STATISTICAL ANALYSIS PLAN

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 Participants with B-cell Malignancies
Name of Test Drug:	Tirabrutinib
Study Number:	GS-US-401-1757
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse events of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
C1D1	cycle 1 day 1
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FL	follicular lymphoma
Hb	Hemoglobin
ID	identification
iNHL	indolent non-Hodgkin lymphoma
LOQ	limit of quantitation
LTSM	long-term safety monitoring
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximal tolerated dose
MZL	marginal zone lymphoma
NLP	natural language processing
non-GCB-DLBCL	non-germinal center B-cell-like diffuse large B cell lymphoma
ORR	overall response rate
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization

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	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
StD	standard deviation
SLL	small lymphocytic lymphoma
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TE-AEI	treatment-emergent adverse event of interest
TFLs	tables, figures, and listings
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and defines key elements including variable definitions for analysis of data of Study GS-US-401-1757 in support of the clinical study report (CSR). This SAP is based on the study protocol Amendment 10/10.1 dated 01 May 2020 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives and Endpoints

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 participants with relapsed or refractory B-cell lymphoproliferative malignancies

- To characterize the safety and tolerability of tirabrutinib combined with obinutuzumab and idelalisib or entospletinib in participants 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

- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab, and idelalisib or entospletinib in participants with relapsed or refractory B-cell lymphoproliferative malignancies

- To evaluate the preliminary efficacy of tirabrutinib alone administered at 80 mg once daily in participants with relapsed or refractory chronic lymphocytic leukemia (CLL)

For the 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 participants 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 participants with relapsed or refractory B-cell lymphoproliferative malignancies
- To evaluate the preliminary efficacy of tirabrutinib combined with obinutuzumab, and idelalisib or entospletinib in participants 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 participants 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 participants with a specific tumor subtype
- To further characterize the safety and tolerability of tirabrutinib combined with obinutuzumab, and idelalisib or entospletinib in participants with a specific tumor subtype
- To characterize the safety and tolerability and evaluate the preliminary efficacy of single-agent tirabrutinib in participants with relapsed or refractory CLL

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[redacted]

The primary endpoints of the study are:

For the Dose Escalation Phase:

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

- Occurrence of AEs and laboratory abnormalities defined as dose limiting toxicities (DLTs)

For the Dose Expansion Phase:

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

- Overall response rate (ORR) at Week 12 for non-CLL participants and Week 24 for CLL participants, defined as the proportion of participants who achieve a complete response (CR) or partial response (PR) as assessed by disease type.

For the Long-Term Safety Monitoring Phase:

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

- The incidence and severity of adverse events (AEs) as defined by Common Terminology Criteria for Adverse Events (CTCAE) v4.03

The secondary endpoints of the study are:

- ORR defined as the proportion of participants who achieve a CR or PR as assessed by disease type.
- 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
- In participants with CLL only: proportion of participants who achieve minimal residual negative disease (< 1 leukemia cell/10,000 leukocytes)
- Pharmacokinetic parameters (Cmax, and AUCtau) for tirabrutinib, idelalisib and idelalisib metabolite GS-563117, and entospletinib, as applicable

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1.2. 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 participants 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: dose-escalation phase, expansion phase, and long-term safety monitoring.

Table 1-1. Study Design Overview

	Treatment Regimen	Patient Population	Dose Escalation	Dose Expansion
Combination I	Tirabrutinib + Idelalisib	B-cell lymphoproliferative malignancies*	Combination I-A and I-B with independent 3 + 3 dose escalation plan	Expansion on specific B-cell malignancy subtype
Combination II	Tirabrutinib + Entospletinib	B-cell lymphoproliferative malignancies*	Combination II-A and II-B with independent 3 + 3 dose escalation plan	Expansion on specific B-cell malignancy subtype
Combination III	Tirabrutinib + Idelalisib + Obinutuzumab	B-cell lymphoproliferative malignancies*	Tirabrutinib + idelalisib dose level decided in the dose escalation part of Combination I, with the addition of obinutuzumab.	Expansion on specific B-cell malignancy subtype
Combination IV	Tirabrutinib + Entospletinib + Obinutuzumab	B-cell lymphoproliferative malignancies*	Tirabrutinib + idelalisib dose level decided in the dose escalation part of Combination II, with the addition of obinutuzumab.	Expansion on specific B-cell malignancy subtype
Group V	Tirabrutinib	CLL	Not applicable	CLL
Group VI^ (refer to Section 1.2.3)	All possible combinations from I to V above	All possible patient population from I to V above	Not applicable	Not applicable

* B-cell lymphoproliferative malignancies include follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), CLL, MCL, Waldenstrom's macroglobulinemia (WM), or non-germinal center B cell like diffuse large B cell lymphoma (non-GCB DLBCL).

