen in the pancreas of rats and monkeys.

The NOAEL for pancreatic toxicity was 3 mg/kg/day in rats, 1 mg/kg/day in male monkeys, and less than 1 mg/kg/day in female monkeys. Mean exposure ($AUC_{0\text{-}24h}$) corresponding to these NOAELs were 686 ng•h/mL in rats and 286 ng•h/mL in monkeys. This corresponds to projected exposure margins of approximately 0.05-fold to 0.1-fold based on mean exposure of 5231 ng•h/mL $AUC_{0\text{-}24h}$ in humans at a dose of 320 mg administered orally once-daily.

Clinically significant changes in amylase, lipase, and glucose have not been noted in Study ONO-4059POE001, but these serum parameters will be monitored closely in clinical trials.

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 2 to 24 times the mean exposure in CLL patients receiving 80 or 600 mg tirabrutinib once daily. Tirabrutinib is not considered genotoxic and is considered not to have the potential to induce phototoxicity. In a TDAR assay in rats, tirabrutinib slightly decreased the anti-KLH IgM and/or IgG titers at doses of 10 mg/kg or higher. These changes were reversible and considered to be consistent with expected pharmacologic effects of BTK inhibition by tirabrutinib.

In pre-clinical testing, tirabrutinib significantly suppressed adenosine 5'-diphosphate sodium salt (ADP) and collagen-induced platelet aggregation in vitro at concentrations of ≥ 10 μmol/L in platelet-rich plasma derived from healthy human volunteers. The NOEL of 6 μmol/L (2.73 μg/mL) corresponds to an estimated exposure multiple of approximately 2.2-fold above the observed C_{max} of 1.26 μg/mL at 320 mg. In contrast, tirabrutinib did not induce platelet aggregation in platelet-rich plasma at concentrations up to the highest tested concentration of 100 μmol/L (45.5 μg/mL) in the absence of aggregation inducers. This corresponds to an estimated exposure multiple of approximately 79-fold above the observed C_{max} of 1.26 μg/mL at 320 mg.

The tirabrutinib clinical starting dose of 20 mg is ≥ 968- and 29- fold lower than the severely toxic dose in 10% of rats (STD10) and highest non-severely toxic dose (HNSTD) in the monkey when converted to a human equivalent dose (HED). Further, projected exposures at the proposed efficacious dose of 320 mg in the Phase 1 study are 2.8- to 8.6-fold (males/females) and 2.8-fold lower than exposures at the STD10 in the rat and HNSTD in the monkey. Overall, the nonclinical pharmacology and toxicology data support the potential clinical utility of tirabrutinib in the treatment of B-cell malignancies.

A more detailed summary of findings from studies of tirabrutinib in rats and dogs is available in the IB. Investigators should refer to this document prior to initiating therapy with tirabrutinib.

1.2.3. Clinical Trials of Tirabrutinib

As of 1 March 2016, 7 clinical studies of tirabrutinib are ongoing.

Ongoing Clinical Trials

- Study ONO-4059POE001, An Open-Label, Multi-Center, Non-Randomized Phase 1 Dose-Escalation Study to Investigate the Safety and Tolerability of tirabrutinib Given as Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin's Lymphoma (NHL) and relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). This study has completed enrollment and all remaining subjects had transitioned to the long-term follow-up study, GS-US-401-1787, as of 31 December 2015. Data analysis and clinical study report are in progress.

- Study ONO-4059-01: An open-label, multi-centre, non-randomised phase 1 dose-escalation study of tirabrutinib given as monotherapy in Japanese patients with relapsed/refractory B-NHL and CLL. No data are available to date.

- Study GS-US-401-1787, An Open-label Study to Assess the Long-term Safety and Efficacy of tirabrutinib in Subjects with Relapsed/Refractory B-cell malignancies: An open-label, multi-center, long term extension study comprised of subjects from ONO-4059POE001. No data are available to date. These subjects may transition to Study GS-US-401-1757 for long-term safety monitoring. Study GS-US-401-1787 will be closed once all subjects complete this transition.

- Study GS-US-401-1767, a Phase 1, partially-blinded, single-dose, crossover, multiple-cohort study of capsule and tablet formulations of tirabrutinib to evaluate the relative bioavailability (rBA), food effect, and interaction with a proton pump inhibitor (PPI), omeprazole, in healthy subjects. The data indicates that there was no difference in plasma exposure (C_{max} and AUC) of tirabrutinib between the capsule formulation and the 10% and 33% drug load formulation tablets when administered as a single 100-mg dose in the fasted state. This data supports switching from capsules to tablets without adjusting dosage. There was a slight increase in C_{max} when the low drug load (10% w/w) tablet and high drug load (33% w/w) tablet was administered with a high-fat meal (19% and 38%, respectively) versus a fasted state, and minimal change in AUC_{inf} (13% and 11% increase, respectively). There was a modest decrease in C_{max} (37%) and minimal change in AUC_{inf} (11% decrease) when the capsule was administered with a high-fat meal. Based on the wide dose/exposure range of tirabrutinib evaluated in subjects with B-cell malignancies that was shown to be well tolerated, the effect of food on tirabrutinib PK is not considered clinically relevant. As such, tirabrutinib may be administered without regard to food. Coadministration of omeprazole at 20 mg (with a 5-day pretreatment at 20 mg once daily) with the tirabrutinib capsule formulation resulted in no change in AUC with a slight decrease in C_{max} (20%) that was not considered clinically relevant. Coadministration of omeprazole 20 mg did not significantly alter the PK of the tirabrutinib low drug load (10% w/w) tablet. The 33% drug load formulation tablet was not evaluated in combination with omeprazole, but it is expected to perform similar to the low drug load (10% w/w) tablet formulation in combination with the gastric acid reducing agent omeprazole based on the comparable PK of the 2 formulations observed in the relative bioavailability and food effect cohorts. As such, tirabrutinib tablets may be co-administered with PPIs such as omeprazole.

- Study GS-US-401-1765, an open-label, crossover, Phase 1 study to evaluate the effects of a single dose and multiple doses of rifampin on the PK of tirabrutinib in healthy subjects. A total of 15 subjects were enrolled; 14 subjects completed the study with 1 subject choosing to withdraw consent. There was a small increase in tirabrutinib exposure (~30% increase in C_{max} and ~11% increase in AUC) when co-administered with a single dose of rifampin 600 mg. The slight increase in tirabrutinib exposure observed in combination with single dose rifampin is not considered clinically relevant and does not preclude coadministration of OATP1B1/1B3 inhibitors. The half-life of tirabrutinib was unchanged and the exposure (C_{max} and AUC) of tirabrutinib was significantly decreased (~70%) following multiple doses of the inducer rifampin. Exclusion of strong CYP3A4/P-gp inducers such as rifampin (i.e. PXR agonists) in combination with tirabrutinib in long-term clinical studies should be considered.

- Study GS-US-401-1768, a single-center, open-label, Phase 1, mass-balance study of tirabrutinib administered as a single, oral dose of radiolabeled [^{14}C]- tirabrutinib in healthy subjects. tirabrutinib and its metabolites were eliminated in both urine and stool, with slightly more recovery in stool. Tirabrutinib was extensively metabolized and primarily eliminated as metabolites. Tirabrutinib metabolism involved oxidation, reduction, hydrolysis, *N*-acetylation, sulfation, glutathione conjugation, and glucuronidation.
- Study GS-US-407-1833, an ongoing Phase 1, double-blinded, placebo-controlled, randomized study evaluating the safety and pharmacokinetics of tirabrutinib in two parts in healthy volunteers and subjects with rheumatoid arthritis (RA). The study consists of three planned cohorts: 10 healthy subjects randomized to receive 20 mg tirabrutinib (8 subjects) or tirabrutinib placebo-to-match-(2 subjects) orally once daily for 1 week; 10 healthy subjects randomized to receive 10 mg tirabrutinib (8 subjects) or tirabrutinib placebo-to-match (2 subjects) orally twice daily for 1 week; and 20 subjects with RA randomized to receive 20 mg tirabrutinib (16 subjects) or tirabrutinib placebo-to-match (4 subjects) orally once daily for 4 weeks. The primary objectives are to assess the safety, tolerability and PK of tirabrutinib in healthy subjects and subjects with RA. This study is currently enrolling the RA cohort.

For additional information, refer to the tirabrutinib IB.

1.3. Idelalisib

PI3Kδ is a central signaling enzyme that mediates the effects of multiple receptors and is critical for primary survival, proliferation, and homing signaling pathways active in malignant B-cells. Idelalisib (Zydelig®) is a PI3Kδ inhibitor which received accelerated approval in the US for the treatment of patients with relapsed FL and SLL who have received at least 2 prior systemic therapies and full approval in combination with rituximab for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Responses for SLL and FL were reported at 58% (0% CR) and 54% (8% CR) respectively with a duration of response of 11.9 months in SLL and not evaluable in FL. In CLL, the hazard ratio for PFS was 0.18 (95% CI; 0.10, 0.32) compared to rituximab alone.{Brown 2014, Flinn 2014, Furman 2014}. Idelalisib as monotherapy or in combination with other agents (such as bendamustine, chlorambucil) and immunotherapy (rituximab, ofatumumab) has been shown to be tolerable and demonstrated clinical efficacy in clinical trials in patients with iNHL, CLL, and other hematological malignancies.

The approved idelalisib dosing regimen is 150 mg twice daily (BID) administered as monotherapy or in combination with rituximab. Dose modification to 100 mg BID due to toxicity is included within prescribing guidelines.

Idelalisib is metabolized primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117. Idelalisib is not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6, CYP3A, or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Idelalisib's primary metabolite, GS-563117, is also not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6 or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

The metabolite, GS-563117, however, is a mechanism-based inhibitor of CYP3A (K_I = 0.18 µM, k_{inact} = 0.033 min-1) which may have implications for coadministration with tirabrutinib which has been identified as a CYP3A substrate. In a clinical study the coadministration of idelalisib with midazolam, a probe CYP3A substrate, resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam due to the CYP3A inhibition by GS-563117. Accordingly, idelalisib is considered to be a strong CYP3A inhibitor.

For current information about idelalisib (Zydelig®), refer to the idelalisib IB.

1.4. Entospletinib

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

Studies have suggested a role for the dysregulation of SYK in B-cell malignancies. SYK is expressed in B cells and is essentially involved in multiple signal transduction pathways downstream of the BCR. SYK trans-autophosphorylates and activates effector molecules such as phospholipase C gamma (PLCγ), PI3K, and mitogen-activated protein kinase (MAPK), and their associated signaling pathways, to induce an array of B-cell responses, including: proliferation, survival, differentiation, and apoptosis. In B-cell malignancies, including CLL, DLBCL, FL, MCL, MZL, and B-lineage acute lymphoblastic leukemia {Efremov 2011}, the BCR can deliver antigen-independent signals that have also been postulated to require SYK activity. Therefore, inhibition of BCR-mediated SYK activity is an attractive therapeutic target which could inhibit the proliferation and survival of malignant B cells.

Preclinical evidence suggests that SYK inhibition may have independent benefit from BTK inhibition in B-cell malignancies. As a proof-of-concept in vitro, treating CLL B cells from an ibrutinib-resistant patient with a SYK inhibitor resulted in a potent anti-proliferative response.

As of Amendment 9, Gilead has conducted an overall assessment of the entospletinib development program and has made a decision to discontinue entospletinib from further development. Therefore, supply of entospletinib to subjects on this study will be limited to 31 December 2020. Subjects who are currently treated with entospletinib as part of a combination regimen with tirabrutinib will stop receiving entospletinib by 31 December 2020 but may continue to be treated with tirabrutinib monotherapy.

1.4.1. Nonclinical Pharmacology

Entospletinib is an adenosine triphosphate (ATP) competitive inhibitor of SYK with an EC_{50} of 8.5 ± 3.6 nM. Entospletinib binds in the ATP pocket of the SYK active site and disrupts the kinase activity of the enzyme. Kinase selectivity profiling showed a > 14-fold selectivity of entospletinib for SYK versus 359 non-mutant kinases and no significant binding (< 50%) to 67 ion channels, transporters, and receptors screened at 1 µM entospletinib. No significant off- target or adverse pharmacological effects of clinical relevance were noted in preclinical evaluations.

Entospletinib was evaluated in a battery of safety pharmacology studies. The IC_{50} for the inhibitory effect of entospletinib on human ether-à-go-go-related gene (hERG) potassium current in vitro was estimated to be > 1 μM. In dogs, entospletinib caused small increases in heart rates at doses ≥ 15 mg/kg, but had no effects on electrocardiograms (ECGs) or blood pressure at up to 150 mg/kg, the highest dose evaluated. Because entospletinib is 97.3% protein bound in human plasma and the total plasma concentration of entospletinib is in the 1 to 3 micromolar range, with a corresponding range of free entospletinib of 27 to 81 nM, it is unlikely that a clinically relevant effect on QT interval would occur.

No entospletinib related effects were noted on neurological or respiratory function in rats at doses up to 1000 mg/kg.

For further information on nonclinical pharmacology, refer to the entospletinib IB.

1.4.2. Nonclinical ADME

High bioavailability of entospletinib was observed in nonclinical species. Consistent with this finding, entospletinib showed high permeability across Caco-2 monolayers and low potential for efflux. Despite high plasma protein binding, entospletinib had a moderate volume of distribution, close to that of total body water. The systemic clearance was low in rats, moderate in dogs, and moderate to high in monkeys.

Single-day dose escalation of entospletinib administered orally to rats, dogs, and monkeys showed a less than dose proportional increase in entospletinib systemic exposure in all species over the dose ranges tested.

Entospletinib showed good metabolic stability with human hepatic material in vitro. Therefore, clearance through metabolism in humans is expected to be low. The primary routes of metabolism of entospletinib involved oxidative opening of the morpholine ring as well as further oxidation or conjugation. In vitro data indicates entospletinib is primarily metabolized by CYP2C9 and to a lesser extent by CYP3A and CYP1A2. Metabolism followed by biliary excretion is likely the major route of elimination of entospletinib and its metabolites, as < 5% of the radiolabeled dose administered orally to rats was recovered in urine.

Entospletinib is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. Entospletinib is also an inhibitor of the uptake transporters OATP1B1 and OATP1B3 as well as the efflux transporters P-gp and BCRP with an IC_{50} value of approximately 2 μM for each of these transporters. Entospletinib may affect the activity of these transporters in vivo at the expected clinical concentrations and could transiently affect the disposition of other drugs, although high plasma protein binding (> 97%) may mitigate some of the potential drug-drug interactions at clinically relevant doses.

Entospletinib is unlikely to cause clinically relevant drug interactions through inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and is not a substrate for OATP1B1, OATP1B3, or OCT1.

For further information on nonclinical drug metabolism and pharmacokinetics, refer to the entospletinib IB.

1.4.3. Nonclinical Toxicology

Entospletinib was well tolerated in single-dose studies at doses of 1000 mg/kg in dogs, and cynomolgus monkeys. In repeat-dose studies in rats, entospletinib was well tolerated for 14 days at doses of 1000 mg/kg/day and for 4 weeks at 50 mg/kg/day. In dogs, entospletinib was well tolerated for 7 days at 50 mg/kg/day and for 4 weeks at 10 mg/kg/day. In cynomolgus monkeys, entospletinib was well tolerated for 13 weeks at 100 mg/kg/day which was the highest dose tested as dosing higher than that did not increase exposure. In rabbits, it was tolerated for 7 days at 300 mg/kg/day.

The target organ(s) of toxicity identified in rats was the duodenum (enteropathy), and in rabbits and dogs were predominantly the gastrointestinal tract (hemorrhage and/or inflammation) and lymphoid organs. No target organs were identified in the cynomolgus monkeys.

Additional organs potentially affected in individual dogs at higher doses included gallbladder, pancreas (rabbits and dogs), urinary bladder, and epididymis. Gastrointestinal tract toxicity in rats, rabbits, and dogs was associated with decreased food consumption and/or decreased body weight or body weight gain. However, decreased food consumption and body weight changes, in rabbits and dogs also occurred at doses lower than those which showed histological evidence of gastrointestinal toxicity.

Increases in total and/or indirect bilirubin in rats, rabbits, and dogs were observed at ≥ 30 mg/kg/day and may have been due to the inhibition of the enzyme UGT1A1. As no histological evidence of hepatobiliary toxicity was noted concurrently with bilirubin increases in entospletinib-treated rats or dogs, and entospletinib levels above the IC_{50} for UGT1A1 were achieved in serum, this seems a plausible mechanism for the noted increases in bilirubin.

Hemorrhage and/or sinus erythrocytosis in lymph nodes with decreases in red cell mass in individual animals was noted in rabbits and dogs, but not in rats or cynomolgus monkeys. Although the mechanism for these changes is not clear, rodents with SYK deficiency or SYK-deficient bone marrow have been associated with hemorrhage, the latter in the presence of normal bleeding times, suggesting normal platelet function {Turner 2000}. No evidence of altered coagulation parameters were noted at any dose level in the entospletinib nonclinical studies and no biologically relevant effects were noted in an in vitro study of platelet aggregation. Other inhibitors of SYK have been found to have no effect on platelet function at efficacious dose levels in patients with rheumatoid arthritis (RA) as determined by ex vivo assays, and similarly, SYK inhibition has not been found to affect bleeding time in rodents {Braselmann 2006}.

Adverse effects on lymphoid tissues including spleen, lymph nodes, and/or the thymus were noted in rabbits and dogs, but not in rats or cynomolgus monkeys despite higher exposures achieved in rats and monkeys. Recently, published data demonstrated that species-specific lymphoid changes can occur in dogs, but not in rats, cynomolgus monkeys, or humans treated

with small molecule kinase inhibitors that inhibit pathways that overlap with SYK signaling pathways; rabbits were not evaluated {Morris 2010}. Lymphoid toxicity also occurs in dogs treated with p38α MAPK inhibitors, but not in rats or cynomolgus monkeys despite higher exposure levels achieved in these species. There has been no evidence of significant immunotoxicity in clinical trials with p38α MAPK inhibitors. The relevance of the findings in rabbits and dogs to humans is unknown.

Entospletinib was negative in bacterial mutation, in vitro chromosomal aberration, and rat micronucleus assays and is, therefore, considered non-genotoxic. Dose-range finding embryo-fetal developmental toxicity studies have been completed in rats and rabbits. Maternal toxicity was demonstrated by dose-dependent decreases in the body weight gains of the dams. Dose-dependent developmental findings included increased incidence of early and late fetal resorptions at 500 mg/kg/day (rat only) and reduced fetal weights (500 and ≥ 15 mg/kg/day; rats and rabbits, respectively) which correlated with the maternal toxicity.

For further information on nonclinical toxicology, refer to the entospletinib IB.