^ Group VI rollover for long-term safety monitoring is added in PA9/9.1 or after.

1.2.1. Dose Escalation

The dose escalation of tirabrutinib monotherapy has been studied previously in Study 4059POE001. Thus, Study GS-US-401-1757 will start with the dose escalation of combination therapy with tirabrutinib. Participants 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 with cohort sizes of 3 to 6 participants 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 size of 3 to 6 participants will be enrolled with the addition of a fixed dose of 1000 mg IV infusion x 8 doses 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 number of DLT occurs during the DLT assessment window (Cycle 1, Day 1 through Cycle 1, Day 28) in each cohort will be used to determine the MTD for the tirabrutinib combination therapies. Approximately 98 participants in total will be enrolled during the dose escalation phase.

The dose levels for dose escalation are specified in Table 1-2, Table 1-3, Table 1-4, and the dose escalation rules are specified in Table 1-5.

Table 1-2. Dose Escalation for Combination I (Tirabrutinib + Idelalisib)

Dose Level	Tirabrutinib	Idelalisib	Tirabrutinib	Idelalisib
	Combination I-A		Combination I-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 (diffuse large B-cell lymphoma) DLBCL only

Table 1-3. 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

Table 1-4. 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 1-2)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 1-3)	1000 mg IV infusion x 8 doses
B Triplet Dose Level 2	Dose determined by results of Combination I Dose Escalation (Table 1-2)	1000 mg IV infusion x 8 doses	Dose determined by results of Combination II Dose Escalation (Table 1-3)	1000 mg IV infusion x 8 doses

Table 1-5. Dose Escalation/DLT Guidelines

No. of Participants with a DLT at a Given Cohort	**Escalation Decision Rule**
0 out of 3	Enroll 3 participants at the next higher cohort. If this cohort is the highest cohort, it will be declared the maximally administered dose, and enroll 3 additional participants at this cohort.
≥ 2 out of 3	Dose escalation will be stopped. This cohort will be declared the maximally administered dose. Three additional participants will be entered at the next lower cohort if only 3 participants were treated previously at that dose.
1 out of 3	Enter 3 additional participants in this cohort. • If 0 of these 3 participants experience a DLT, proceed to the next higher cohort. • If 1 or more of these 3 participants experience a DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional participants will be entered at the next lower cohort if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level at or below the maximally administered dose	This is the MTD and generally the recommended Phase 2 dose. At least 6 participants 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.

1.2.2. Dose Expansion

Cohorts of up to approximately 30 participants may be enrolled 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 of tirabrutinib + idelalisib or tirabrutinib + entospletinib combined with obinutuzumab in specific B cell malignancies 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 participants 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.

1.2.3. Long-Term Safety Monitoring

As of Amendment 9/9.1, all participants (in Combination I, II, III, IV and Group V) remaining on the study at this time will transition into long-term safety monitoring.

All active participants who have no clinical evidence of disease progression and transition to long-term safety monitoring 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.

Group VI: Tirabrutinib (Participants off study 1787 or 1757 Roll Over to Long-Term Safety Monitoring [LTSM])

Participants from Study GS-US-401-1787 and participants who came off Study GS-US-401-1757 or Study GS-US-401-1787 but continued to receive treatment (Tirabrutinib single agent) via named patient use will be enrolled into Group VI to participate in long-term safety monitoring. Participants enrolled in Group VI will continue the same treatment regimen in Study GS-US-401-1787 or named patient use starting from LTSM Cycle 1 Day 1 (C1D1).

Participants from 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 LTSM C1D1 visit on the same day. Participants on named patient use who enroll into Group VI should have their Study GS-US-401-1757 Screening and LTSM C1D1 visit on the same day.

1.3. Sample Size and Power

The trial employs the standard National Cancer Institute definition of MTD (starting dose associated with DLT in < 33.3% of participants 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 1-6).

Table 1-6. 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 participants will be needed for the planned dose escalation phase of the study. Under the assumption that ~10% of enrolled participants may not be evaluable for DLT, approximately 98 participants will be enrolled during the dose escalation phase.

During the dose expansion phase, up to 270 participants will be enrolled under the assumption that up to 9 dose levels and/or disease types will be selected and up to approximately 30 participants 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 participants achieve response, then the expansion of the cohort will be stopped; else the enrollment will continue to 30 participants. 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 9.1, up to 8 additional participants from Study GS-US-401-1787 or previously enrolled in Study GS-US-401-1757 or Study GS-US-401-1787 receiving continued treatment via named patient use may be enrolled into Group VI for long-term safety monitoring.

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

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

After the participants enrolled under Protocol Amendment 8.1 (or earlier versions) completed their efficacy assessments, an interim analysis was performed on these participants in June 2021.

2.2. Final Analysis

The final analysis will be performed after all participants (except ongoing UK participants) have completed or discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

A few ongoing UK participants will transition to the MHRA's Special scheme, per investigators' requests. Data after the transition will not be captured in the GS-US-401-1757 study database and will not be covered in the final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and sorted by dose level assigned, participant identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The dose level to which participants were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity information for each participant will be presented in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by treatment combination.

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who received a participant ID number in the study after screening.

The All Enrolled Analysis Set will be used for data listings, unless otherwise specified.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of any study drug. This is the primary analysis set for safety analyses.

3.1.3. Dose-Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set includes all participants in the dose escalation, in Combination I, II, III, IV, who complete all treatment for at least 21 days within the first 28 days, or experienced a DLT prior to Day 28, inclusive.

During the DLT assessment window, if a participant who fails to receive study treatment of tirabrutinib and idelalisib or entospletinib at least for 21 total days for reasons other than DLT, another participant will be enrolled at the same dose level for replacement. For participants who are replaced but received at least 1 dose of study drug, they will be included in the Safety Analysis Set and not in the DLT Analysis Set.

3.2. Participant Grouping

For analyses based on the All Enrolled Analysis Set, participants will be grouped according to the treatment to which they were assigned. For analyses based on the Safety Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the treatment assigned at enrollment only when their actual treatment differs from assigned treatment for the entire treatment duration.

In general, participants will be grouped according to the treatment regimen and study part as follows:

- Combination I: tirabrutinib and idelalisib
- Combination II: tirabrutinib and entospletinib
- Combination III: tirabrutinib, idelalisib, and obinutuzumab
- Combination IV: tirabrutinib, entospletinib, and obinutuzumab
- Group V: tirabrutinib
- Group VI: tirabrutinib (Participants off study 1787 or 1757 roll over to LTSM)

Within combination I and II, different dose levels have been administered to different B-cell lymphoproliferative malignancy subtypes including FL, MZL, CLL, SLL, MCL, WM, and DLBCL. However, due to the limited sample size, breaking participants down by both dose level and disease types spontaneously may not be feasible. Thus, the following grouping rules will be applied to combination I and combination II:

Analysis Category	Grouping Rules
Enrollment	By dose level
Disposition Demographics and baseline characteristics Prior anticancer therapy	By dose level
	By disease subtypes: FL, MZL, CLL, SLL, MCL, WM, and DLBCL
Drug exposure duration	By dose level
	By disease types: CLL, DLBCL, MCL, FL, and other Non-Hodgkin's Lymphoma (NHL)
Disease history	Separate tables by NHL* (further break down by the subtypes within the table) and CLL (further break down by dose level within the table)
Treatment-Emergent Lab abnormality Tables Hematology shift from baseline Tables Treatment Emergent Adverse Event Tables (except for DLT) Death	By dose level
	By disease types: NHL* and CLL
Treatment-Emergent Dose Limiting Toxicity	By dose level
All others	By dose level only

* NHL is the non-Hodgkin lymphoma including DLBCL, FL, MZL, SLL, MCL, and WM.

For combination III or IV, one dose level was used to treat indolent NHL participants. For group V, one dose level was used to treat CLL participants.

For these regimen combinations (Combination III, IV and Group V), no further break down by disease subtype will be made.