1.4.4. Clinical Trials

Entospletinib has been administered to 540 subjects (328 healthy subjects, 7 subjects with RA, 76 subjects with CLL, and 155 subjects with NHL) in 11 Phase 1 and Phase 2 clinical studies. Single agent efficacy has been demonstrated with entospletinib in subjects with relapsed or refractory hematologic malignancies (CLL, MCL, DLBCL, FL, LP, WM, SLL, or MZL). PFS rates are 70.1% (95% CI: 51.3%, 82.7%) at 24 weeks for subjects with CLL (n=41) and 50.2% (95% CI: 29.3%, 67.9%) at 24 weeks in subjects with FL (n=41).

The most common AEs (observed in ≥ 15% of subjects) in hematology patients receiving entospletinib alone (n = 186) include fatigue (52.5%), nausea (43.3%), diarrhea (40.8%), decreased appetite (27.1%), constipation (23.8%); cough (22.5.0%), dizziness (19.6%), pyrexia (18.8%), vomiting (18.3%), headache (17.9%), dyspnea (16.7%), insomnia (15.8%), dehydration (15.0%), and upper respiratory infection (15.0%). Thirty four subjects (14.2%) reported an AE of rash.

Entospletinib is expected to produce asymptomatic and transient elevations of unconjugated (indirect) bilirubin due to inhibition of UGT1A1. In studies of subjects with hematologic malignancies, 9 of 252 subjects had elevations of direct bilirubin with the onset of elevation ranging from Day 8 to 85, except for 1 subject at Day 169. Bilirubin elevations were generally self-limited and did not result in discontinuation of entospletinib.

In a phase 2, open label study evaluating the efficacy, safety, tolerability, and pharmacodynamics of the combination of entospletinib (MSA formulation) and idelalisib administered twice daily over multiple 28 day cycles to subjects with relapsed or refractory lymphoid malignancies, pneumonitis was reported in 12 of 66 subjects (18.2%), leading to the discontinuation of further evaluation of this combination. All subjects were to receive treatment with entospletinib and idelalisib twice daily under fasted conditions and the study allowed intra-subject dose escalations every 2 weeks. Of the 12 pneumonitis AEs, 11 (91.7%) were SAEs, 7 were Grade 3, 2 were

Grade 4, and 2 were Grade 5. The protocol was amended to allow a subset of subjects to receive monotherapy with entospletinib after a 14 to 28 day washout period with no subsequent cases of pneumonitis reported. Pneumonitis has not been identified as a risk with entospletinib monotherapy.

Other AEs of interest included diarrhea (28.8%), rash (16.7%) and transaminase increase (21.2%). Increased transaminases were noted in some subjects approximately 2 weeks after completion of study drug.

For current information about clinical studies, refer to the entospletinib IB.

1.5. Obinutuzumab

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

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

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

The safety and efficacy of obinutuzumab combined with idelalisib 150 mg twice daily or chlorambucil has been evaluated in a randomized, open-label Phase 3 study (GS-US-312-0118). The safety run-in of 8 subjects treated with obinutuzumab and idelalisib with a follow-up duration ranging from 37 to 177 days underwent review in October 2015. Grade 3 or 4 treatment emergent AEs included neutropenia (n=4), thrombocytopenia (n = 2), anemia (n = 1), transaminase elevations (n = 3) and infusion reactions (n = 1) which were all manageable with conservative management or temporary treatment interruption and subsequent re-initiation of idelalisib.

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

Obinutuzumab has also demonstrated an improvement in PFS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.34 - 0.68; $P < .0001$) in patients with relapsed FL when combined with bendamustine compared to bendamustine alone. Median progression-free survival was not reached in the obinutuzumab group, but was 13.8 months in the group receiving bendamustine alone. The most common Grade 3/4 hematologic adverse events included neutropenia (in 33.0% of the combination group and 26.3% of the monotherapy group), thrombocytopenia (10.8% vs 16.2%), anemia (7.7% vs 10.1%), febrile neutropenia (4.6% vs 3.5%), and leukopenia (1.0% vs 1.5%). The most common non-hematologic adverse events included vomiting, decreased appetite, and fatigue.

For further information on obinutuzumab, refer to the approved local prescribing information.

1.6. Rationale for This Study

Despite an increase in the therapeutic options for B-cell lymphoma in the relapsed and refractory setting, complete responses are uncommon and treatment is usually administered chronically until toxicity or progression. An unmet need remains for novel targeted therapies that might improve complete response rates, improve progression free and overall survival, are associated with less toxicity, and/or require a shorter duration of therapy.

Although more than half of patients have demonstrated improved PFS upon treatment with either ibrutinib (CLL, MCL, WM) or idelalisib (CLL, FL, SLL), as monotherapy, neither of these therapies alone are curative and complete responses are uncommon. Additionally, these and alternative agents are usually chronically administered until there is evidence of toxicity, intolerability, or disease progression, highlighting the need for more effective therapies across these diseases.

Tirabrutinib, idelalisib and entospletinib each show significant single agent clinical activity in a variety of B-cell lymphoproliferative diseases.

Pre-liminary *in vitro* data from ABC-DLBCL, MCL, and CLL cells have shown additive or synergistic growth inhibition when combining tirabrutinib and idelalisib or entospletinib, suggesting the potential for improved and more durable responses with combination treatment. While single mutations in drug targets have been shown to be sufficient for resistance to

single-agent therapy, combination therapy has the potential to improve duration of response by creating a higher threshold for the emergence of drug resistant malignant clones. Even with doses reduced from those used as single-agents, combining tirabrutinib and idelalisib in vitro demonstrated efficacy, supporting the possibility that low dose combinations of targeted agents may improve efficacy with less toxicity.

The addition of an anti-CD20 antibody to CLL, iNHL, and DLBCL therapy has established benefit, with the potential superiority of obinutuzumab compared with rituximab demonstrated in CLL and iNHL (Genentech Inc 2016).

1.6.1. Dose Rationale

Tirabrutinib has been evaluated in a Phase 1 study conducted in the UK and France. As of the last formal data cutoff period of 30 April 2014, 69 subjects with CLL or NHL had received doses from 20 to 600 mg once daily. According to investigator reported IWCLL criteria (using a modified definition of partial response (PR) which includes PR with lymphocytosis), the CLL population demonstrated rapid reductions in lymphadenopathy between Cycle 1 and Cycle 3, accompanied by an increase in absolute lymphocyte count and durable responses over treatment up to 2 years. Subjects who demonstrated a very good clinical response during the first 6 months of treatment, but who started to exhibit signs of progression or who met the criteria for disease progression, but still showed evidence of clinical benefit in the opinion of the treating investigator prior to the end of the 6 months response assessment visit, had the option to increase their dose at, or after, their 6 month visit. The dose of tirabrutinib administered in these situations was limited to the highest dose that had been found to be safe and well tolerated in the dose escalation process up to that date. The ORR in CLL was 84% (21/25) and responses in NHL were also observed; 41% (7/17) in non-GCB-DLBCL, 60% (6/10) in MCL and WM 50% (1/2). No responses were observed in small subsets of FL (n =5), MZL (n = 1) and SLL (n = 1).

In Study ONO-4059POE001, 480 mg once daily was identified as the MTD in the NHL cohort, based on DLT events of rash and non-immune reaction at the 600 mg once daily dose of tirabrutinib. No MTD was identified in the CLL cohort at dosing up to 600 mg once daily. There was no observed relationship (or trend) between the initial dose (20, 40, 80, 120, 240, 360, 400, and 480 mg) and the frequency of SAEs, overall AEs, drug-related AEs or Grade 3-5 AEs, in either disease cohort.

Based on the promising early phase results, Gilead proposes to evaluate tirabrutinib both as a single agent in CLL and in combination with the PI3Kδ inhibitor, idelalisib, or the SYK inhibitor, entospletinib, in the following B-cell malignant lymphoproliferative diseases: CLL, SLL, MCL, WM, FL, MZL, and DLBCL.

Subjects will be administered tirabrutinib once or twice daily and either idelalisib twice daily or entospletinib once or twice daily (based on the dose escalation level assigned), to evaluate the safety, tolerability, PK, and pharmacodynamics of tirabrutinib in combination with idelalisib or entospletinib. Obinutuzumab will be administered at the approved 1000 mg dose and schedule. The study will evaluate up to 376 subjects with relapsed or refractory FL, SLL, MCL, MZL or

WM who have received at least 2 prior therapies and for non-GCB-DLBCL (who are not transplant candidates) or CLL, at least 1 prior therapy. All subjects must have measurable disease at baseline by standard criteria. In addition, as of Amendment 9, up to 8 additional subjects from Study GS-US-401-1787 or previously enrolled in this study or Study GS-US-401-1787 who are currently receiving continued treatment via named patient use may be enrolled for long-term safety monitoring.

In all arms of the study, antitumor activity will be evaluated at baseline and at appropriate intervals for specific malignancies using standard response criteria, with adjustment for redistribution lymphocytosis, consistent with the known effects of BTK and PI3Kδ inhibition. The results of this study will provide information on the safety profile of tirabrutinib alone and combined with idelalisib or entospletinib and obinutuzumab, and subjects will be monitored with regard to the incidence of AEs of interest, including diarrhea/colitis, transaminase elevation, rash, and pneumonitis, which have been reported with idelalisib and/or entospletinib administration and which may occur beyond the standard 28-day DLT window. Intra-subject dose escalation will not be permitted to evaluate the long-term safety of each dose level.

Dose Rationale for tirabrutinib and idelalisib

This study is a Phase 1b sequential dose-escalation study using a 3+3 design (maximum of 6 subjects/cohort) to evaluate approximately 5 dose levels. The initial dose level tested will be 20 mg tirabrutinib administered once daily combined with 50 mg of idelalisib administered twice daily. Tirabrutinib is a CYP3A4 substrate; co-administration with idelalisib, a CYP3A4 inhibitor, may increase the exposure of tirabrutinib. Idelalisib is a strong CYP3A inhibitor at the registered dose of 150 mg twice daily, but is expected to be a moderate CYP3A inhibitor at the lower dose of 50 mg twice daily. A physiologically based pharmacokinetic model (PBPK) was used to simulate the drug-drug interaction of idelalisib 50 mg twice daily with the CYP3A4-sensitive substrate midazolam; plasma exposure (C_{max} and AUC) of midazolam increased 1.8- and 2.6-fold, respectively. Thus, the exposure of 20 mg tirabrutinib once daily when administered with 50 mg idelalisib twice daily may be similar to the exposure of approximately 36 mg (estimate of C_{max}) to 52 mg (estimate of AUC) tirabrutinib dosed as a single agent. Responses were observed in both CLL (1/3) and NHL (1/3) cohorts at 40 mg once daily in Study ONO-4059POE001and this dose is 1/12th of the MTD observed for the single agent in the NHL cohort. The initial idelalisib dose is proposed to be 50 mg BID, which is the lowest dose which demonstrated efficacy in a Phase 1 study of subjects with NHL or CLL. As preclinical data suggest synergistic effects in some cell lines, greater efficacy with less toxicity may be observed at doses which are lower than the dose used when either agent is given as monotherapy. Additional dosing regimens of idelalisib (up to 100 mg once daily) may also be considered based on emerging safety and efficacy data.

The dose escalation for the combination of tirabrutinib and idelalisib will proceed with idelalisib remaining at 50 mg twice daily, while tirabrutinib will be increased by doses of ≤ 100% in each cohort. Once daily and twice daily dosing of tirabrutinib will be tested, as preclinical data suggests that twice daily dosing of tirabrutinib may provide greater efficacy than once daily dosing {Yoshizawa 2014}. The MTD for tirabrutinib once-daily will be determined separately from the MTD for tirabrutinib twice-daily.

Dose Rationale for tirabrutinib and entospletinib

This study is a Phase 1b sequential dose-escalation study using a 3+3 design. The initial dose level tested in the tirabrutinib and entospletinib arm is proposed to be 40 mg tirabrutinib administered once daily combined with 200 mg of entospletinib administered once daily. This initial dose of tirabrutinib is chosen as a potentially minimally effective dose based on responses observed in both CLL (1/3) and NHL (1/3) cohorts at 40 mg of tirabrutinib once daily in Study ONO-4059POE001; this dose is 1/12th of the MTD observed for the single agent in the NHL cohort. Given that the entospletinib is not expected to lead to a clinically relevant change in tirabrutinib PK, the exposure of tirabrutinib at the 40 mg once daily in combination with entospletinib is expected to be similar to the exposure of tirabrutinib at the 20 mg once daily in combination with idelalisib.

The initial dose of entospletinib in the combination arm will be 200 mg once daily. Entospletinib has been well tolerated at doses of up to 800 mg twice daily in patients with CLL. The dose and schedule used in the monotherapy setting resulted in consistent inhibition of a biomarker of SYK activity over the dosing interval. However, in vitro data indicates there may be additive or synergistic inhibition when entospletinib is combined with tirabrutinib. A 200 mg once daily dose of entospletinib is expected to provide plasma concentrations above EC_{50} for approximately 12 hours a day and it is anticipated that target inhibition by entospletinib will be approximately 24% at trough drug levels. Additionally, a starting dose of 200 mg of entospletinib once daily is 1/8th the total daily dose that has been shown to be tolerated in patients. Additional dose levels/regimens of entospletinib (up to 400 mg once daily), may be studied based on emerging safety, efficacy, pharmacodynamic, and PK data.

The dose escalation for the combination of tirabrutinib and entospletinib will proceed in 2 arms with entospletinib remaining at 200 mg once daily in Arm A, while tirabrutinib will be increased by ≤ 100% in each cohort. In Arm B, tirabrutinib will remain at 40 mg once daily, while total daily doses of entospletinib will be increased by ≤ 100% in each cohort. Additional dose level combinations may be evaluated based on emerging safety, efficacy, pharmacodynamic, and PK data.

Dose Rationale for Single Agent tirabrutinib in Subjects with CLL

The Phase 1 study, ONO-4059POE001 enrolled approximately 3 subjects with CLL at each dose level across a wide range of doses (20 mg to 600 mg once daily; total n = 28) and did not identify an MTD. No clear association between dose and toxicity was observed, but the small number of subjects at each dose level limited the ability to inform any firm conclusions. It is reassuring, however, that no SAE of a bleeding event in the CLL cohort occurred at a dose of < 400 mg.

Evaluating an association of dose and efficacy was similarly limited by the small numbers of subjects in the ONO/GS-4059POE001 study; responses were observed in CLL at all dose levels but at doses ≥ 80 mg, all evaluable subjects reported a response, suggesting that 80 mg may be required in the single agent setting. In this ongoing study (GS-US-401-1757), early limited data suggests that full BTK occupancy of PBMCs requires once daily dosing of ≥ 40 mg. Taken together, this limited information suggests for subjects with CLL, single agent tirabrutinib at 80 mg once daily may be an appropriate dose to maximize efficacy and minimize toxicity. The

addition of this single-agent arm with dose adjustments down to 40 mg once daily for toxicity and up to 160 mg once daily for lack of response (or progression) after at least 24 weeks of therapy will provide additional important data on the safety, tolerability and efficacy of the 80 mg dose of tirabrutinib in the CLL patient population; which would be also important to demonstrate its contribution to the proposed combinations.

1.6.2. Risk/Benefit Assessment for the Study

Tirabrutinib

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

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

Please refer to the IB for more information.

Idelalisib

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

Patients with lymphoid cancers receiving idelalisib have developed serious and fatal infections during therapy. Opportunistic infections, most notably PJP and CMV infection, have been reported with idelalisib, particularly in the context of concurrent myelosuppressive therapy such as rituximab and bendamustine.

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

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

Entospletinib

Entospletinib has been well tolerated across the 11 clinical studies in which it is being evaluated. Treatment emergent AEs commonly reported across the studies involving healthy volunteer subjects include headache, somnolence, and GI symptoms (nausea and abdominal pain), all of which were mild and reversible.

Increased transaminases were noted in some subjects and were reversible.

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

Spleen tyrosine kinase deficiency and SYK-deficient bone marrow in rodents have been associated with hemorrhage. In an ex vivo platelet function assay, entospletinib showed no biologically relevant inhibition or activation of platelets at concentrations up to 12.3 μM. No evidence of altered coagulation parameters was noted at any dose level in the entospletinib nonclinical studies.

In rats the predominant organ affected was the duodenum, and in rabbits and dogs the gastrointestinal tract and lymphoid organs. No target organs were identified in the cynomolgus monkey. Oral administration of entospletinib to rats for up to 26 weeks or cynomolgus monkeys for up to 39 weeks showed no evidence of GI toxicity or lymphoid changes at exposures which overlapped with or exceeded those in dogs. Clinical assessments will monitor for signs and symptoms of infection, hemorrhage, GI distress, and changes in clinical pathology parameters (changes in hemoglobin, neutrophils, lymphocytes, liver enzymes, and total and indirect bilirubin) that could occur after entospletinib administration. Because evidence of lymphoid tissue depletion was noted in rabbits and dogs at high doses, clinical assessments will also include monitoring for signs and symptoms of infection.

Obinutuzumab

Obinutuzumab is an anti-CD20 monoclonal antibody approved in the US and EU for use in combination with chlorambucil for the treatment of patients with previously untreated CLL. It is also approved for use in the US and EU in combination with bendamustine for the treatment of patients with FL who are relapsed or refractory to rituximab-containing regimen.

The most common obinutuzumab-related adverse events are infusion related reactions and tumor lysis syndrome most commonly during the initial administration. Some patients receiving obinutuzumab have experienced cytopenias or infections. Obinutuzumab use has been associated with hepatitis B virus (HBV) reactivation and very rare cases of progressive multifocal leukoencephalopathy.

Mitigation strategies are defined in the study design. To reduce the incidence and severity of obinutuzumab-related infusion reactions, established premedication regimens and infusion modification algorithms have been included (Section 5.3.1). To mitigate the risk of *Pneumocystis jirovecii* pneumonia, antibiotic prophylaxis is required (Section 7.5.1.6)

To mitigate the risk of HBV reactivation, subjects will be excluded who screen positive for a prior history of or evidence of hepatitis B infection.

Specific instructions for supportive care in response to myelosuppression are described. Investigators are instructed to institute prophylaxis and monitoring for tumor lysis syndrome for subjects with a high tumor burden, high circulating lymphocyte count (>25x10^9/L) or renal impairment (CrCl<70mL/min).

Combination

No potentially curative therapy exists for the patient population to be evaluated in this study. Dosing of each component in the dose escalation phase of this study starts at the lowest dose which may provide benefit to patients; the starting dose for tirabrutinib is < 1/12th of the MTD in monotherapy study, the starting dose of idelalisib is 1/3rd of the approved dose, and starting dose of entospletinib is 1/4th of the dose demonstrated to be tolerable in monotherapy study (no MTD identified).