For Group VI, more than one dose level was used to treat NHL and CLL participants. Considered the limited number of participants, Group VI will be grouped by disease type only.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants. No covariates will be included in the analyses.

3.4. Examination of Participant Subgroups

Overall summary of treatment-emergent adverse events will be examined in the following subgroups for Combination I, II (by disease type and by dose level) and Group V:

- Age group
  - < 65 years
  - >=65 years
- Gender
  - Male
  - Female
- Race
  - White
  - All other races

Due to limited sample size in combination III, IV and VI, no subgroup examination will be performed.

3.5. Adjustment for Multiplicity

Adjustments for multiplicity will not be made, since no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 5.2.1. The handling of missing or incomplete dates for disease under study diagnosis is described in Section 5.4, for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 5.6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic, and the COVID-19 pandemic has caused a disruption in the regular visit schedules for this study. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides guidance on how to handle special situations due to COVID-19 in the analysis.

3.7.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be created.

3.7.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviation related to COVID-19. A separate listing will be provided for participants with non-important protocol deviation related to COVID-19.

3.7.3. Missed and Virtual Visits Due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order. Information regarding virtual or missed visits due to COVID-19 was collected as free text in the CRF comment fields. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 1.

3.7.4. Adverse Events Due to COVID-19

Adverse events (AEs) due to COVID-19 will be included in AE analyses if applicable, which will be determined through COVID-19 Standardized MedDRA Queries (SMQ) broad search. A by-participant listing of AEs of COVID-19 will be provided.

3.8. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

3.9. Analysis Visit Windows

3.9.1. Baseline

Baseline (value) is defined the last measurement that was observed on or prior to the first dosing date of study drug, unless otherwise specified.

For Group VI participants, the first dosing date will be at LTSM C1D1.

3.9.2. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

3.9.3. Analysis Visit Windows

In general, the nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum post baseline toxicity grade.

For Group VI participants, the first nomial visit (after screening) will LTSM C1D1.

3.9.4. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. PROTOCOL DEVIATIONS

Participants who did not meet at least one eligibility criterion for study entry, but enrolled in the study will be summarized by treatment combination regardless of whether they were exempted by the sponsor or not, based on the All Enrolled Analysis Set. The summary will also present the number and percentage of participants who did not meet specific criteria. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason (e.g., eligibility criteria, informed consent) will be summarized by treatment combination for the All Enrolled Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

5. PARTICIPANT INFORMATION

5.1. Participant Enrollment and Disposition

Key study dates (i.e.,first participant screened, first participant enrolled, last participant enrolled, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided for Combination I (by dose level), II (by dose level), III, IV, Group V and Group VI, for each country, investigator, and overall. The summary will present the number and percentage of participants enrolled.

A summary of participant disposition using all screened participants will be provided by treatment combination (Combination I, Combination II, Combination III, Combination IV, Group V, Group VI) and Total. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not enrolled with reasons participants not enrolled, the number of participants in All Enrolled Analysis Set and the number of participants in each of the categories listed below.

Additional disposition tables for Combination I (by dose level and disease type), Combination II (by dose level and disease type) and Group VI (by disease type) will be provided as specified in Section 3.2 using All Enrolled Analysis Set.

- Safety Analysis Set
- Ongoing on Any Study Drug
- Discontinued/Completed all study drugs
- Tirabrutinib completion status
  - Ongoing study drug
  - Completed study drug
  - Discontinued study drug with reasons
- Idelalisib completion status
  - Ongoing study drug
  - Completed study drug
  - Discontinued study drug with reasons
- Entospletinib completion status
  - Completed study drug
  - Discontinued study drug with reasons

- Obinutuzumab completion status
  - Completed study drug
  - Discontinued study drug with reasons
- Study completion status
  - Ongoing Study
  - Completed study
  - Discontinued the study with reasons

For the status of study drug and study completion, and reasons for study drug and study discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column.