Assessments for AEs and monitoring for laboratory abnormalities will be conducted on Days 1, 8, 15, and 22 of the first 28-day cycle. As toxicities related to study drug may manifest beyond the 28-day DLT window, no intra-subject dose escalation is allowed and frequent protocol mandated monitoring continues for all subjects beyond the first 28-day cycle: every 14 days until Week 24, then every 4 weeks, at the end of treatment, and at the 30-day safety follow-up visit. Physical examinations will be performed on Day 1 of each 28-day cycle until end of treatment followed by a 30-day safety follow-up visit. This monitoring frequency is considered to be sufficient to identify potential AEs as they emerge.

In addition to initiating at low doses and disallowing intra-subject dose escalation, the expansion arms of up to approximately 30 subjects with a single disease type will provide the opportunity for close evaluation for potential long-term toxicities such as liver function test (LFT) elevations, rash, diarrhea, fatigue, or pneumonitis. Should they occur, these important safety events are expected to be relatively infrequent and therefore a sample size of up to approximately 30 subjects will allow a larger degree of confidence in the safety and tolerability of these combinations prior to proceeding with future development. Additionally, guidelines for managing these AEs have been incorporated into this protocol including actions to be taken in response to toxicity including interruption, discontinuation, dose modification, and rechallenge.

In addition, the inclusion and exclusion criteria are designed to ensure subjects have acceptable organ function to be eligible for this study such that confounding significant co-morbidities are excluded. Subjects enrolling in the study are required to receive PJP prophylaxis per Section 5.3.2.1 and not have evidence of active CMV infection. Surveillance for active disease will occur approximately every 4 weeks throughout the course of treatment and if there is evidence of an active infection by clinical and laboratory assessments, the subject must permanently discontinue idelalisib and receive anti-CMV treatment according to local guidelines. Study medications will continue until disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment.

1.6.3. Potential Benefits

The potential benefits to a subject participating in this study include a higher likelihood of achieving a partial or complete response, and longer durability of the response compared to other available therapies.

1.7. Compliance

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

2. OBJECTIVES

The primary objectives of the study are:

For the dose escalation phase:

- To characterize the safety and tolerability of tirabrutinib combined with idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To characterize the safety and tolerability of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies

For the dose expansion phase:

- To evaluate the preliminary efficacy of tirabrutinib combined with idelalisib or entospletinib in B-cell lymphoproliferative malignancies (subtype[s] to be determined based on the dose escalation phase)
- To characterize the safety and tolerability and evaluate the preliminary efficacy of single-agent tirabrutinib in subjects with relapsed or refractory CLL.
- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies

For long-term safety monitoring phase:

- To evaluate the long-term safety of tirabrutinib as a monotherapy, and in combination with idelalisib or entospletinib, with or without obinutuzumab, in subjects with relapsed or refractory B-cell lymphoproliferative malignancies.

The secondary objectives of the study are:

For the dose escalation phase:

- To evaluate the preliminary efficacy of tirabrutinib combined with idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the pharmacokinetics (PK) of tirabrutinib administered alone and in combination with idelalisib or entospletinib in subjects with relapsed or refractory B-cell lymphoproliferative malignancies

For the dose expansion phase:

- To further characterize the safety and tolerability of tirabrutinib combined with idelalisib or entospletinib in subjects with a specific tumor subtype (to be determined)
- To further characterize the safety and tolerability of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in subjects with a specific tumor subtype (to be determined)
- To further characterize the safety and tolerability of tirabrutinib alone administered at 80 mg once daily in subjects with relapsed or refractory CLL.

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3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.1.

3.2. Study Design

This is a Phase 1b, open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary efficacy of tirabrutinib in combination with idelalisib or entospletinib in subjects with B-cell lymphoproliferative malignancies who have refractory or relapsed disease. The safety, tolerability, pharmacodynamics and efficacy of tirabrutinib in combination with obinutuzumab and idelalisib or entospletinib will also be evaluated in subjects with relapsed or refractory B-cell lymphoproliferative malignancies.

3.2.1. Dose Escalation

Subjects with B-cell malignancies who have refractory or relapsed disease will be sequentially enrolled at progressively higher dose levels in a standard 3 + 3 study design to receive oral tirabrutinib combined with idelalisib (Combination I) or entospletinib (Combination II).

Once a dose level of the oral tirabrutinib combined with idelalisib or entospletinib has been deemed safe and tolerable, an additional cohort of subjects will be enrolled with the addition of obinutuzumab to the combination of oral targeted agents [tirabrutinib + idelalisib (Combination III) or tirabrutinib + entospletinib (Combination IV)]. Up to 2 dose levels for each triplet combination will be evaluated.

The dose escalation rules are specified in Table 3-1, Table 3-2, Table 3-3, and Table 3-4.

Combination I: Tirabrutinib and idelalisib:

Initially, 3 subjects will enroll in Cohort 1A of Combination I; the starting dose will be 20 mg once daily of tirabrutinib and 50 mg twice daily of idelalisib. If a dose-limiting toxicity (DLT) occurs within 28 days from Cycle 1, Day 1 in Cohort 1A, this cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Cohort 1A, (ie, ≥ 2 subjects experience DLTs) development of the combination of tirabrutinib and idelalisib will discontinue.

If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 1A, then Cohort 2A will open. Cohort 2A will enroll 3 subjects with tirabrutinib dosed at 40 mg once daily and idelalisib 50 mg twice daily. Once enrollment is complete in Cohort 2A, Cohort 2B will enroll 3 subjects with tirabrutinib dosed at 20 mg twice daily and idelalisib 50 mg twice daily. Cohorts 2A and 2B will dose escalate independently and in parallel; if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2A and Cohort 2B has completed enrollment, then the next 3 subjects will be enrolled in Cohort 3A with tirabrutinib

dosed at 80 mg once daily and idelalisib 50 mg twice daily. Similarly, if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects at Cohort 2B, Cohort 3B will enroll 3 subjects with tirabrutinib dosed 40 mg twice daily and idelalisib 50 mg twice daily. Subsequent cohorts will enroll if no DLTs in 3 subjects or < 2 DLTs in up to 6 subjects are observed. If a second DLT is observed in any cohort, the maximum tolerated dose (MTD) of tirabrutinib combined with idelalisib will have been exceeded and the prior cohort will be the MTD. The MTD for tirabrutinib once-daily will be determined separately from the MTD for tirabrutinib twice-daily.

A new cohort will not open for enrollment until the last subject has completed the 28-day safety period for the prior cohort. All available safety, tolerability, and PK data will be reviewed prior to proceeding to the next cohort. The design will be adaptive, with cohorts reduced or intermediate cohorts added based on emerging safety, PK, pharmacodynamics, and efficacy results. Additionally, either tirabrutinib once daily or tirabrutinib twice daily cohorts may be discontinued based on emerging safety and efficacy data. Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2. If there is no evidence of clear benefit of twice daily dosing of tirabrutinib compared with once daily dosing based on available tolerability, efficacy, PK and pharmacodynamic data, dose escalation in the twice daily dosing arm may be terminated prior to identifying an MTD. Accordingly, as of 25 March 2016, enrollment in the cohorts evaluating twice daily dosing of tirabrutinib combined with idelalisib was discontinued due to 2 of 5 subjects reporting Grade 4 neutropenia (1 DLT with associated fever and infection and 1 DLT without) within the first 28 days of dosing in Cohort 2B.

Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2.

The doses for each cohort are shown in the following table.

Table 3-1. Dose Escalation for Combination I (of Tirabrutinib + Idelalisib)

Dose Level	Tirabrutinib	idelalisib	Tirabrutinib	idelalisib
	A		B	
1	20 mg QD	50 mg BID	—	—
2	40 mg QD	50 mg BID	20 mg BID	50 mg BID
3	80 mg QD	50 mg BID	—	—
4	80 mg QD	100 mg QD	—	—
5	160 mg QD	100 mg QD*	—	—

QD= Once daily dosing, BID = Twice daily dosing, * Dose Level 5 (Combination I-A) will be limited to DLBCL only

Once the MTD of the combination of tirabrutinib with 50 mg of idelalisib twice daily has been determined, based on safety and efficacy, additional cohorts may be enrolled at up to the MTD of tirabrutinib combined with 100 mg of idelalisib once daily.

Combination II: Tirabrutinib and Entospletinib

Initially 3 subjects will enroll in Cohort 1A of Combination II; the starting dose will be 40 mg once daily of tirabrutinib and 200 mg once daily of entospletinib (Table 3-2). If a DLT occurs within 28 days from Cycle 1, Day 1 in Cohort 1A of Combination II, this cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Cohort 1A of Combination II, (ie, ≥ 2 subjects experience DLTs), development of the combination of tirabrutinib and entospletinib will discontinue. If no DLTs in 3 subjects or < 2 DLTs in up to 6 subjects are observed, then the dose will be escalated to Dose Level 2.

Table 3-2. Dose Escalation for Combination II (Tirabrutinib + Entospletinib)

Dose Level	Tirabrutinib	Entospletinib	Tirabrutinib	Entospletinib
	Combination II-A		Combination II-B	
1	40 mg QD	200 mg QD	—	—
2	80 mg QD	200 mg QD	40 mg QD	400 mg QD
3	150 mg QD	200 mg QD	80 mg QD	400 mg QD
4	—	—	160 mg QD	400 mg QD

QD= Once daily dosing, BID = Twice daily dosing * Dose Level 4 (Combination II-B) will be limited to DLBCL only

Dose Level 2 will consist of 2 cohorts: Cohort 2A with tirabrutinib 80 mg once daily and entospletinib 200 mg once daily and Cohort 2B with tirabrutinib 40 mg once daily and entospletinib 400 mg once daily. The first 3 subjects enrolled in Dose Level 2 will be assigned to Cohort 2A; the next 3 subjects will be assigned to Cohort 2B.

Cohorts 2A and 2B will dose escalate independently; if 1 DLT occurs in Cohort 2A, then Cohort 2A will be expanded to enroll 3 additional subjects. Similarly, if 1 DLT occurs in Cohort 2B, then Cohort 2B will be expanded to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2A then Cohort 3A may begin enrollment. Similarly, if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects in Cohort 2B then Cohort 3B may begin enrollment.

If ≥ 2 DLTs are observed in Cohort 2A and < 2 DLTs occur in up to 6 subjects in Cohort 2B, then the MTD of tirabrutinib combined with entospletinib is 40 mg once daily. Cohort 3A will not be enrolled, however, Cohort 3B may continue with enrollment.

Similarly if ≥ 2 DLTs are observed in Cohort 2B and < 2 DLTs occur in up to 6 subjects in Cohort 2A, then the MTD of entospletinib combined with tirabrutinib is 200 mg once daily. Cohort 3B will not be enrolled, however, Cohort 3A may continue with enrollment.

A new cohort will not open for enrollment until the last subject has completed the 28 day safety period for the prior cohort. All available safety, tolerability, and PK data will be reviewed prior to proceeding to the next cohort.

The maximum dose to be tested will be 160 mg total daily dose of tirabrutinib and 400 mg total daily dose of entospletinib, however, the dose escalation will be adaptive, with cohorts for reduced dosing, intermediate dosing or different schedule (QD vs BID) added based on emerging safety, PK, pharmacodynamics, and efficacy results. Dose level 5 (Combination I-A) and Dose level 4 (Combination II-B) are limited to subjects with non-GCB DLBCL only.

Combination III and Combination IV: The addition of obinutuzumab to Combination I or II

Once a dose escalation cohort in Combination I or II has completed a 28 day safety review, an additional cohort of 3 (+3) subjects may be enrolled at this Dose Level with the addition of obinutuzumab. Up to 2 dose levels for each triplet combination may be evaluated. Initially 3 subjects each will enroll at the chosen dose level(s) in Combination III and Combination IV in parallel (see Table 3-3). If 1 DLT occurs within 28 days from Cycle 1 in Combination III, the Combination III cohort will be expanded to enroll 3 additional subjects. Similarly if 1 DLT occurs within 28 days from Cycle 1 in Combination IV, the Combination IV cohort will be expanded to enroll 3 additional subjects. If ≥ 2 DLTs occur in Combination III or IV, (ie, ≥ 2 subjects experience DLTs), development of the specific Combination (III or IV) will be discontinued.

Based on the results of Combination I and Combination II, the dose levels for each triplet combination (III and IV) will be determined.

Table 3-3. Dose Evaluation for triplet combinations (Combination III and IV)

	Combination III		Combination IV	
Dose Level	**Tirabrutinib + idelalisib**	**Obinutuzumab**	**Tirabrutinib + Entospletinib**	**Obinutuzumab**
A Triplet Dose Level 1	Dose determined by results of Combination I Dose Escalation (Table 3-1)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 3-2)	1000 mg IV infusion x 8 doses
B Triplet Dose Level 2	Dose determined by results of Combination I Dose Escalation (Table 3-1)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 3-2)	1000 mg IV infusion x 8 doses

During the DLT assessment window, subjects who fail to complete at least 21 total days of tirabrutinib and idelalisib or entospletinib for reasons other than DLT will not be evaluable for DLT assessment and additional subjects may be enrolled to that cohort in order to provide adequate safety data for dose escalation decisions. In Combination III and Combination IV, subjects who only receive Study Day 1 obinutuzumab and do not receive any doses of tirabrutinib are not evaluable for DLT and will be replaced.

Decisions to open the next higher cohort to enrollment or expand the current cohort will be determined by the sponsor in consultation with study principal investigators (PIs).

The MTD is defined as the highest tested dose associated with an observed DLT rate of <33% during the DLT window.

A minimum of 6 subjects need to be treated in a cohort before this cohort can be determined as MTD.

The recommended dosing regimen of the combination of tirabrutinib and idelalisib or entospletinib for use in future clinical trials in subjects with FL, MZL, CLL, SLL, MCL, WM, and non-GCB DLBCL will be chosen based on safety and efficacy data and supported by pharmacodynamics and PK data.

Table 3-4. Dose escalation/ DLT Guidelines

No. of Subjects with a DLT at a Given Cohort	Escalation Decision Rule
0 out of 3	Enroll 3 subjects at the next higher cohort. If this cohort is the highest cohort, it will be declared the maximally administered dose, and enroll 3 additional subjects at this cohort.
≥ 2 out of 3	Dose escalation will be stopped. This cohort will be declared the maximally administered dose. Three additional subjects will be entered at the next lower cohort if only 3 subjects were treated previously at that dose.
1 out of 3	Enter 3 additional subjects in this cohort. • If 0 of these 3 subjects experience a DLT, proceed to the next higher cohort. • If 1 or more of these 3 subjects experience a DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional subjects will be entered at the next lower cohort if only 3 subjects were treated previously at that dose.
≤ 1 out of 6 at highest dose level at or below the maximally administered dose	This is the maximum tolerated dose (MTD) and generally the recommended Phase 2 dose. At least 6 subjects must be enrolled at the MTD or the recommended Phase 2 dose. The MTD for tirabrutinib once-daily will be determined separately from the MTD for tirabrutinib twice-daily.

3.2.2. Dose Expansion

Cohorts of up to approximately 30 subjects may be enrolled to explore safety and preliminary efficacy in a single B-cell lymphoproliferative malignancy disease type to further evaluate efficacy, safety, tolerability, PK, and pharmacodynamics of tirabrutinib combined with idelalisib or entospletinib in a specific B-cell malignancy subtype (eg, CLL, MCL, FL, non-GCB-DLBCL). Expansion cohorts of a triplet combination combined with obinutuzumab in specific B cell malignancies (CLL, iNHL, and non-GCB DLBCL) may also be evaluated.

The disease and dose chosen for expansion cohort(s) will be based on emerging safety, PK, pharmacodynamics, and efficacy result for the dose escalation. Dose expansion may occur after the next higher dose cohort has opened in the dose escalation.

Group V: Tirabrutinib single agent

Additionally, a cohort of up to approximately 30 subjects with relapsed or refractory CLL may be enrolled to receive tirabrutinib 80 mg once daily to provide preliminary safety and efficacy data at this dose as a single agent.

The choice of enrolling a subject into a specific dose escalation arm (idelalisib or entospletinib or combination with obinutuzumab) or expansion arm (idelalisib or entospletinib or combination with obinutuzumab) will be based on the treatment slots open at the time of screening and at the discretion of the investigator. The tirabrutinib single agent arm will be limited to subjects with CLL.

3.2.3. Long-Term Safety Monitoring

As of Amendment 9, all subjects currently on the study will transition into long-term safety monitoring. Subjects from the ongoing Study GS-US-401-1787 and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use (or individual expanded use) will be enrolled into Group VI to participate in long-term safety monitoring. Subjects enrolled in Group VI will continue the same treatment regimen in Study GS-US-401-1787 or named patient use starting from Long-Term Safety Monitoring Cycle 1 Day 1.

Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 end of treatment (EOT) visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day.

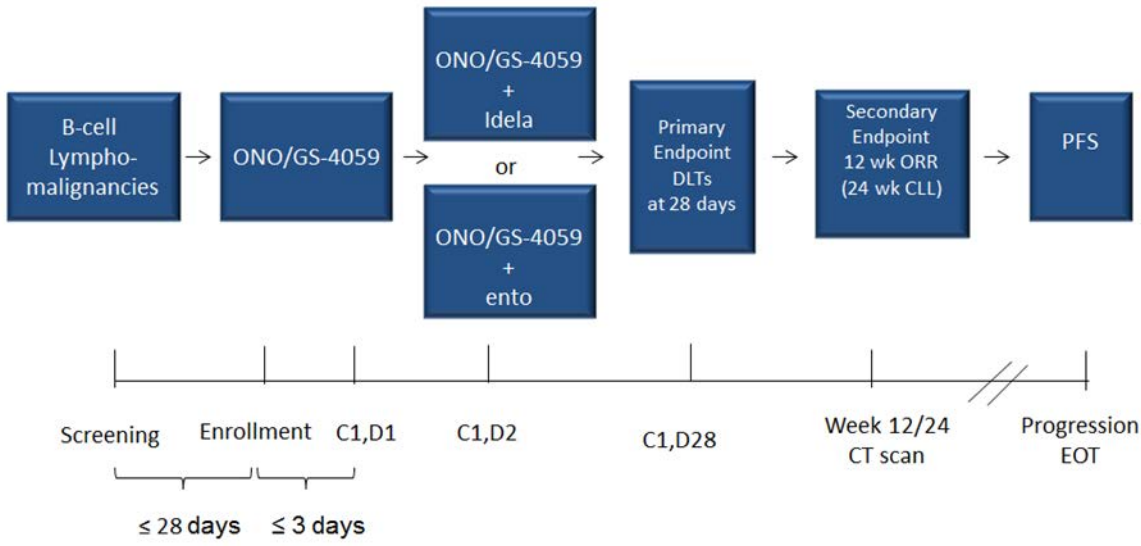
All active subjects who have no clinical evidence of disease progression will transition to long-term safety monitoring and will continue the same treatment regimen. Study visits will be completed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase.

3.3. Study Treatments

For Combination I and II, subjects who meet eligibility criteria will receive a single dose of tirabrutinib on Cycle 1, Day 1 and then initiate idelalisib or entospletinib in combination with tirabrutinib on Cycle 1, Day 2. The first cycle will consist of 28 days (1 day single agent tirabrutinib and 27 days of combination treatment), and each subsequent cycle will be 28 days of combination treatment.

The Study Schemas for Combination I and II are presented in Figure 3-1 below:

Figure 3-1. Dosing Schema for Dose Escalation (Combination I and II)

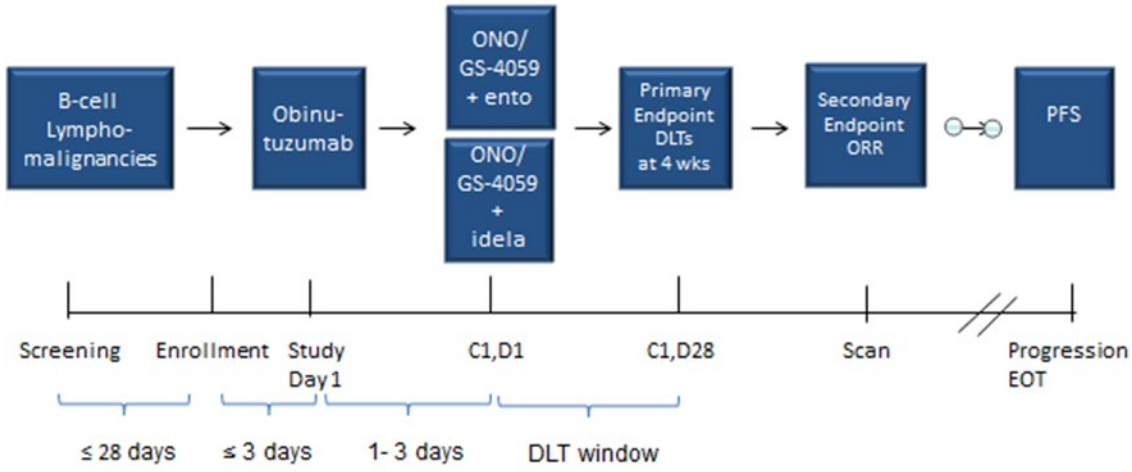


For subjects enrolled in Combination III or IV, obinutuzumab will be initiated on Study Day 1 with a test dose of 100 mg. If the dose is tolerated well, the remaining 900 mg may be administered. Alternatively, the remaining 900 mg may be given the next day, on Study Day 2. On Study Day 2 or 3 the combination of oral targeted agents (tirabrutinib + idelalisib or tirabrutinib + entospletinib) will be initiated. The day that tirabrutinib combination starts will be considered C1D1.

Subsequent infusions of obinutuzumab will be administered on Week 2 Day 1, Week 3 Day 1, Week 5 Day 1 and then every 4 weeks through Week 21 for up to 8 intravenous infusions of 1000 mg each. The combination of oral targeted agents will continue to be taken daily on a schedule (once daily or twice daily) as determined by the results of the previous cohorts. The 28 day window for DLT evaluation will start with the initiation of the oral agent combination. Subjects who withdraw or discontinue study after only receiving obinutuzumab, will not be considered evaluable for the purposes of DLT determination and will be replaced.

The Study Schemas for Combination III and IV are presented in Figure 3-2 below:

Figure 3-2. Dosing Schema for Dose Expansion (Combination III and IV)



For Group V subjects who meet eligibility criteria will initiate tirabrutinib alone on Cycle 1, Day 1. The first and subsequent cycles will be 28 days of combination treatment.

A subject who does not show evidence of disease progression by clinical assessment or by CT (or MRI) as per disease subtype (Appendix 4, Appendix 5, and Appendix 6) may continue receiving study drugs daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.6. After discontinuation of treatment, subjects will be followed for safety for 30 days.

Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, tirabrutinib and idelalisib or entospletinib PK, pharmacodynamics markers, and biomarkers at applicable visits), urine pregnancy (every 4 weeks while receiving tirabrutinib and idelalisib or entospletinib in females of childbearing potential), and assessment of AEs. In addition, subjects will undergo a CT (or MRI) scan every 12 weeks, except DLBCL and CLL. Subjects with DLBCL will have an additional scan at Week 6. Subjects with CLL will only undergo scans at baseline, 24 weeks, and at the time of progression. As of Amendment 7, CT/MRI scans will no longer be performed and will only be performed at the time of disease progression or at study discontinuation.

Long-Term Safety Monitoring:

As of Amendment 9, all subjects currently on the study will transition to long-term safety monitoring and will continue to receive the same treatment regimen starting from Long-Term Safety Monitoring Cycle 1 Day 1. Subjects from the ongoing Study GS-US-401-1787 and subjects who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to

receive treatment via named patient use will be enrolled into Group VI to participate in long-term safety monitoring. Group VI subjects will receive the same treatment administered in Study GS-US-401-1787 or named patient use starting from Long-Term Safety Monitoring Cycle 1 Day 1.

Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 EOT visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI in this study should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Study visits will be completed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per Appendix 3.

3.4. Duration of Treatment

Treatment will continue in the absence of disease progression, unacceptable toxicity, pregnancy, and substantial noncompliance with study procedures or study drug, initiation of another anti-cancer or experimental therapy, study discontinuation, or withdrawal from study. As of Protocol Amendment 8, the maximum participation in the treatment period for any subject is an additional 6 years from the date of that amendment (ie, until November 2025).

As of Amendment 9, entospletinib will be provided until 31 December 2020 to subjects enrolled in Combination II and IV who are currently receiving entospletinib. Subjects treated with entospletinib as part of a combination regimen with tirabrutinib will stop receiving entospletinib by 31 December 2020 but may continue to be treated with tirabrutinib monotherapy.

Tirabrutinib is supplied as 40 mg, 80 mg, and 100 mg until study completion. Idelalisib is supplied as 50 mg tablets until 31 December 2020 and 100 mg tablets until study completion.

Subjects assigned to the 50 mg once daily idelalisib dose will be given the option, at the investigator's discretion, to switch to 100 mg once daily idelalisib dose leading to an increase in total daily dose from 50 mg to 100 mg idelalisib, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment. Subjects receiving 50 mg once daily of idelalisib must not experience any ≥ Grade 3 AEs related to idelalisib to be eligible for this dose increase. Following the dose increase, if the subjects experience any drug-related ≥ Grade 3 toxicity, they will discontinue idelalisib and be given the option to continue tirabrutinib monotherapy, at the investigator's discretion.

Subjects assigned to the 50 mg twice daily idelalisib dose will be given the option, at the investigator's discretion, to switch to the 100 mg once daily idelalisib dose with no change to the total daily dose, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment.

In subjects who have a tumor flare after the discontinuation of therapy or are at a high risk of such an event, the investigator and medical monitor should discuss and agree prior to the treatment being reinstituted or continued following progression until initiation of subsequent therapy and record this on the electronic case report form (eCRF).

3.5. Dose Limiting Toxicities

A DLT is a toxicity (defined below) which occurs during the DLT assessment window (Day 1 through Day 28) in each cohort:

1) All Grade ≥ 4 hematological toxicities persisting for > 7 days
2) All Grade ≥ 3 non-hematological toxicities (except for tumor lysis or alopecia, or Grade 3 nausea, vomiting, diarrhea, or constipation that resolves within 72 hours with medical intervention)
3) All Grade ≥ 4 non hematologic laboratory abnormalities
4) Febrile Neutropenia (defined as ANC < 1.0 x 10^9/L with a single temperature > 38.3ºC [101ºF] or sustained temperature ≥ 38ºC [100.4ºF] for more than 1 hour)
5) Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk

All AEs should be considered relevant in determining DLTs and to reporting unless the event can clearly be determined to be unrelated to tirabrutinib and/or idelalisib or entospletinib. Lymphocytosis will not be considered a DLT.

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and medical monitor, may take place to determine if this AE should be assessed as a DLT and necessitate dose interruption or dose reduction.

3.6. Criteria for Discontinuation of Study Drug and Study

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Pregnancy
- Investigator discretion
- Non-compliance with study drug
- 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
- Death
- Unacceptable toxicity, as defined in the toxicity management section of the protocol (Section 6.5), or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

3.7. Criteria for Removal from Study

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

- Documented progression of malignant disease
- Death
- Pregnancy
- Investigator discretion
- Non-compliance with study drug
- Subject never dosed with study drug
- Protocol violation
- Withdrawal of consent
- Lost to follow-up
- Study termination by the sponsor

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 98 subjects in the dose escalation phase and up to 270 subjects in the dose expansion phase will be enrolled.

As of Amendment 9, all subjects currently on this study will transition into long-term safety monitoring. Up to 6 additional subjects in the UK from the ongoing Study GS-US-401-1787 and up to 2 subjects in total in the US and UK who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment via named patient use will be enrolled into Group VI to participate in long-term safety monitoring.

4.2. Inclusion Criteria

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

1) Male or female ≥ 18 years of age

2) Diagnosis of FL, MZL, SLL, CLL, MCL, WM or non-GCB DLBCL as documented by medical records and with histology based on criteria established by the WHO.

   a) FL Grades 1, 2, or 3a

   b) SLL with absolute lymphocyte count of < 5 x 10^9 /L at initial diagnosis

   c) MZL (splenic, nodal, or extra-nodal)

   d) WM, measurable disease defined as serum monoclonal IgM > 0.5 g/dL or meeting at least 1 of the recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia for requiring treatment (Appendix 4)

3) Prior treatment for FL, MZL, SLL, MCL or WM with ≥ 2 or for CLL or non-GCB DLBCL with ≥1 chemotherapy-based or immunotherapy-based regimen who are not transplant eligible and have had either documented disease progression or no response (stable disease) to the most recent treatment regimen

4) For diseases other than WM, presence of radiographically measurable lymphadenopathy or extra-nodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or MRI)

5) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or bone marrow parameters [any of Grade 1 or 2 permitted])

6) ECOG PS ≤ 2

7) Adequate organ function defined as follows:

   a) Hematologic: Platelets ≥ 50 x 10^9/L; Hemoglobin ≥ 8.0 g/dL; ANC ≥ 1.0 x 10^9/L (without platelet transfusion or any growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)

   b) Hepatic: Aspartate transaminase (AST) / Alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) Total or conjugated bilirubin ≤ 1.5 x ULN

   c) Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockcroft-Gault method

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-specified method of contraception as described in Appendix 8.

9) Male subjects of reproductive potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 8

10) Able and willing to provide written informed consent to participate in the study

11) Willingness and ability to comply with protocol-specified *Pneumocystis jirovecii* pneumonia PJP prophylaxis

Group VI only (Numbers 12-18):

12) Currently enrolled in Study GS-US-401-1787 or previously enrolled in Study GS-US-401-1757 or Study GS-US-401-1787 and currently receiving continued treatment via named patient use

13) Continuing to benefit from the current treatment regimen in the opinion of the investigator/treating physician

14) Negative urine pregnancy test is required for female subjects of childbearing potential as described in Appendix 8

15) 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

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

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

18) 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) History of lymphoid malignancy other than those allowed per Inclusion Criteria

2) Known active central nervous system or leptomeningeal lymphoma. Imaging documentation of the absence or presence of central disease is not required.

3) History of myelodysplastic syndrome

4) History of or current Richter's transformation

5) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to start of study therapy, or any other cancer that has been in complete remission for ≥ 5 years.

6) Less than 21 days since receiving treatment with biologic, small molecule, immunotherapy, chemotherapy, radiation, or other agent for lymphoid malignancy, including other investigational products.

7) Ongoing liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension

8) Hepatitis B surface Antigen (HBsAG) positive or hepatitis B core antibody positive

9) HCV antibody positive

10) Known HIV infection

11) Ongoing CMV infection, treatment, or prophylaxis within the past 28 days prior to the screening test for active CMV (subjects on study may receive CMV prophylaxis)

12) Ongoing symptomatic pneumonitis

13) Ongoing inflammatory bowel disease

14) Pregnancy or breastfeeding

15) History of prior therapy with any inhibitor of AKT, BTK, PI3K (including idelalisib, GS-9820, GS-9901), JAK, mTOR, or SYK except for group V (single-agent tirabrutinib), for which only prior BTK treatment is excluded

16) Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of lymphoid malignancy. Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (≤ 5 mg/day of methylprednisolone or equivalent) is permitted. During study participation, subjects may receive systemic or other corticosteroids as needed for treatment-emergent comorbid conditions.

17) Life expectancy < 4 months as per investigator assessment

18) Concurrent participation in another therapeutic clinical trial

19) History of long QT syndrome or whose QTc interval measured (Fridericia method) at screening is prolonged (> 450 ms)

20) History of stroke or intracranial hemorrhage within 12 months prior to enrollment

21) Use of strong CYP3A4 and P-gp inducers within 2 weeks prior to the first dose of study drug for both arms of the study.

22) For subjects enrolling in the entospletinib arm only:

    a) Use of strong CYP3A4 or CYP2C9 inducers or moderate CYP2C9 inducers within 2 weeks prior to the first dose of study drug

    b) Use of a proton pump inhibitor during the screening window. H2 receptor antagonists are allowed.

23) History of sensitivity or intolerance to any of the excipients of the drug to be administered based on the study arm (tirabrutinib, idelalisib, entospletinib, or obinutuzumab)

24) For subjects enrolling in the idelalisib arm only: History of serious allergic reaction including anaphylaxis and toxic epidermal necrolysis

25) For subjects enrolling in the obinutuzumab arms; prior treatment with obinutuzumab and/or any active infection

Group VI only (Numbers 26-27):

26) History of sensitivity or intolerance to any of the excipients of the drug to be administered based on the study arm (tirabrutinib, idelalisib, or entospletinib)

27) Evidence of clinical or radiological disease progression

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

5.1.1. Enrollment

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, 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 from the IWRS. This is an open-label study.

All baseline tests and procedures must be completed prior to the administration of the first dose of study drug on Cycle 1, 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 Study Drugs

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 or 25 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The tirabrutinib capsules contain the following inactive ingredients: microcrystalline cellulose, low-substituted hydroxypropyl 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, 40 mg, contain the equivalent of 40 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The 33% drug load formulation tablet is an orange, plain-faced, round, film-coated tablet. The tirabrutinib film-coated tablets, 40 mg, contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6/sunset yellow FCF aluminium lake, and iron oxide yellow.

Tirabrutinib film-coated tablets, 75 mg, contain the equivalent of 75 mg tirabrutinib as the hydrochloride salt (GS-4059-01). The 33% drug load formulation tablet is an orange, plain-faced, round, film-coated tablet. The tirabrutinib film-coated tablets, 75 mg, contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow#6/sunset yellow FCF aluminum lake, and iron oxide yellow.

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

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.

As of Amendment 9, tirabrutinib is supplied as 40 mg, 80 mg, and 100 mg tablets until study completion.

5.2.1.2. Packaging and Labeling

Tirabrutinib capsules are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 capsules. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction sealed and aluminum-faced liner.

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

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), and/or other local regulations.

5.2.1.3. Storage and Handling

Study drug tirabrutinib should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

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

5.2.2. Idelalisib

5.2.2.1. Formulation

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

As of Amendment 9, idelalisib is supplied as 50 mg tablets until 31 December 2020 and as 100 mg tablets until study completion.

5.2.2.2. Packaging and Labeling

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

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), and/or other local regulations.

5.2.2.3. Storage and Handling

Idelalisib bottles should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling idelalisib.

5.2.3. Entospletinib

5.2.3.1. Formulation

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

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

As of Amendment 9, entospletinib is supplied as 200 mg tablets until 31 December 2020.

5.2.3.2. Packaging and Labeling

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

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), and/or other local regulations.

5.2.3.3. Storage and Handling

Entospletinib tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F).

To ensure stability of the tablets and proper product identification, the drug should not be stored in a container other than the container in which it is supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.2.4. Obinutuzumab

5.2.4.1. Formulation

Obinutuzumab is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B-cells. The molecular mass of the antibody is approximately 150 kDa.

Obinutuzumab is produced by mammalian cell (CHO) suspension culture. It is a sterile, clear, colorless to slightly brown, preservative free liquid concentrate for intravenous administration. The product is formulated in 20 mM L-histidine/L-histidine hydrochloride, 240 mM trehalose, 0.02% poloxamer 188. The pH is 6.0.

5.2.4.2. Packaging and Labeling

Obinutuzumab is supplied at a concentration of 25 mg/mL in 1000 mg/40 mL single use vials.

5.2.4.3. Storage and Handling

Obinutuzumab vials are stable at 2 °C to 8 °C (36 °F to 46 °F). Do not use beyond expiration date stamped on carton. Obinutuzumab vials should be protected from light. Do not freeze or shake obinutuzumab vials.

For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 to 20 mg/mL for 24 hours at 2 °C to 8 °C (36 °F to 46 °F) followed by 48 hours (including infusion time) at room temperature (≤ 30 °C/86 °F). Obinutuzumab does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2 °C to 8 °C. When splitting the first dose (1000 mg) into 2 infusions (Day 1 = 100 and Day 2 = 900 mg) the same vial may be used for the preparation of both infusions, but the second infusion must begin within 24 hours of the preparation. No incompatibilities between obinutuzumab and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 to 20.0 mg/mL after dilution of obinutuzumab with 0.9% sodium chloride.

5.3. Dosage and Administration of Study Drugs

Tirabrutinib capsules or tablets, idelalisib or entospletinib tablets and obinutuzumab will be provided by Gilead Sciences, Inc. and will be taken orally. Initiation of treatment with the study drug will take place after enrollment and cohort assignment. Subjects will take only tirabrutinib on Cycle 1, Day 1 and then take tirabrutinib and idelalisib or entospletinib on Cycle 1, Day 2. Starting on Cycle 1, Day 2, subjects will continue to take both tirabrutinib and idelalisib or entospletinib at approximately the same time each day. To reduce variability, subjects will be instructed to take entospletinib approximately 1 hour before or 2 hours after a meal. Tirabrutinib and idelalisib may be taken without regard to food.

For patients assigned to the 150 mg tirabrutinib dose, 75 mg tirabrutinib capsules/tablets may be exchanged for 80 mg tirabrutinib tablets leading to an increase in total daily dose from 150 mg to 160 mg. Based on the range of exposures of tirabrutinib observed in subjects with B-cell malignancies, the slight increase in daily dose is not considered clinically relevant.