The following by-participant listings will be provided to support the above summary tables:

- Enrollment (sorted by treatment combination, cohort, then by participant ID in ascending order)
- Participant disposition (with reasons for study drug or study discontinuation)
- Reasons for screen failure (will be provided by screening ID number in ascending order)

5.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

5.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks and/or cycles using up to 1 decimal place (e.g., 4.5 weeks). If the last study drug dosing date is missing (including the ongoing UK participants), the latest non-missing date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for participants included in the final analyses. If month and year of the last dose are known, and the last study drug dosing date imputed above is different from the month collected, the last date of that month will be used. If only year of the last dose is known, and the last study drug dosing date imputed above is after the year collected, the last date of that year will be used; if the last study drug dosing date imputed above is before the year collected, the first date of that year will be used.

The total duration of exposure to study drug in weeks will be summarized using descriptive statistics. Summaries will be provided by treatment combination and dose level for the Safety Analysis Set.

For tirabrutinib/idelalisib/entospletinib, the number of cycles participants were exposed to study drug will be summarized using descriptive statistics, as well as the number and percentage of participants exposed to a given cycle category (≥ 1, ≥ 3, ≥ 6, ≥ 9, ≥ 12, ≥ 18, ≥ 24 etc. cycles). Each cycle consists of 28 days.

For obinutuzumab, the number of infusions will be summarized using descriptive statistics. Summaries will be provided by treatment combination for the Safety Analysis Set.

The number and percentage of participants who have dose reduction or interruptions, and the reasons, will be summarized by treatment combination.

No formal statistical testing is planned.

5.2.2. Adherence to Study Drug

For tirabrutinib, idelalisib and entospletinib, the presumed total amount of doses administered to a participant will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Amount of Study Drug Administered} = \left(\sum \text{No. of Doses Dispensed} \times \text{Strength}\right) - \left(\sum \text{No. of Doses Returned} \times \text{Strength}\right)$$

5.2.2.1. On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a participant's actual on-treatment period based on the study drug regimen.

Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account. For tirabrutinib, idelalisib and entospletinib, if there are treatment periods that bottles are not returned or the return information is missing, these periods will be excluded from the on-treatment adherence calculation for both total amount of study drug administered and study drug expected to be administered. If participants never returned any bottle, the adherence will be set as missing.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}}\right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of participants belonging to adherence categories (e.g., {< 75%, ≥ 75%}) will be provided by treatment combination and dose level for the Safety Analysis Set.

No formal statistical testing is planned.

A by-participant listing of study drug administration and drug accountability will be provided.

5.3. Demographics and Baseline characteristics

Participant demographics (ie, age, sex, race, and ethnicity) and baseline characteristics (ie, body weight, height, boday mass index [BMI; in kg/m^2], and Eastern Cooperative Oncology Group [ECOG] Performance Status) will be summarized using descriptive statistics for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, Group V and Group VI (by disease type) for the All Enrolled Analysis Set.

A by-participant demographics and baseline characteristics listing, including the informed consent date, will be provided by treatment combination, cohort and participant ID number in ascending order.

5.4. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Disease types of participants are classified as:

- CLL,
- NHL (SLL, FL, MZL, MCL, WM, and DLBCL).

CLL disease history will be summarized for Combination I (by dose level), Combination II (by dose level), Group V and Group VI based on the All Enrolled Analysis Set. NHL Disease history will be summarized for Combination I (by disease type), Combination II (by disease type), Combination III, Combination IV and Group VI based on the All Enrolled Analysis Set.

Time since disease diagnosis (years) will be calculated by (first dosing date of study drug – date of disease diagnosis) / 365.25. Time since disease diagnosis will be summarized using summary statistics for a continuous variable. Disease stage at screening will be summarized using summary statistics for a categorical variable. Disease diagnosis subtype will be summarized using summary statistics for a categorical variable for DLBCL (only for NHL disease history tables) participants. No inferential statistics will be generated.

General medical history data will not be coded and will be listed only.

In deriving the time since disease diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

5.5. Prior Anticancer Theray

Number of prior regimens, time since the completion of last regimen, and time since progression in the last regimen will be summarized for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, and Group V using descriptive statistics based on the All Enrolled Analysis Set. A partial completion date will be imputed using the algorithm defined in Section 5.4.

The regimens and prior therapies that the participants received will be summarized. The last regimen participants received prior to study entry and the best response to the last regimen will be summarized by treatment combination, dose level/disease type as specified in Section 3.2.

Number of participants who received prior radiation therapy and surgery will also be summarized.