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

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

Subjects who are enrolled in Combinations III or IV will receive obinutuzumab infusion on Study Day 1. Obinutuzumab will be administered as 8 intravenous infusions of 1000 mg each over approximately 21 weeks. A test dose of 100 mg will be administered on Study Day 1. If the dose is tolerated well, the remaining 900 mg will be administered. Alternatively, the remaining 900 mg may be given the next day, on Study Day 2. Subsequent infusions of obinutuzumab will be administered on Cycle 1, Day 6 (+/- 2 days), Cycle 1, Day 13 (+/- 2 days), Cycle 2, Day 1 (+/- 3 days) and then every 28 days(+/- 3 days) until Cycle 6, Day 1 (+/- 3 days).

The combination of tirabrutinib with idelalisib or entospletinib will be initiated 1-3 days after Study Day 1. The first day of dosing these oral agents is considered Cycle 1, Day 1. The oral agents will be dosed daily (either once or twice daily) as determined by the results of the Combination I and II dose escalations. 28-day cycles will start with the first day of the oral combination.

As of Amendment 9, tirabrutinib is supplied as 40 mg, 80 mg, and 100 mg tablets. Idelalisib is supplied as 50 mg tablets until 31 December 2020 and 100 mg tablets until study completion.

Subjects assigned to the 50 mg once daily idelalisib dose will be given the option, at the investigator's discretion, to switch to 100 mg once daily idelalisib dose leading to an increase in total daily dose from 50 mg to 100 mg idelalisib, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment. Subjects receiving 50 mg once daily of idelalisib must not experience any ≥ Grade 3 AEs related to idelalisib to be eligible for this dose increase. Following the dose increase, if the subjects experience any drug-related ≥ Grade 3 toxicity, they will discontinue idelalisib and be given the option to continue tirabrutinib monotherapy, at the investigator's discretion.

Subjects assigned to the 50 mg twice daily idelalisib dose will be given the option, at the investigator's discretion, to switch to the 100 mg once daily idelalisib dose with no change to the total daily dose, or to discontinue from the study by 31 December 2020 and transition to standard of care treatment.

Entospletinib supply will be provided until 31 December 2020 to subjects enrolled in Combination II and IV who are currently receiving entospletinib. Subjects treated with entospletinib as part of a combination regimen with tirabrutinib will stop receiving entospletinib by 31 December 2020 but may continue to be treated with tirabrutinib monotherapy.

For the long-term safety monitoring phase, subjects currently on the study will continue the same treatment regimen. Subjects enrolled into Group VI will receive the same treatment administered in Study GS-US-401-1787 or named patient use starting from Long-Term Safety Monitoring Cycle 1 Day 1.

5.3.1. Dosage and Administration of Obinutuzumab

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

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

First infusion of obinutuzumab

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

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

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

Subsequent infusions of obinutuzumab

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

the investigator‘s discretion. As during the first cycle, the investigator should consider withholding antihypertensive medication 12 hours prior and until 1 hour after the obinutuzumab infusion.

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

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

- Adequate hydration (eg, intravenous administration of 1000 – 4000 mL NaCl 0.9% starting 12 – 24 hours before treatment),
- Prophylactic administration of an uric acid reducer (eg, allopurinol 300 mg once daily starting 72 hours prior to initiation of treatment) and/or
- Rasburicase.

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

Infusion Rates

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

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

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

Management of infusion-related reactions (IRRs)

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

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

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

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

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

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

Table 5-1. Guidance on the management of infusion-related reactions (IRRs)

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

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

5.3.2. Prior and Concomitant Medications

5.3.2.1. *Pneumocystis (carinii) jirovecii* Pneumonia Prophylaxis

Antibiotic prophylaxis for PJP is mandatory for subjects on idelalisib therapy and should be continued for 2 to 6 months after idelalisib discontinuation. PJP prophylaxis should be instituted for patients with CLL irrespective of treatment arm unless medically contraindicated. PJP prophylaxis should be considered for up to 12 months following obinutuzumab treatment and throughout study drug therapy, particularly in subjects with multiple risk factors for *Pneumocystis* infection {Green 2007}.

5.3.2.2. G-CSF

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

5.3.2.3. IVIg

Administration of IVIg is permitted per institutional standard of care.

5.3.3. Tirabrutinib

In vitro data indicate tirabrutinib is a substrate of CYP3A4. Co-administration of CYP3A4 inhibitors may increase tirabrutinib exposure. However, preliminary PK data from this study (GS-US-401-1757) indicates 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 on tirabrutinib and ≥ 2 weeks prior to study drug administration. Examples of strong CYP3A4 and P-gp inducers are provided in the table below.

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

5.3.4. Idelalisib

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

5.3.5. Entospletinib

In vitro and in vivo data indicate that entospletinib is a substrate of CYP2C9 and to a lesser extent CYP3A. As such, coadministration of strong CYP3A and CYP2C9 inducers and moderate CYP2C9 inducers is prohibited in this study. Administration of these medicines is also prohibited for 2 weeks prior to study drug administration. Examples of these medicines are provided in Table 5-2.

Caution should be exercised when coadministering drugs that are moderate or strong inhibitors of CYP2C9 (eg, fluconazole, voriconazole, and amiodarone) as they may increase entospletinib exposure.

In vitro data indicates that entospletinib has the potential to inhibit several transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when coadministering medications that are metabolized or transported by UGT1A1, OATP1B1, OATP1B3, MATE1, P-gp, and BCRP. The investigator should review the prescribing information of the concomitant medication for guidance on coadministration with an inhibitor of these transporters, such as additional monitoring, dose modifications or avoiding coadministration. In a study in healthy volunteers, entospletinib 400 mg twice daily increased rosuvastatin exposure by approximately 4-fold; as such the following restrictions apply for subjects receiving entospletinib in this study:

Table 5-2. Dosing restrictions for HMB-CoA reductase inhibitors for subjects receiving entospletinib

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

Studies in healthy volunteers have demonstrated a significant reduction in entospletinib exposure when proton pump inhibitors are coadministered. Therefore, proton pump inhibitors (eg, omeprazole) are prohibited in combination with entospletinib.

Table 5-3. Examples of Concomitant Medications Prohibited in this Study

	Strong	Moderate[a]
CYP3A4/P-gp Inducer	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide, rifabutin, phenobarbital, mitotane, avasimibe	Not prohibited
CYP2C9 Inducer[a]		carbamazepine, rifampin, ritonavir, enzalutamide
Proton pump inhibitors[a]	omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole	

a Prohibited only in combination with entospletinib

5.3.6. Obinutuzumab

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

5.3.6.1. Tumor Lysis Syndrome

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

5.3.6.2. Antihypertensive Medication

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

5.4. Accountability for Study Drugs

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

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

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

5.4.1. Investigational Medicinal Product Return or Disposal

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

Please see Section 9.1.7 for more information.

6. STUDY PROCEDURES

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

As of Amendment 9, only study procedures for the long-term safety monitoring phase are to be conducted for each subject enrolled, as presented in Appendix 3. Screening procedures will only apply to Group VI. Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 EOT visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI in this study should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Clinical evaluations and laboratory assessments will be performed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care.

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

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that each subject is eligible for the study before enrollment. Please refer to Section 5.1 for details about enrollment and treatment assignment.

6.2. Study Procedure Descriptions

During the treatment period, all visits may be performed within the specified window for that study visit (see Appendix 2). As of Amendment 9, only visits for the long-term safety monitoring phase are to be performed within the specified window for that study visit (see Appendix 3).

6.2.1. Informed Consent

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

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

As of Amendment 9, all subjects currently on the study must be re-consented and assessed for clinical evidence of disease progression prior to transitioning to the long-term safety monitoring phase. If there is clinical evidence of disease progression, a confirmatory radiologic assessment should be performed per institutional standard of care.

6.2.2. Medical and Medication History

A complete medical history will be obtained by the Investigator or designee. Medical history will include information on the subject's significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent illnesses. Obtain smoking history at screening (for the past 60 Days) and at Day 1 of each Cycle (for the past 28 Days).

As of Amendment 9, any ongoing AE at the time of enrollment will be considered medical history on this study and should be reported in the eCRFs and followed to resolution.

6.2.3. Physical Examination

The Investigator or qualified designee will perform a physical examination at Screening and time points outlined in the Study Procedures Tables (Appendix 2). Screening and End of Treatment 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 (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 the first dose of study treatment baseline physical examination which represent a clinically significant deterioration will be documented on the AE page of the eCRF.

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

As of Amendment 9, physical examinations will no longer be required. Clinical evaluations will be performed per institutional standard of care.

6.2.4. Vital Signs

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

As of Amendment 9, vital signs will no longer be required. Clinical evaluations will be performed per institutional standard of care.

6.2.5. Electrocardiogram Assessment

12-lead ECGs will be obtained in triplicate at the visits outlined in the Study Procedures Tables (Appendix 2) and transferred to a central vendor for storage. Subjects should be resting in supine position 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.

As of Amendment 7, ECGs will no longer be required. Clinical evaluations will be performed per institutional standard of care.

6.2.6. ECOG Performance Status

ECOG PS will be performed at the time points listed in the Study Procedures Tables (Appendix 2). ECOG will be scored using the scale index in Appendix 9.

As of Amendment 9, ECOG PS will no longer be required. Clinical evaluations will be performed per institutional standard of care.

6.2.7. Prior and Concomitant Medications

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

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

6.2.8. Adverse Events

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

Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The site will contact the study subject by phone approximately 30 days after the last dose of study drug to assess AEs. Please refer to Appendix 7 for CTCAE grading criteria.

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

6.2.8.1. Evaluation for Gastrointestinal Events/Colitis

For subjects who report diarrhea of colitis, obtain history of onset and duration, including description of the number of stools and stool composition (watery, bloody, nocturnal), travel history, diet changes and medication review to identify possible causes. Perform physical examination, including assessment for fever, dizziness, abdominal pain/cramping, and weakness

(ie, evaluate for sepsis, bowel obstruction, dehydration). Differentiation between small-bowel and large-bowel diarrhea: maybe possible on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy.

- Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), possible associated dehydration weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.

- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, generally smaller stool volume with gross blood frquently found in the stool; Condsider a colonoscopic evaluation and biopsy.

- Ensure good hydration status

For Grade ≥2 colitis and diarrhea (unless clinical diagnosis is established from medical history and physical examination), the following testing is required:

- Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species, Clostridium difficile toxin, Rotavirus, Cytomegalovirus, Adenovirus)

- Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen

For grade ≥ 3 or persistent grade 2 colitis or diarrhea, without clear etiology (eg, clostridium difficile enterocolitis),endoscopy with biopsy is required. All biopsy samples should include immunohistochemistry (IHC) and PCR for CMV and adenovirus. If an ileal biopsy is performed, consider Acid Fast Bacillus staining.

6.2.9. Radiology Assessment

CT (preferred) or MRI will be obtained to document disease and identify index lesions using the criteria in Appendix 4, Appendix 5, and Appendix 6 to assess response and disease progression. Imaging of the neck, chest, abdomen and pelvis by CT scan will be performed at the time points outlined in the Study Procedures Tables (Appendix 2). Scans taken as part of standard medical practice up to 28 days prior to first dose of tirabrutinib can be used for Screening. During the treatment phase, scans may be performed at time points other than specified in the Study Procedures Tables (Appendix 2) as clinically indicated to assess tumor progression. Scans should continue to be performed at time points outlined in the Study Procedures Tables (Appendix 2) for subjects who stop study treatment but did not have disease progression (eg. experienced unexpected toxicity) until radiographic progression is documented or until the subject starts a new systemic anti-cancer therapy other than the study treatment, whichever is earlier. Scans will be transferred to a central reader for collection and future analysis. The same imaging procedure and specifications (eg., contrast agent, scanner, slice thickness, etc.) used to define index and non-index lesions must be used throughout the study for the same subject.

All relevant clinical and radiographic information required to make each assessment must be made available for source verification. Investigators will assess the status of each subject's disease status using the criteria in Appendix 4, Appendix 5, and Appendix 6. Scans will be transferred to a central reader for collection and future analysis.

As of Amendment 7, CT/MRI scans will no longer be performed and will only be performed at the time of disease progression or at study discontinuation.

As of Amendment 9, investigators will clinically assess each subject's disease status every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care (Appendix 3). If there is clinical evidence of disease progression, a confirmatory radiologic assessment should be performed per institutional standard of care.

6.2.10. Tumor Status Assessments

The determination of disease response and progression will be based on standardized criteria {Cheson 2007, Hallek 2008, Owen 2013} as specifically modified for this study to reflect current recommendations which consider the mechanism of action of idelalisib or entospletinib and similar drugs {Cheson 2012}. During the course of the study, investigators will clinically assess the status of each subject's disease at 4 week intervals for the first 24 weeks. 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 and for potential submission to an Independent Review Committee (IRC).

6.2.10.1. Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies/aspirates (type of test at the investigator's discretion). Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

In a subject who has a baseline bone marrow biopsy/aspirate showing bone marrow FL, MZL, CLL, or SLL or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy/aspirate documentation of the absence of bone marrow FL, MZL, or SLL. In a subject who has a baseline bone marrow biopsy/aspirate showing no evidence of FL, MZL, CLL, or SLL, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met. In a subjects with CLL, regardless of baseline findings, if a clinical CR is achieved a bone marrow analysis will be evaluated for minimal residual disease analysis (PCR or flow cytometry).

6.2.10.2. Biopsy and Cytology

Diagnosis of FL, MZL, SLL, CLL, MCL, WM, or non-GCB DLBCL will be documented by medical records and with histology based on criteria established by the WHO. Non-GCB DLBCL subtype may be determined by immunohistochemical testing (non-GCB) or gene expression profiling (ABC).

Lymph node biopsy is not required in the determination of subject eligibility. However, subjects with evidence of transformed aggressive lymphoma on lymph node biopsy, other tissue biopsy or fluid cytology are ineligible for study participation.

During study participation, a subject who has a biopsy or cytology indicating transformation to an aggressive lymphoma will be considered to have progressive disease (PD) even in the absence of other evidence of PD. If the subject has no earlier objective documentation of PD, the date of the biopsy or cytology will be considered the date of disease progression.

6.2.10.3. Definitions of Tumor Response and Progression

Responses will be categorized as CR, PR, SD, or PD using the criteria in Appendix 4, Appendix 5, and Appendix 6.

In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is absence of tumor both at baseline and on treatment.

Every attempt should be made to keep the subject in the study and continue collecting CT or MRI scans for tumor assessment as per the schedule of assessments (Appendix 2) until disease progression or initiation of systemic anti-tumor therapy other than treatment per protocol. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. The subject will be asked to attend the post-treatment follow-up assessment visit when discontinuing from the study 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 counted in the denominators in calculations of tumor response rates. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

As of Amendment 7, CT/MRI scans will no longer be performed and will only be performed at the time of disease progression or at study discontinuation.

As of Amendment 9, investigators will clinically assess each subject's disease status every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care (Appendix 3). If there is clinical evidence of disease progression, a confirmatory radiologic assessment should be performed per institutional standard of care.

6.2.11. Blood and Urine Samples

Blood and urine for laboratory safety tests will be collected according to the Study Procedures Tables (Appendix 2). The date and time of blood and urine collection will be recorded in the subject's source documentation. The date and time of previous tirabrutinib and idelalisib or entospletinib dose will be recorded in the subject's source documentation on days where PK is collected. The tests will be analyzed using standard procedures. White blood cell (WBC) differentials will be reported as absolute counts. All laboratory tests must be reviewed for clinical significance by the Investigator or qualified designee. Eligibility will be based on central laboratory assessments and will be collected within -28 days of Cycle 1, Day 1.

Cycle 1, Day 1 pre-dose samples may be drawn up to 2 days prior to the Cycle 1, Day 1 visit.

As of Amendment 9, clinical evaluations and laboratory assessments will be performed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care (Appendix 3). The eligibility of subjects enrolling in Group VI will be based on local urine pregnancy testing as per local standard of care, if applicable. For Group VI, urine pregnancy testing performed up to 30 days and imaging performed up to 90 days prior to enrollment may be used to fulfill eligibility criteria.

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

6.2.12. Biomarker Samples to Address the Study Objectives

As of Amendment 7, biomarker samples will no longer be collected.

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

CCI [redacted]

CCI [redacted] Blood Samples

Pharmacodynamic activity of tirabrutinib alone or combined with idelalisib or entospletinib and obinutuzumab will be evaluated in blood samples using available assay such as BTK occupancy and signaling pathway biomarkers such as Syk, AKT, S6, NF-kB, PLCg2, ERK, NF-κB. Blood samples for pharmacodynamics will be collected at timepoints as outlined in the table of assessments. CCI [redacted]

Circulating tumor DNA will also be explored in these plasma samples if technically feasible and where it may be informative for specific disease cohorts and to evaluate biomarkers such as MRD.

Peripheral blood samples will be collected at CR from CLL and MCL subjects to assess MRD status using either flow cytometry or DNA analysis by PCR or sequencing.

CLL, SLL, and MCL subjects:

Exploratory biomarkers related to disease progression including mechanisms of resistance, response to treatment, and overall prognosis, will be assessed in peripheral blood samples. For these assessments, peripheral blood will be collected prior to therapy at Cycle 1, Day 1 and at

disease progression. CCI [redacted]

6.2.12.2. Tumor Tissue Samples

If clinically feasible, lymph node biopsies will be performed on Cycle 1, Day 1 (- 7 days), Cycle 1 Day 8, and at disease progression and will be collected for tumor DNA, RNA, and protein expression analysis. These samples will be used to understand biomarkers associated with the disease, clinical responses, drug responses, and potential mechanisms of resistance. Signaling pathway activation such as signatures associated with BCR, NF-κB signaling, etc. will be assessed by gene expression analysis and protein biomarkers (phosphorylated AKT, S6, BTK, and SYK pathway markers) will be evaluated using immunohistochemistry based on available reagents in paired tumor specimens. Given the possibility that not all subjects will respond to therapy or subsets of patients will have greater magnitude of responses, tumor characteristics that may be associated with clinical responses will be investigated (MYD88, CD79b mutations) using samples collected at baseline.

Bone marrow samples will be collected per Appendix 2 from WM subjects to determine DNA mutations such as MYD88 and CXCR4 and their association with responses. Bone marrow and blood samples will be collected at CR from CLL and MCL subjects to evaluate minimal residual disease (MRD) using either flow cytometry or molecular methods.

Fifteen (15) recently prepared (not more than 2 weeks prior to submission) unstained slides from archival tumor tissue will be requested for all subjects who have tissue available and biopsy is not medically feasible.

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.2.15. Pregnancy Test for Females of Childbearing Potential

All female subjects of childbearing potential (as defined in Appendix 7) will have a serum pregnancy test at Screening and a urine pregnancy test prior to Day 1 dosing, every 28 days thereafter, then every 12 weeks as of amendment 7 and at the EOT visit. The results must be confirmed as negative prior to continued administration of study drug.

As of Amendment 9, female subjects of childbearing potential must have a negative urine pregnancy test at Screening to enroll into long-term safety monitoring. For Group VI, urine pregnancy testing performed up to 30 days may be used to fulfill eligibility criteria.

6.2.16. Pharmacokinetic Samples

Dose Escalation (Combination I and II):

PK samples will be collected on Cycle 1, Day 1 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and CCI [redacted] post-dose of tirabrutinib and Cycle 1, Days 2 and 8 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, CCI [redacted] and 24 hours post-dose of tirabrutinib and idelalisib or entospletinib. CCI [redacted] PK sample should be collected prior to evening dose when study drug is administered BID and 24 hour sample will be collected 24 hours post-dose relative to morning dose. PK samples will be collected in all cohorts at pre-dose and 1-6 hours post-dose on Cycle 1 Day 15. A sparse PK sample will also be collected anytime on the first day of Cycles 2 to 6.

Plasma concentrations of tirabrutinib, idelalisib, GS-563117, and entospletinib, as applicable, will be determined and PK evaluated. Plasma protein binding of each analyte may be evaluated.

As of Amendment 7, PK samples will no longer be collected.

Dose expansion (Combination I and II):

A PK sample will be collected on Cycle 1, Day 1 between 1.5 and 4 hours (inclusive) post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours (inclusive) post-dose of tirabrutinib and idelalisib or entospletinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

Plasma concentrations of tirabrutinib, idelalisib, GS-563117, and entospletinib, as applicable, will be determined. Plasma protein binding of each analyte may be evaluated.

The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling time points may be eliminated or modified based upon emerging data.

As of Amendment 7, PK samples will no longer be collected.

Dose Escalation and Dose Expansion Combinations III and IV:

A PK sample will be collected on Cycle 1, Day 1 between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

As of Amendment 7, PK samples will no longer be collected.

Dose Expansion Group V:

In all subjects, a PK sample will be collected on Cycle 1, Day 1 between 1.5 and 4 hours post dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

Up to 10 subjects will undergo more intensive PK sampling; Cycle 1, Day 8 at pre-dose and 2, 4, 6, 8, CCI and 24 hours post-dose of tirabrutinib. Note: If a subject has intensive PK sampling on Cycle 1, Day 8, sparse PK samples do not need to be collected on Cycle 1, Day 8.

As of Amendment 7, PK samples will no longer be collected.

Long-Term Safety Monitoring:

No PK samples will be collected.

6.2.17. Pharmacodynamic Samples

Dose Escalation (Combination I and II):

Blood samples for pharmacodynamics will be collected on Cycle 1, Day 1 at pre-dose, 2, and 6 hours post-dose; on Cycle 1, Days 2 and 8 at pre-dose, 2, 6, and 24 hours post-dose; and at the EOT or disease progression. When study drug is administered twice daily, the 24 hour sample will be collected 24-hours post-dose relative to the morning dose. The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling time points may be eliminated or modified based upon emerging data.

As of Amendment 7, pharmacodynamics samples will no longer be collected.

Dose Expansion (Combination I and II):

Pharmacodynamic samples will be collected on Cycle 1, Day 1 at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a pharmacodynamic sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib and at the EOT or disease progression.

The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling time points may be eliminated or modified based upon emerging data.

As of Amendment 7, pharmacodynamics samples will no longer be collected.

Dose Evaluation of Combinations III and IV:

Pharmacodynamic samples will be collected on Cycle 1, Day 1 at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a pharmacodynamic sample will be collected at pre-dose and between 1.5 and 4 hours post-dose of tirabrutinib and idelalisib or entospletinib and at the EOT or disease progression.

As of Amendment 7, pharmacodynamics samples will no longer be collected.

Dose Expansion Group V:

Pharmacodynamic samples in these same subjects will be Cycle 1, Day 1 pre-dose and between 1.5 and 4 hours post dose of tirabrutinib. Cycle 1, Day 8 and Cycle 2, Day 1 at pre-dose and between 1.5 and 4 hours and at the EOT or disease progression.

As of Amendment 7, pharmacodynamics samples will no longer be collected.

Long-Term Safety Monitoring:

No pharmacodynamic samples will be collected.

Table 6-1. Blood and Urine Samples Collected During the Course of the Study[ef]

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Glucose Blood urea nitrogen Creatinine[b] ALT AST GGT Cholesterol Triglycerides Uric Acid Alkaline phosphatase Total bilirubin[a] Total protein Albumin Calcium Magnesium Phosphate LDH Amylase Lipase Insulin C-peptide (subjects receiving exogenous insulin only)	White Blood Cell (WBC) Count Hemoglobin Hematocrit Platelet Count Neutrophils (ANC) Lymphocytes Monocytes Basophils Eosinophils	Tirabrutinib, idelalisib, GS-563117, and entospletinib, as applicable, plasma concentrations Other metabolites of tirabrutinib, idelalisib or entospletinib may be measured Blood and Tissue Biomarkers HBsAG Hepatitis B core antibody Hepatitis C antibody CMV serology CMV PCR or PP65 Ag[d] Beta-2 microglobulin Serum quantitative immunoglobulins (IgG, IgM, IgA Lymphocyte Immunophenotyping by flow cytometry MRD Serum CH50 level
	Coagulation	
	PT/INR aPTT	
Pregnancy Testing	**Urine**	
Serum Qualitative β-HCG (females) Urine Pregnancy (females)	Urinalysis **Dipstick** pH Occult blood Protein Glucose Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase **Microscopic[c]** WBC/High Power Field RBC/High Power Field Urine protein immunoelectropheresis	

a Includes direct bilirubin
b Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula
c To be performed only if the dipstick results are abnormal Note: Additional components, abnormal, and/or atypical cells will also be reported if present
d Subjects on treatment with idelalisib only
e As of Amendment 7, pharmacokinetics and pharmacodynamics samples will no longer be collected
f As of Amendment 9, clinical evaluations and laboratory assessments will be performed every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase per institutional standard of care. For subjects on treatment with idelalisib, CMV surveillance by PCR or PP65 Ag testing and clinical evaluation for CMV reactivation, to be done as per local standard of care at Long-Term Safety Monitoring Cycle 1 Day 1, every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase.

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CH50 = 50% hemolytic complement activity; CMV = cytomegalovirus; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

6.2.18. Unscheduled Procedures

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

6.3. Post-treatment Assessments

6.3.1. Post-Study Phone Call

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

6.4. Criteria for Discontinuation of Study Treatment

See Sections 3.4 and 3.5 for discontinuation criteria.

6.5. Dose Interruption and Reduction

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

If a subject experiences a DLT prior to completion of dosing during Cycle 1 (Day 1-29 inclusive), no further doses of either drug will be administered and the subject will be observed for resolution of the toxicity. The exception is if, in the Investigator's opinion, the toxicity is solely due to idelalisib/entospletinib and the subject is deemed at risk for a withdrawal reaction from the sudden discontinuation of tirabrutinib, then tirabrutinib may be continued alone.

Upon the initiation of Cycle 2, Day 1, an interruption of tirabrutinib and/or idelalisib or entospletinib administration of up to 2 weeks will be acceptable to allow for any reversal of toxicity between doses of tirabrutinib and/or idelalisib or entospletinib. If the toxicity does not resolve to CTC Grade ≤ 2 within 2 weeks, additional doses of the interrupted drug(s) will not be administered unless the toxicity is deemed related to the subject's underlying disease in the opinion of the investigator. If the toxicity is deemed to be related to one agent (tirabrutinib or idelalisib or entospletinib), the subject may resume the other drug as a single agent, however, the discontinued drug may not be re-initiated on this study.

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

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

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

NCI CTCAE Grade	Recommendation	
	Idelalisib	**Tirabrutinib**
HEMATOLOGICAL ADVERSE EVENTS		
Neutropenia		
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule. Blood counts must be monitored at least weekly until Grade ≤2.	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection	Delay until Grade ≤2 (ANC ≥1 x 10^9/L and consider G-CSF support. Resume at same or reduced dose level at investigator discretion. Blood counts must be monitored at least weekly.	Withhold tirabrutinib until resolved to Grade 2 or baseline (recovery). Tirabrutinib may be reinitiated at the previous dose or decrease one dose level. If the toxicity recurs, decrease by one dose level. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib.
Thrombocytopenia		
Grade ≤ 3 Thrombocytopenia	Withhold for clinically significant bleeding	Withhold for clinically significant bleeding
Grade 4 Thrombocytopenia	Withhold tirabrutinib and idelalisib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and idelalisib may be reinitiated at the previous dose. If the toxicity recurs, decrease by one dose level. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and idelalisib.	
HEMATOLOGICAL ADVERSE EVENTS		
Hemorrhage		
		Hold tirabrutinib for clinically significant bleeding. Reinitiate treatment at the prior dose after hemostasis is achieved.

NCI CTCAE Grade	Recommendation	
	Idelalisib	**Tirabrutinib**
NON-HEMATOLOGICAL ADVERSE EVENTS		
Dermatological/Rash		
Grade ≤ 2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 3 or 4	Withhold tirabrutinib and idelalisib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and idelalisib may be resumed at a lower dose. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and idelalisib.	
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis		
Any Grade	Permanently discontinue idelalisib. Interrupt any co-administered medications potentially associated with SJS or TEN. Institute systemic immunosuppression per institutional standards.	
Bowel perforation		
Any grade	Discontinue idelalisib	
Diarrhea		
Grade ≤ 1	Provide anti-diarrheal (eg, loperamide) and maintain current tirabrutinib and idelalisib dose level and schedule	
Grade 2	Withhold idelalisib until Grade ≤ 1. Provide anti-diarrheal (eg, loperamide). Resume idelalisib at previous dose level. If rechallenge results in recurrence, resume lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). If toxicity persists or recurs following a dose reduction discontinue idelalisib. Refer to Section 6.2.8.1 for required evaluation.	Withhold tirabrutinib until resolved to Grade ≤1. If resolution occurs within 7 days, tirabrutinib may be reinitiated at the previous dose. If the toxicity recurs, decrease by one dose level. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib.
Grade 3 or 4	Withhold study drug. Rule out infectious etiology including CMV (see Section 6.2.8.1). Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). At Grade ≤1, may resume at lower dose level or discontinue study drug at investigator discretion. If toxicity persists or recurs following a dose reduction permanently discontinue idelalisib. Refer to Section 6.2.8.1 for required evaluation.	Withhold tirabrutinib until Grade ≤1. Provide anti-diarrheal (eg, loperamide). Resume at lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). If toxicity persists or recurs following 2 dose reductions permanently discontinue tirabrutinib.

NCI CTCAE Grade	Recommendation	
	Idelalisib	**Tirabrutinib**
NON-HEMATOLOGICAL ADVERSE EVENTS		
Hepatic Adverse Events (elevations in ALT, AST or bilirubin)		
Grade 1 (ALT/AST ≤ 3xULN) (Bilirubin ≤ 1.5xULN)	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 2 (ALT/AST > 3-5xULN) (Bilirubin>1.5 -≤ 3xULN)	Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 3 (ALT/AST > 5-20xULN) (Bilirubin > 3-10xULN)	Withhold tirabrutinib and idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib and idelalisib at previous dose level. If bilirubin abnormality was Grade ≥ 3, resume tirabrutinib and idelalisib at lower dose level.	
Grade 4 (ALT/AST > 20xULN) (Bilirubin > 10xULN)	Withhold tirabrutinib and idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade ≤ 3, resume tirabrutinib and idelalisib at lower dose level. If bilirubin was Grade 4, discontinue tirabrutinib and idelalisib. In case of Grade 4 ALT/AST with bilirubin elevation idelalisib must be discontinued	
Organizing Pneumonia		
Any Grade	Required Action: Discontinue idelalisib permanently. Institute supportive care as appropriate.	May resume tirabrutinib only at investigator discretion.
Pneumonitis		
Grade 1 (asymptomatic)	Required Action: Withhold idelalisib until resolution to baseline.	Maintain current dose level and schedule.
Grade 2	Required Action: Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.	Withhold tirabrutinib until Grade ≤ 1, consider systemic corticosteroids and Pneumocystis treatment. Upon resolution may resume at initial or lower dose level at investigator discretion.
Grade 3	Required Action: Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.	Withhold tirabrutinib until Grade ≤ 1. Consider systemic corticosteroids and Pneumocystis treatment. Upon resolution, may resume at lower dose level (after discussion with the sponsor) or discontinue tirabrutinib at investigator discretion.
Grade 4	Required Action: Discontinue idelalisib and tirabrutinib permanently and institute therapy as clinically appropriate.	
Pneumocystis pneumonia (PJP Infection)		
Any Grade	Discontinue idelalisib	

NCI CTCAE Grade	Recommendation	
	Idelalisib	Tirabrutinib
NON-HEMATOLOGICAL ADVERSE EVENTS		
Unequivocal CMV infection		
Any Grade	Discontinue idelalisib and undergo effective antiviral treatment according to established clinical guidelines.	
Hypersensitivity		
Any Grade	Consider interrupting or discontinuing tirabrutinib treatment	
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS		
Grade 1	Maintain current dose level and schedule	
Grade 2	Withhold tirabrutinib and idelalisib until Grade ≤1 or baseline. May resume tirabrutinib and idelalisib at initial or lower dose level or discontinue tirabrutinib and idelalisib at investigator discretion.	
Grade 3	Withhold tirabrutinib and idelalisib until Grade ≤1 or baseline. May resume tirabrutinib and idelalisib at lower dose level or discontinue tirabrutinib and idelalisib at investigator discretion.	
Grade 4	Discontinue tirabrutinib and idelalisib.	

Table 6-3. Restarting Doses of Tirabrutinib after Treatment Interruption for Drug-related Grade 3 or 4 Toxicity*

Tirabrutinib Dose at the time of the first toxicity	1st dose reduction	2nd dose reduction
40 mg QD	Discontinue	-
80 mg QD	40 mg QD	Discontinue
100 mg QD	80 mg QD	40 mg QD
150 mg QD or 160 mg QD	80 mg QD	40 mg QD
400 mg QD	240 mg QD	140 mg QD
480 mg QD	300 mg QD	140 mg QD

* Toxicity may be a new event or recurrence of a prior Grade 3 or 4 toxicity
Use Table 6-2 to guide Grade 4 hematologic drug related toxicity dose reductions

Table 6-4. Restarting Doses of Idelalisib after Treatment Interruption for Drug-related Grade 3 or 4 Toxicity*†

Idelalisib Dose at the time of the toxicity	1st dose reduction	2nd dose reduction
50 mg BID or 100 mg QD	50 mg QD†	Discontinue

* Toxicity may be a new event or recurrence of a prior Grade 3 or 4 toxicity.
† After 31 December 2020, subjects receiving 100 mg QD who experience any drug-related ≥ Grade 3 toxicity will discontinue idelalisib and be given the option to continue tirabrutinib monotherapy, at the investigator's discretion.
Use Table 6-2 to guide Grade 4 hematologic drug related toxicity dose reductions

Table 6-5. Dose Adjustments, Withholding and Discontinuation Related to Entospletinib and/or Tirabrutinib

NCI CTCAE Grade	Recommendation	
	Entospletinib	**Tirabrutinib**
HEMATOLOGICAL ADVERSE EVENTS		
Neutropenia		
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection	Withhold tirabrutinib and entospletinib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and entospletinib may be reinitiated at the previous dose or decrease one dose. If the toxicity recurs, decrease by one dose level. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and entospletinib.	
Thrombocytopenia		
Grade ≤ 3 Thrombocytopenia	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 4 Thrombocytopenia	Withhold tirabrutinib and entospletinib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and entospletinib may be reinitiated at the previous dose. If the toxicity recurs, decrease by one dose level. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and entospletinib.	
Hemorrhage		
	Consider holding entospletinib for clinically significant bleeding. Reinitiate treatment at the prior dose after hemostasis is achieved.	Hold tirabrutinib for clinically significant bleeding. Reinitiate treatment at the prior dose after hemostasis is achieved.
NON-HEMATOLOGICAL ADVERSE EVENTS		
Dermatological		
Grade ≤ 2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 3 or 4	Withhold tirabrutinib and entospletinib until resolved to Grade 1 or baseline (recovery). Tirabrutinib and entospletinib may be resumed at a lower dose. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and entospletinib.	
Diarrhea		
Grade ≤ 1	Provide anti-diarrheal (eg, loperamide) and maintain current tirabrutinib and entospletinib dose level and schedule	
Grade 2	Withhold entospletinib until Grade ≤ 1. Provide anti-diarrheal (eg, loperamide). Resume entospletinib at previous dose level. If rechallenge results in recurrence, resume lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). If toxicity persists or recurs following 2 dose reductions discontinue entospletinib.	Withhold tirabrutinib until resolved to Grade ≤1. If resolution occurs within 7 days, tirabrutinib may be reinitiated at the previous dose. If the toxicity recurs, decrease by one dose level. A second reduction may be considered as needed. If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib.
Grade 3 or 4	Withhold tirabrutinib and entospletinib until Grade ≤1. Provide anti-diarrheal (eg, loperamide). Resume at lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide). If toxicity persists or recurs following 2 dose reductions discontinue tirabrutinib and entospletinib.	

NCI CTCAE Grade	Recommendation	
	Entospletinib	**Tirabrutinib**
NON-HEMATOLOGICAL ADVERSE EVENTS		
Hepatic Adverse Events (elevations in ALT, AST or bilirubin)		
Grade 1 (ALT/AST ≤ 3xULN) (Bilirubin ≤ 1.5xULN)	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 2 (ALT/AST > 3-5xULN) (Bilirubin>1.5 -≤ 3xULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 3 (ALT/AST > 5-20xULN) (Bilirubin > 3-10xULN)	Withhold tirabrutinib and entospletinib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade < 3, resume tirabrutinib and entospletinib at previous dose level. If bilirubin abnormality was Grade ≥ 3, resume tirabrutinib and entospletinib at lower dose level.	
Grade 4 (ALT/AST > 20xULN) (Bilirubin > 10xULN)	Withhold tirabrutinib and entospletinib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1 or baseline. If bilirubin abnormality was Grade ≤ 3, resume tirabrutinib and idelalisib at lower dose level. If bilirubin was Grade 4, discontinue tirabrutinib and entospletinib.	
Pneumonitis		
Grade 1	Maintain current dose level and schedule. Consider Pneumocystis therapy	
Grade 2	Withhold tirabrutinib and entospletinib until Grade ≤ 1, consider systemic corticosteroids and Pneumocystis treatment. Upon resolution may resume at initial or lower dose level at investigator discretion.	
Grade 3	Withhold tirabrutinib and entospletinib until Grade ≤ 1, consider systemic corticosteroids and consider Pneumocystis treatment. Upon resolution may resume at lower dose (after discussion with the sponsor) level or discontinue tirabrutinib and entospletinib at investigator discretion.	
Grade 4	Discontinue tirabrutinib and entospletinib.	
Hypersensitivity		
Any Grade	Consider interrupting or discontinuing tirabrutinib treatment	
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS		
Grade 1	Maintain current dose level and schedule	
Grade 2	Withhold tirabrutinib and entospletinib until Grade ≤1 or baseline. May resume tirabrutinib and entospletinib at initial or lower dose level or discontinue tirabrutinib and entospletinib at investigator discretion.	
Grade 3	Withhold tirabrutinib and entospletinib until Grade ≤1 or baseline. May resume tirabrutinib and entospletinib at lower dose level or discontinue tirabrutinib and entospletinib at investigator discretion.	
Grade 4	Discontinue tirabrutinib and entospletinib.	