All prior and on study radio-therapy, prior and on study surgeries and procedures will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

All prior anticancer therapies will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

5.6. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

5.6.1. Prior Medications

Prior medications are defined as any medications taken before a participant took the first study drug.

5.6.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study treatment. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each treatment combination. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term (PT) in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study treatment and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study treatment will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study treatment will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study treatment or a start date after the last dosing date of study treatment will be excluded from the concomitant medication summary. Medications with partially or completely missing start and stop dates will be included in the concomitant medication summary, unless the partial missing date suggested otherwise. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

5.7. Post Treatment Anti-cancer Therapies

All post treatment anti-cancer therapies (other than those allowed per-protocol) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

6. EFFICACY ANALYSES

6.1. Changes From Protocol-Specified Efficacy Analyses

The protocol-specified efficacy analyses were performed at the interim analysis in June 2021. Considering that data collected after the interim analyis is limited to safety, no efficacy analyses will be perfomed at the final analysis.

7. SAFETY ANALYSES

In general, all safety data collected during the study including long-term safety monitoring phase will be included in final analysis for Combination I, Combination II, Combination III, Combination IV, Group V and Group VI, unless otherwise specified. For Group VI participants, due to limited data, no summaries will be provided for laboratory evaluations, vital signs and electrocardiogram data.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Treatment

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Missing or incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent. In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.
- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

For AEs described below, The number and percentage of participants who experienced at least 1 TEAE will be summerized by system organ class (SOC), PT, maximum severity, combination, and dose level:

- All TEAEs
- TEAEs with Grade 3 or higher
- TEAEs related to tirabrutinib
- TEAEs related to idelalisib (Comb I and III only)
- TEAEs related to entospletinib (Comb II and IV only)
- TEAEs related to obinutuzumab (Comb III and IV only)

- TEAEs related to tirabrutinib of Grade 3 or higher
- TEAEs related to idelalisib of Grade 3 or higher (Comb I and III only)
- TEAEs related to entospletinib of Grade 3 or higher (Comb II and IV only)
- TEAEs related to obinutuzumab of Grade 3 or higher (Comb III and IV only)
- TE SAEs
- TE SAEs related to tirabrutinib
- TE SAEs related to idelalisib (Comb I and III only)
- TE SAEs related to entospletinib (Comb II and IV only)
- TE SAEs related to obinutuzumab (Comb III and IV only)
- TEAEs leading to dose reduction of tirabrutinib
- TEAEs leading to dose reduction of idelalisib (Comb I and III only)
- TEAEs leading to dose reduction of entospletinib (Comb II and IV only)
- TEAEs leading to dose reduction of obinutuzumab (Comb III and IV only)
- TEAEs leading to dose temporary interruption of tirabrutinib
- TEAEs leading to dose temporary interruption of idelalisib (Comb I and III only)
- TEAEs leading to dose temporary interruption of entospletinib (Comb II and IV only)
- TEAEs leading to dose temporary interruption of obinutuzumab (Comb III and IV only)
- TEAEs leading to discontinuation of tirabrutinib
- TEAEs leading to discontinuation of idelalisib (Comb I and III only)
- TEAEs leading to discontinuation of entospletinib (Comb II and IV only)
- TEAEs leading to discontinuation of obinutuzumab (Comb III and IV only)
- TEAEs leading to discontinuation of study
- TEAEs leading to death

An overall summary of AEs described above will be provided for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, Group V and Group VI (by disease type). In addition, TEAEs leading to discontinuation of any study drug, TEAEs leading to discontinuation of all study drug and all death will also be included in the overall summary.

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first of SOC, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TEAEs of Grade 3 or higher, and TE SAEs will be summarized by PT only, in descending order of total frequency, for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, Group V and Group VI (by disease type).

TEAEs leading to death, Treatment related TE SAEs will be summarized by SOC and PT, for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, Group V and Group VI (by disease type). In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- SAEs
- Deaths
- AEs leading to death
- AEs leading to discontinuation of study drug
- AEs leading to dose reduction or temporary interruption of study drug
- AEs leading to discontinuation of study

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

DLT analysis will be performed for paticipants in DLT Analysis set (including only participants involved in dose escalation phase, in Combination I, II, III, IV).