Table 6-6. Restarting Doses of Entospletinib after Treatment Interruption for Drug-related Grade 3 or 4 Toxicity*

Entospletinib dose at the time of the first toxicity	1st dose reduction	2nd dose reduction
200 QD	Discontinue	-
200 BID or 400 QD	200 QD	Discontinue

* Toxicity may be a new event or recurrence of a prior Grade 3 or 4 toxicity.
Use Table 6-2 to guide Grade 4 hematologic drug related toxicity dose reductions

Table 6-7. Dose Adjustment Guidelines for Subjects Receiving Obinutuzumab

NCI CTCAE Grade	Recommendation Toxicity attributable to obinutuzumab
HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤ 2 Neutropenia	Maintain current dose level and schedule.
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule. Consider G-CSF support
Grade 4 neutropenia (or occurrence of neutropenic fever or infection	Delay obinutuzumab until Grade ≤ 2 (ANC ≥ 1 × 10^9/L) and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider G-CSF support to avoid delays. If delay is > 4 weeks, discontinue obinutuzumab.
Thrombocytopenia	
Grade ≤ 3 Thrombocytopenia	Maintain current dose level and schedule.
Grade 4 Thrombocytopenia	Delay obinutuzumab until Grade ≤ 3 (platelets ≥ 25 × 10^9/L); thereafter, resume at full dose. If delay is > 4 weeks, discontinue obinutuzumab, unless the Grade 4 thrombocytopenia occurred after the first 3 weekly doses.
Hemorrhage	
	Hold obinutuzumab in case of platelets < 20,000/μL. If Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved). If Day 15 is delayed then skip Day 15 dosing and administer Day 29 of obinutuzumab as scheduled (if symptomatic bleeding has resolved). At the discretion of the study investigator, for subjects who are on low molecular weight heparin (LMWH), when thrombocytopenia with platelets <20,000/μL develops, reduce the dose of LMWH or new oral anticoagulants (NOAC) used.
	At the discretion of the study investigator, for subjects who are on platelet inhibitors, when thrombocytopenia with platelets <20,000/μL develops, consideration should be given to temporarily pause obinutuzumab. Hold tirabrutinib and obinutuzumab for clinically significant bleeding (irrespective of platelet count) until it resolves.

NCI CTCAE Grade	Recommendation Toxicity attributable to obinutuzumab
NON-HEMATOLOGICAL ADVERSE EVENTS	
Cutaneous	
Grade ≤ 2	Maintain current dose level and schedule.
Grade 3 or 4	Delay obinutuzumab until Grade ≤ 1; thereafter, may resume at full dose or discontinue obinutuzumab at investigator discretion.
Gastrointestinal Inflammation/Diarrhea	
Grade ≤ 2	Maintain current dose level and schedule.
Grade 3 and 4	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Hepatic Adverse Events (elevations in ALT, AST or bilirubin)	
Grade ≤ 2 (ALT/AST ≤ 3xULN) (Bilirubin ≤ 1.5xULN)	Maintain current dose level and schedule.
Grade 3 (ALT/AST > 5-20xULN) (Bilirubin > 3-10xULN)	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. If bilirubin abnormality was Grade ≥ 3, resume tirabrutinib and entospletinib at lower dose level.
Grade 4 (ALT/AST > 20xULN) (Bilirubin > 10xULN)	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule. If bilirubin abnormality was Grade ≥ 3, resume tirabrutinib and entospletinib at lower dose level.
Pneumonitis	
Grade 1	Maintain current dose level and schedule. Consider Pneumocystis therapy
Grade 2	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade ≥ 3	Delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue obinutuzumab at investigator discretion.
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS	
Grade ≤ 2	Maintain current dose level and schedule
Grade ≥ 3	If felt to be related to obinutuzumab, delay obinutuzumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue obinutuzumab at investigator discretion.

6.6. End of Study

End of study will be defined when the last subject reaches the last scheduled follow-up timepoint, is lost to follow-up, withdraws from the study, dies, or the time at which the Sponsor closes the study. At the end of the study, subjects will transition onto standard of care treatment.

6.7. Post Study Care

There is no plan to provide post study care to subjects that have participated in this study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- 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) or serious adverse drug reactions (SADR) 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.

Disease Progression and Death Related to Disease Progression:

Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drugs will not be considered 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 (i.e., by a means other than lack of effect). Unrelated disease progression 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).

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 adverse event 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 adverse event 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 adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event 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 (Appendix 7). For each episode, the highest severity grade attained should be reported.

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

Table 7-1. Grading of Adverse Event Severity

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

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

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the electronic case report form eCRF: all SAEs and adverse events 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 adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that 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 CRF/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 CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

  Gilead PVE: Fax: 1-650-522-5477
  Email: Safety_FC@Gilead.com

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

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the 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. Toxicity Management

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

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

7.5.1. Warnings and Precautions

7.5.1.1. Hemorrhage

Tirabrutinib: 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, and petechiae, and major hemorrhagic events such as small intestinal hemorrhage and subdural hematoma.

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

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

7.5.1.2. Dermatological and Hypersensitivity Events

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

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

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in subjects receiving idelalisib. Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN has been confounded by the coadministration of antineoplastic agents (e.g., bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (e.g., allopurinol). If SJS or TEN is suspected, idelalisib and all coadministered medications associated with SJS or TEN should be interrupted and the subject treated accordingly.

Subjects should be monitored for the development of SJS, TEN, or other severe cutaneous reactions and idelalisib treatment must be permanently discontinued if such events occur.

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

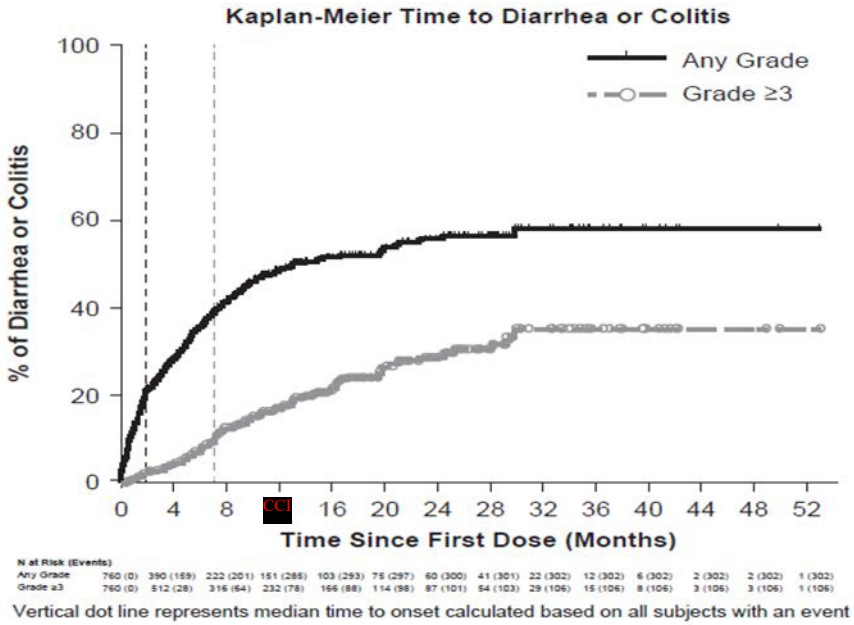
7.5.1.3. Gastrointestinal Events

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

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

For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered. Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0–29.8), of grade 1 or 2 was 1.5 months (range, 0.0-15.2) and of grade 3 or 4 was 7.1 months (range, 0.5–29.8). Kaplan–Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib- treated patients in Figure 7-1 {Coutre 2015}.

Figure 7-1. Kaplan-Meier Time to Diarrhea or Colitis



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

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

7.5.1.4. Hepatic Events

Idelalisib: Transaminase Elevations: Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were also observed early in the idelalisib program in phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations have been consistent with the ongoing experience with idelalisib treatment and transaminase elevations are now well characterized as most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

Entospletinib: Entospletinib is expected to produce asymptomatic and transient elevations of unconjugated (indirect) bilirubin due to inhibition of UGT1A1. In studies of subjects with hematologic malignancies, 3.6% (9/252) subjects had elevations of direct bilirubin with the onset of elevation ranging from Day 8 to 85, except for 1 subject at Day 169. Bilirubin elevations were generally self-limited and did not result in discontinuation of entospletinib. Transaminase increase was reported as an AE in approximately 45% of subjects. Increased transaminases were noted in some subjects approximately 2 weeks after completion of study drug.

7.5.1.5. Hematological and Immunological Events

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

Idelalisib: In the Phase 1 experience with idelalisib in patients with NHL and CLL, subjects with Grade ≥3 neutropenia, anemia, and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during idelalisib administration were largely due to minor fluctuations in these parameters among subjects with pre-existing hematological abnormalities due to disease or prior therapy. Thus, idelalisib did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed.

Treatment-emergent Grade 3 or 4 neutropenia events including those accompanied by fever or infection have occurred in subjects treated with idelalisib, most commonly in the context of myelosuppressive agents such as bendamustine. All subjects will have their absolute neutrophil count monitored at least every two weeks for the first 24 weeks of idelalisib treatment. Management of neutropenia, including administration of G-CSF should be per established clinical guidelines and institutional standard of care.

No modification of any drug for changes in circulating CD4+ counts or Ig levels is planned.

7.5.1.6. Infectious Events

Tirabrutinib: 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.

Idelalisib: Patients with lymphoid cancers receiving idelalisib have developed serious and fatal infections during therapy. Opportunistic infections, most notably PJP and CMV infection, have most frequently occurred within the first 6 months of treatment with idelalisib and are increased in the context of concurrent myelosuppressive therapy such as bendamustine.

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

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

In high-risk subjects (history of recurrent infection, allogeneic transplant, treatment with alemtuzumab, hypogammaglobulinemia) other infection prophylaxis should be considered per consensus guidelines. Administration of intravenous immunoglobulin is permitted per standard institutional practice {Raanani 2009}. For subjects who develop an infection, appropriate medical therapy should be instituted in a timely manner.

7.5.1.7. Pulmonary Events

Idelalisib: Documented bacterial, fungal, viral, and PJP infections have been observed in patients receiving idelalisib, primarily in patients with CLL. Some study subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis or organizing pneumonia, respectively without documented pulmonary infection. Some of these events have required mechanical ventilation or have been fatal. Nonclinical evaluations of pulmonary function and pathology do not indicate a direct toxic effect of idelalisib on the lungs, and disease-related factors or toxicity from prior or concomitant therapies may have contributed to these clinical events. In subjects presenting with serious lung events, idelalisib should be interrupted and the subject assessed for an explanatory etiology. If organizing pneumonia is diagnosed, treatment with idelalisib should be permanently discontinued and the subject treated accordingly.

Entospletinib: Documented pneumonia has been identified in patients receiving single agent entospletinib. Pneumonitis has not been identified as a risk with entospletinib monotherapy.

Tirabrutinib: Documented pneumonia has been identified in patients receiving single agent tirabrutinib. In an ongoing Phase 1 single agent study in Japanese subjects, an SAE of pneumonitis has been reported in 1 subject who had pre-existing organizing pneumonia. The pneumonitis resolved with interruption of tirabrutinib and treatment with corticosteroids.

Given the potential for infectious or drug-related pulmonary adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of ≥5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT) should be evaluated. Potential bacterial, fungal, or viral etiologies should be assessed. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

As appropriate for the clinical situation and culture results, subjects should be treated empirically or given specific antibiotics, antifungals, or antiviral agents for a cultured organism. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary.

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. For subjects with suspected Grade ≥ 2 pneumonitis (eg, new onset or worsening of baseline of cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate. Entospletinib and/or tirabrutinib should be interrupted and therapy with systemic corticosteroids (eg, prednisone, 60mg/day) should be instituted rapidly {Liote 2010}. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary.

7.5.1.8. Secondary Malignancies

Idelalisib: Subjects receiving idelalisib for CLL or iNHL have developed pre-malignant and secondary malignant diseases, such as basal cell carcinoma, myelodysplastic syndrome, myeloproliferative disorders, and more aggressive lymphoid malignancies (eg, have had Richter transformation). Generally this has occurred in subjects who have received multiple previous lines of therapy and when idelalisib is combined with other therapies such as rituximab or bendamustine. The specific association of the therapeutic agents with these types of events has not been determined.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to 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 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:
Gilead PVE: Fax: 1-650-522-5477
Email: Safety_FC@Gilead.com

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

7.6.2.2. Reporting Other Special Situations

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

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situation 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 Endpoints

8.1.1. Primary Endpoint

Dose Escalation Phase: The primary endpoint is safety. Safety will be evaluated by:

- Occurrence of AEs and laboratory abnormalities defined as DLTs

Dose Expansion Phase: The primary endpoint is efficacy. Efficacy will be evaluated by:

- ORR at Week 12 for non-CLL subjects and Week 24 for CLL subjects, defined as the proportion of subjects who achieve a CR or PR as assessed by disease type (Appendix 4, Appendix 5, and Appendix 6). In subjects with CLL, the proportion of subjects achieving CR and negative minimal residual disease (MRD) will also be evaluated.

Long-Term Safety Monitoring Phase: The primary endpoint is safety. Safety will be evaluated by:

- The incidence and severity of AEs as defined by CTCAE v4.03.

8.1.2. Secondary Endpoints

- ORR defined as the proportion of subjects who achieve a CR or PR as assessed by disease type.
- PFS defined as the interval from the start of the study therapy to the earlier of the first documentation of definite disease progression or death from any cause
- Duration of response (DOR) defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definite disease progression or death from any cause.
- Time to response (TTR) defined as the interval from start of treatment to the first documentation of CR or PR
- In subjects with CLL only: proportion of subjects who achieve minimal residual negative disease (< 1 leukemia cell/10,000 leukocytes)
- Pharmacokinetic parameters (C_{max}, and AUC_{tau}) for tirabrutinib, idelalisib and idelalisib metabolite GS-563117, and entospletinib, as applicable

CCI [redacted]

8.2. Analysis Sets

8.2.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who are enrolled in the study. This analysis set will be used in the analyses of subject characteristics, disposition, and efficacy. Subjects will be grouped by dose level assigned, and overall where appropriate.

8.2.1.1. Safety Analysis Set

Safety Analysis Set includes subjects who receive at least 1 dose of study treatment. Subjects will be grouped by dose level received, and overall where appropriate.

8.2.1.2. Pharmacokinetics Analysis Set

The Pharmacokinetic Analysis Set includes subjects who receive at least one dose of study treatment and have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest. This analysis set will be used in the analysis of tirabrutinib, idelalisib, GS-563117 and entospletinib plasma pharmacokinetics, as applicable.

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, 90% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2 sided. 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. 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.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

8.4. Demographic Data and Baseline Characteristics

A listing of all enrolled subjects will be generated to describe site, subject number, first screening date, first treatment date, dose level, duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened but not treated may be listed separately.

Subject demographic and baseline characteristics will be listed and summarized by dose level using the all enrolled analysis set.

8.5. Efficacy Analysis

Response criteria for each disease are included in Appendix 4, Appendix 5, and Appendix 6.

8.5.1. Primary Analysis

Overall response rate along with the 95% CI will be estimated. Subjects who do not have sufficient baseline or on study tumor assessment to characterize response will be counted as non-responders.

Duration of response and progression free survival will be analyzed using Kaplan-Meier (KM) methods. The KM estimate of the survival function will be computed and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided. In addition, the estimated rate at 12, 18 and 24 months will be reported.

The following censoring rules will be applied:

- For a subject who is not known to have relapsed or died by the end of the study follow-up or data cutoff, PFS and DOR are censored on the date of the last available disease assessment of the subject.

8.6. Safety Analysis

All safety data collected on or after the date of first dose of study treatment up to 30 days after the date of last dose of treatment will be summarized by dose level and overall.

8.6.1. Extent of Exposure

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 and idelalisib or entospletinib 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).

8.6.2. Adverse Events

The focus of AE summarization will be on TEAE. A TEAE is defined as an AE that onset in the period from the first dose of study treatment to 30 days after the last dose of study treatment. All adverse events, if reported, will be included in data listings.

Adverse events will be classified using MedDRA (http://www.meddramsso.com) with descriptions by System Organ Class, High-Level Group Term, High Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the adverse event to the study treatment will be assessed by the investigator and categorized as related or unrelated.

Treatment-emergent adverse events will be summarized. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. Adverse event 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 adverse events:

- Study-drug-related adverse events
- Adverse events that are Grade ≥ 3 in severity
- Adverse events leading to study treatment interruption and/or dose modification
- Adverse events leading to study treatment discontinuation
- Serious adverse events
- DLT will be listed and summarized; DLT rate will be presented by phase and dose level and the corresponding 90% CIs will be presented

8.6.3. 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 to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade >=1 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 central 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.

Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

Concentrations of tirabrutinib, idelalisib, GS-563117, and entospletinib (as applicable) in plasma will be determined using a validated bioanalytical assay. Plasma concentrations will be displayed as individual concentration vs. time using scheduled sampling times. Concentrations and PK parameters (C_{max}, C_{tau}, AUC_{last}, AUC_{tau}, T_{max}, and $t_{½}$, as applicable) will be listed by subject and summarized using descriptive statistics (eg, n, arithmetic mean, geometric mean, % coefficient of variation [CV], StD, median, Q1, Q3, min, and max). Mean (±StD) plasma concentration-time curves will be plotted in both semi-logarithmic and linear formats.

8.8. Biomarker Analysis

Changes in biomarkers will be evaluated descriptively. Data explorations may be performed to evaluate potential associations between subject characteristics and outcome measures. Explorations may also be performed to assess the potential associations between different outcomes measures (eg, relationships between biomarkers and clinical endpoints of response).

8.9. Sample Size

The trial employs the standard National Cancer Institute (NCI) definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window) to determine dose escalation. The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next cohort of the study if the true underlying probability of DLT is low. For example, if the true underlying proportion of DLT is low (eg, ≤ 10%) at the current dose level, there is a high probability (≥ 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, ≥ 60%) at the current dose level, there is a low probability (≤ 0.08) of escalation to the next dose level (see Table 8-1).

Table 8-1. Probability of Dose Escalation (N=3+3)

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

It is estimated that approximately 90 evaluable subjects will be needed for the planned dose escalation phase of the study. Under the assumption that ~10% of enrolled subjects may not be evaluable for DLT, approximately 98 subjects will be enrolled during the dose escalation phase.

During the dose expansion phase, up to 270 subjects will be enrolled under the assumption that up to 9 dose levels and/or disease types will be selected and up to approximately 30 subjects are to be enrolled in each expansion cohort. The sample size of the expansion cohort is determined based on Simon's 2-stage optimal design. If 3 or less out of the first 11 subjects achieve response, then the expansion of the cohort will be stopped; else the enrollment will continue to 30 subjects. The design will have about 83% power to rule out that ORR is below 25% based on a 1-sided binomial test at 0.05 significance level with assumed response rate of 50%.

In addition, as of Amendment 9, up to 8 additional subjects from Study GS-US-401-1787 or previously enrolled in Study GS-US-401-1757 or Study GS-US-401-1787 who are currently receiving continued treatment via named patient use may be enrolled for long-term safety monitoring.

Therefore, up to 376 subjects may be enrolled in the study.

8.10. Timing of Analyses

8.10.1. Interim Analysis

After the subjects enrolled under Protocol Amendment 8 (or earlier versions) complete their efficacy assessments, interim analysis will be performed on these subjects.

8.10.2. Final Analysis

Final study reporting is expected to occur after all subjects have discontinued from the 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 Harmonization (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 sub investigator'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/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC 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/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 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/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, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

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

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

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

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

9.1.6. Case Report Forms

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

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGEMENT

A Phase 1b Dose Escalation and Dose Expansion Study of Tirabrutinib (ONO/GS-4059) in Combination with other Targeted Anti-cancer Therapies in Subjects with B-cell Malignancies

GS-US-401-1757, Protocol Amendment 10, 01 May 2020

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

PPD

Name (Printed)
Author

S PPD

May 1 2020

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table (Dose Escalation and Dose Expansion)

Study Phase	Screening		First 29 Days					Cycle 2 and 3 Day 1 and every 2 weeks, Cycle 4 +, Day 1 and every 4 weeks[ee]	Cycle 2 and 3 Day 8	Every 12 weeks (6 weeks for DLBCL)[a,ee]	Every 12 weeks as of amendment 7 [ff]	EOT	30-day Safety Follow-up[b]
Cycle Day	Day -28	Study Day 1	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22						
Window (day)	-28		0	±1	±1	±2	±2	±7	±7	±7	±7	±7	±7
Informed Consent	X												
Medical and Medication History[c]	X		X					X			X		
Physical Examination[d]	X		X		X	X	X	X			X	X	
Vital Signs[e]	X		X		X	X	X	X			X	X	
ECOG Performance Status	X		X		X	X	X	X			X	X	
Single 12-lead ECG dose escalation[f]	X		X	X	X			X					
Single 12-lead ECG dose expansion[f]	X		X					X[g]					
Adverse events/Concomitant medications[h]	X		X		X	X	X	X			X	X	X
IP Accountability and/or Dispensing[i]			X	X	X	X	X	X			X	X	
Obinutuzumab[dd]		X											
Pneumocystis jirovecii pneumonia (PJP) prophylaxis			X[cc]								X[cc]		
CBC with differential	X		X		X	X	X	X[bb]			X	X	
Chemistry	X		X		X	X	X	X	X[j]		X	X	

Study Phase	Screening		First 29 Days					Cycle 2 and 3 Day 1 and every 2 weeks, Cycle 4 +, Day 1 and every 4 weeks[ee]	Cycle 2 and 3 Day 8	Every 12 weeks (6 weeks for DLBCL)[a,ee]	Every 12 weeks as of amendment 7 [ff]	EOT	30-day Safety Follow-up[b]
Cycle Day	Day -28	Study Day 1	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22						
Window (day)	-28		0	±1	±1	±2	±2	±7	±7	±7		±7	±7
Coagulation (INR, aPTT)	X		X		X			X[k]			X	X	
Lymphocyte Immunophenotyping and Immunoglobulins[l]	X							X[l]		X			
Hepatitis Serology[m]	X												
CMV Serology [n]			X										
Evaluation for CMV reactivation	X		X					X[aa]			X[aa]		
Urinalysis and Urine Chemistry			X		X			X[k]					
Pregnancy Testing[o]	X		X					X			X	X	
PK sampling in dose escalation[p]			X	X	X	X		X					
PK sampling in dose expansion[q]			X		X			X[k]					
Pharmacodynamic sampling in dose escalation[r]			X	X	X								
Pharmacodynamic sampling in dose expansion[s]			X		X			X[s]					
CCI													

Study Phase	Screening		First 29 Days					Cycle 2 and 3 Day 1 and every 2 weeks, Cycle 4 +, Day 1 and every 4 weeks[ee]	Cycle 2 and 3 Day 8	Every 12 weeks (6 weeks for DLBCL)[a,ee]	Every 12 weeks as of amendment 7 [ff]	EOT	30-day Safety Follow-up[b]
Cycle Day	Day -28	Study Day 1	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22						
Window (day)	-28		0	±1	±1	±2	±2	±7	±7	±7		±7	±7
Disease biomarkers (CLL, MCL, SLL only)[u]			X										
Archival Tumor Tissue[v]			X										
CCI													
Bone marrow evaluation[x]	X												
CCI													
Radiographic Tumor evaluation[a]	X									X		X	
Treatment Response Assessment[z]								X		X			

\+ Day 1 of subsequent cycles.

a Tumor evaluation by neck, chest abdomen and pelvis will be performed during screening (within 28 days of Cycle 1, Day 1) and every 12 weeks (in DLBCL every 6 weeks for the first 12 weeks). Subjects with CLL will only undergo scans at baseline, 24 weeks and at the time of progression. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. Scan at EOT visit is not necessary if restaging scan is performed within 4 weeks of the EOT. Scans will be transferred to a central reader for collection and future analysis. Tumor evaluation for WM will include serum IgM. If Complete Response, bone marrow evaluation may be required for some diseases and/or to evaluate MRD (as per Appendix 4, Appendix 5, and Appendix 6). As of Amendment 7, CT/MRI scans will no longer be performed and will only be performed at the time of disease progression or at study discontinuation.

b Subjects who miss the 30 day Safety Follow-up visit will be contacted by phone 30 days (± 7 days) after the last dose of tirabrutinib and idelalisib or entospletinib to assess AEs.

c Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses. Obtain smoking history at screening (for the past 60 days) and at Day 1 of each Cycle (for the past 28 Days).

d Screening and End of Treatment will be complete physical examinations. 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). Weight (without shoes) should be measured at each PE. Height (without shoes) should be measured at screening only.

e Cycle 1, Day 1 vital signs will be taken within 15 min pre-tirabrutinib dose and 2 and 4 hours post dose (+/- 15 min); vital signs will be taken pre-dose only at all subsequent visits. For subjects in Group V the 2 and 4 hour post-dose vital signs are not required.

f ECG: ECGs should be performed in triplicate. Subjects should be resting quietly in supine position 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 and transferred to a central vendor for storage. As of Amendment 7, this will no longer be performed.

g In dose expansion ECGs will occur at screening, baseline and then C1D1 up to C6. As of Amendment 7, ECGs will no longer be performed.

h Adverse events will be assessed at pre- and post-tirabrutinib and idelalisib or entospletinib dosing during applicable clinic visits. Subjects will also return to clinic at 30-day post last IP dose, to assess AEs and SAEs. If an AE of diarrhea is reported see Section 6.2.8.1 for full evaluation details.,

i Tirabrutinib will be dispensed on Cycle 1, Day 1. Idelalisib or entospletinib will be dispensed on Cycle 1, Day 2. Tirabrutinib and idelalisib or entospletinib will be dispensed on Day 1 of all subsequent cycles.

j Liver Function Tests only on Day 8 of Cycle 2 and 3; AST, ALT, Alkaline phosphatase, GGT, total bilirubin, direct bilirubin

k Discontinue after Cycle 6, Day 1

l Lymphocyte Immunophenotyping by flow cytometry serum quantitative immunoglobulins (IgG, IgM, IgA) , serum CH50 at screening, C2D1, C4D1, then every 12 weeks, end of treatment (EOT) and 30 day safety follow-up visits. As of Amendment 7, this will no longer be performed.

m Hepatitis Serology includes: HBsAG, Hepatitis B core antibody and Hepatitis C antibody.

n CMV Serology testing includes: CMV serology.

o Serum pregnancy test will be performed at screening for all women of childbearing potential (defined in Appendix 8). Urine pregnancy test will be conducted prior to Cycle 1, Day 1, every 28 days thereafter, then every 12 weeks as of amendment 7 and at EOT visit. The results must be confirmed as negative prior to continued administration of [redacted]

q A plasma sample will be collected on Cycle 1, Day 1 between 1.5-4 hours inclusive post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a PK sample will be collected at pre-dose and one between 1.5 and 4 hours inclusive post-dose of tirabrutinib and idelalisib or entospletinib. A sparse PK sample will also be collected anytime on the first day of Cycles 3 to 5 and at pre-dose on the first day of Cycle 6.

r Blood samples for pharmacodynamics will be collected on Cycle 1, Day 1 at pre-dose, 2 and 6 hours post-dose, Cycle 1, Days 2 and 8 at pre-dose, 2, 6 and 24 hours post-dose and end of treatment or disease progression. When study drug is administered BID, the 24 hour sample will be collected 24 hours post-dose relative to morning dose. The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling time points may be eliminated or modified based upon emerging data. As of Amendment 7, Pharmacodynamics samples will no longer be collected.

s Pharmacodynamic samples will be collected on Cycle 1, Day 1 at predose and between 1.5 and 4 hours inclusive post-dose of tirabrutinib. On Cycle 1, Day 8 and Cycle 2, Day 1, a pharmacodynamic sample will be collected at pre-dose and between 1.5 and 4 hours inclusive post dose of tirabrutinib and idelalisib or entospletinib. Pharmacodynamic samples should be collected at approximately the same time as PK samples, where applicable. As of Amendment 7, Pharmacodynamics samples will no longer be collected.

t [redacted]

u Disease specific biomarkers (e.g. prognostic) for CLL, SLL, MCL subjects: peripheral blood will be collected prior to therapy at Cycle 1, Day 1 and at disease progression. For CLL and MCL patients, a blood sample will be collected at CR for MRD testing. As of Amendment 7, Pharmacodynamics samples will no longer be collected.

v If available, paraffin embedded archival tumor tissue block for shipment to Gilead or its designee will be requested after Cycle 1, Day 1 only if biopsy is not medically feasible.

w CCI [redacted]

x For Waldenstrom's macroglobulinemia subjects, bone marrow aspirates will be collected prior to the first dose if MYD88 and CXCR4 mutation status is not known and at disease progression. For CLL and MCL subjects, bone marrow aspirates will be collected at CR for MRD testing. As of Amendment 7, these will no longer be collected.

y CCI [redacted]

z Clinical Assessment of response based on available data every 4 weeks starting with Cycle 2, Day 1 until Cycle 6, Day 1, and then every 12 weeks. As of Amendment 7, these will no longer be performed.

aa For subjects on treatment with idelalisib, CMV surveillance by PCR or PP65 Ag testing and clinical evaluation for CMV reactivation, to be done as per local standard of care at screening, C1D1, approximately every 28 days and every 12 weeks as of amendment 7.

bb CBC with differential every 2 weeks for the first 24 weeks of Idelalisib treatment

cc Antibiotic prophylaxis for PJP is mandatory for subjects on idelalisib therapy and should be continued for 2-6 months after idelalisib discontinuation. PJP prophylaxis should be instituted for patients with CLL irrespective of treatment arm unless medically contraindicated. PJP prophylaxis should be considered for up to 12 months following obinutuzumab treatment and throughout study drug therapy, particularly in subjects with multiple risk factors for *Pneumocystis* infection.

dd Obinutuzumab will be initiated on Study Day 1 with a test dose of 100 mg. If this dose is tolerated well, the remainder of the full dose will be subsequently administered on Study Day 1. Alternatively, the remaining 900 mg will be administered on Study Day 2. Subsequent infusions of obinutuzumab will be administered on Cycle 1, Day 6 (+/- 2 days), Cycle 1, Day 13 (+/- 2 days), Cycle 2, Day 1 (+/- 3 days) and then every 28 days(+/- 3 days) until Cycle 6, Day 1 (+/- 3 days) for up to 8 intravenous infusions of 1000 mg each.

ee As of amendment 7, these assessments will no longer be completed after subjects have completed at least 1 year on treatment.

ff As of amendment 7, study visits will occur every 12 weeks after subjects have completed at least 1 year on treatment.

Appendix 3. Study Procedures Table (Long-Term Safety Monitoring)

Study Phase	Screening[a,b]	Long-Term Safety Monitoring	Every 12 Weeks (First 12 Months)	Every 24 Weeks (After First 12 Months)	EOT	30-day Safety Follow-up
Cycle Day	**Day -28**	**Cycle 1 Day 1[b]**				
Window (day)	-28	0	±7	±7	±7	±7
Informed Consent	X					
Verification of Eligibility[a]	X					
Clinical Assessment	X[f,g]	X[f,g]	X[g]	X[g]		
Medical and Medication History[e]	X	X				
Adverse Events/ Concomitant Medications	X	X	X	X	X	X
IP Accountability and/or Dispensing		X	X	X	X	
Pneumocystis jirovecii Pneumonia (PJP) Prophylaxis[c]		X	X	X	X	
Evaluation for CMV Reactivation[d]		X	X	X		
Urine Pregnancy Testing	X[a]	X	X	X	X	

AE = adverse event; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; EOT = end of treatment; IP = investigational product; PJP = *Pneumocystis jirovecii* pneumonia

a Screening will only apply to Group VI. Urine pregnancy testing performed up to 30 days prior to enrollment and imaging performed up to 90 days prior to enrollment may be used to determine eligibility.

b Subjects from the ongoing Study GS-US-401-1787 who enroll into Group VI in this study should have their Study GS-US-401-1787 EOT visit, Study GS-US-401-1757 Screening, and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day. Subjects on named patient use who enroll into Group VI in this study should have their Study GS-US-401-1757 Screening and Long-Term Safety Monitoring Cycle 1 Day 1 visit on the same day.

c Antibiotic prophylaxis for PJP is mandatory for subjects on idelalisib therapy and should be continued for 2 to 6 months after idelalisib discontinuation. PJP prophylaxis should be instituted for patients with CLL irrespective of treatment arm unless medically contraindicated. PJP prophylaxis should be considered for up to 12 months following obinutuzumab treatment and throughout study drug therapy, particularly in subjects with multiple risk factors for *Pneumocystis* infection.

d For subjects on treatment with idelalisib, CMV surveillance by PCR or PP65 Ag testing and clinical evaluation for CMV reactivation, to be done as per local standard of care at Long-Term Safety Monitoring Cycle 1 Day 1, every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase.
e Medical and medication history will only apply to Group VI. Medical history should include AE that are ongoing at the time of enrollment in this study.
f Subjects in screening and subjects currently on the study who have no clinical evidence of disease progression may enroll or transition into long-term safety monitoring. If there is clinical evidence of disease progression, a confirmatory radiologic assessment should be performed per institutional standard of care.
g Clinical assessment should include assessment for disease progression and laboratory assessments per institutional standard of care.

Appendix 4. Waldenstrom's Macroglobulinemia Assessment

Category	Finding
Laboratory	Serum monoclonal IgM > 0.5 g/dL Hemoglobin level < 10 g/dL Platelet count < 100 x 10^9 /L
Laboratory + symptoms	Cryoglobulinemia with symptoms Hyperviscosity with symptoms
Physical Findings	Bulky adenopathy Organomegaly
Symptoms	Recurrent fevers Night sweats Weight loss Fatigue Symptomatic neuropathies
Organ Disease	Nephropathy Amyloidosis
Pathology	Disease Transformation

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, ie, 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, ie, 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, ie, 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, ie, lymphadenopathy/splenomegaly if present at baseline; 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 5. 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, idelalisib, entospletinib and similar drugs.

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 LD × the LPD will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) for each index lesion and the 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 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 s 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, PR with Lymphocytosis, 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 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 $\geq 100 \times 10^9$/L without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

1.4.2. Minimal Residual Disease (MRD)

- Achieving MRD is defined as < 1 leukemia cell/10,000 leukocytes (10^{-4}) in patients who have also achieved a CR

1.4.3. 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 Appendix 4, Section 1.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Appendix 4, 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)

1.4.4. 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

1.4.5. 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 or aspirate 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

1.4.6. 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.

1.4.7. PR with Lymphocytosis

- Tirabrutinib, idelalisib, 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 and idelalisib or entospletinib 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 Sections 3.6 and 3.7.

Appendix 6. Follicular Lymphoma, Marginal Zone Lymphoma, Small Lymphocytic Lymphoma, Diffuse Large Cell Lymphoma and Mantle Cell Lymphoma Response Assessment

The determination of FL, MZL, SLL, DLBCL and MCL 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

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.

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 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 Appendix 5, 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.

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 to be fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

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

Currently, insufficient data exists for any of the 3 Gilead study drugs to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen in this study.

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

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Also, subjects must not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Cycle 1, Day 1 visit prior to dosing. Urine pregnancy tests will be performed at 28-day intervals thereafter, then every 12 weeks as of Amendment 7 and at the EOT visit.

As of Amendment 9, female subjects of childbearing potential must have a negative urine pregnancy test at Screening to enroll into long-term safety monitoring. Urine pregnancy tests will be performed at Long-Term Safety Monitoring Cycle 1 Day 1, every 12 weeks for the first 12 months, and then every 24 weeks during the long-term safety monitoring phase, and at the EOT visit.

Female subjects of childbearing potential must agree to one of the following from Screening until 30 days following the final dose of either tirabrutinib, idelalisib, or entospletinib, or until 18 months following the final dose of obinutuzumab (whichever is later).

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization
  - 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 following the final dose of either tirabrutinib, idelalisib, or ENTO, or until 18 months following the final dose of obinutuzumab (whichever is later).

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects who can father a child must limit intercourse to female partners who are surgically sterile, post-menopausal, or use effective contraception; or agree to use a recommended method of contraception during heterosexual intercourse throughout the study treatment period and until 90 days following the final dose of either tirabrutinib, idelalisib, or entospletinib, or until 18 months following the final dose of obinutuzumab (whichever is later). Additional contraception recommendations should also be considered if the female partner is not pregnant.

For this study, a man is considered able to father a child unless he has had a vasectomy on both sides, had had removal of both testicles, or is undergoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) drug such as goserelin acetate (Zoladex®), leuprolide acetate (Lupron®), or triptorelin pamoate (Trelstar®).

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

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

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

Appendix 9. Eastern Cooperative Oncology Group (ECOG) Performance Status

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