Summaries of DLTs will be presented by SOC, PT and severity, for Combination I (by dose level), Combination II (by dose level), Combination III and Combination IV. A listing of the

DLTs will be provided by treatment combination including combination name with dose level, participant ID, actual dose amount prior to or on the start date of the AE, DLT term from investigator as well as CTCAE term and associated severity grade, if available.

7.1.7.2. Treatment-Emergent Adverse Events of Interest (TE-AEIs)

The treatment-emergent adverse events of interest (TE-AEIs) include:

AEI	Grouped Terms
Haemorrhage/Bleeding	MST: Bleeding/Haemorrhage_excluding menstruation-related bleeding
Infections	SOC: Infections and infestations
Hypersensitivity	SMQ: Hypersensitivity broad
Cytopenia	MST: KUR_Cytopenia_KITE-CT
Cardiac Arrhythmias	MST: Cardiac arrhythmia and bradycardia
Diarrhoea	PT: Diarrhoea
Rash	MST: Drug induced rash excluding hypersensitivity events

The following summaries will be provided by SOC, PT, and maximum severity, for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV, Group V and Group VI (by disease type):

- TE-AEIs
- TE-AEIs leading to dose modifications or temporary interruption of any study drug
- TE-AEIs leading to discontinuation of any study drug

A data listing of AEIs will be provided by alphabetic ascending order of AEI name, then by dose level assigned, participant ID number, and then in chronological order within the participant.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data listed in Appendix 2 will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for participants who have permanently discontinued study drug, or all available data at the time of the database finalization for ongoing UK participants. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.8.

A by-participant listing for laboratory test results will be provided for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

Participants in Group VI will not be included in any analyses using laboratory results due to limited data.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided for Combination I (by dose level), Combination II (by dose level), Combination III, Combination IV and Group V for each laboratory test specified in the study protocol as follows:

- Baseline values
- Postbaseline maximum value
- Change and percentage change from baseline to postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.9.4. In the event that both central and local lab results are collected in the clinical database, baseline flag, worst toxicity and toxicity shift should be derived using both central and local lab results. Both central lab and local lab results will be included in the summary. All central and local laboratory values will be listed.

7.2.2. Graded Laboratory Values

CTCAE Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for participants who permanently discontinued study drug, or the last available date for ongoing UK participants at the time of database finalization. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for participants who permanently discontinued study drug, or the last available date for ongoing UK participants at the time of database finalization. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the time frame specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline time visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test for Combination I (by dose level and disease type), Combination II (by dose level and disease type), Combination III, Combination IV and Group V; Participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with non-missing post-baseline values up to 30 days after last dosing date in the safety analysis set.

A by-participant listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of participants who met at least 1 of the above criteria will be provided.

Liver-Related Postbaseline Laboratory Events will be summarized for Combination I (by dose level), Combination II (by dose level), Combination III, Combination IV and Group V.

7.2.4. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to the worst postbaseline grade.

The hematology and chemistry shift table will be provided for Combination I (by dose level and disease type), Combination II (by dose level sand disease type), Combination III, Combination IV and Group V.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided for body weight and vital signs as follows:

- Baseline value
- Postbaseline maximum

- Change and percent change from baseline to postbaseline maximum value
- Postbaseline minimum
- Change and percent change from baseline to postbaseline minimum value

The body weight and vital signs table will be provided for Combination I (by dose level), Combination II (by dose level), Combination III, Combination IV and Group V.

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection and postbaseline maximum and minimum selection.

A by-participant listing of vital signs will be provided. Temperature, heart rate, respiratory rate, blood pressure, height, body weight and BMI will be included in the listing.

7.4. Electrocardiogram Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval.

7.4.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at worst outcome among postbaseline visits compared with baseline values will be presented using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

The ECG table will be provided for Combination I (by dose level), Combination II (by dose level), Combination III, Combination IV and Group V.

By-participant listings for 12-Lead ECG results and overall ECG assessment will be provided.

7.5. Other Safety Measures

No additional safety measures are specified in the protocol.

7.6. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) AND IMMUNOGENICITY ANALYSES

The protocol-specified PK analyses were performed at interim analysis on June 2021. PK analyses will not be performedin the final analysis, considering that the data collected after the interim analysis is limited to safety and does not include PK data.

9. BIOMARKER ANALYSIS

The protocol-specified biomarker analyses were performed at interim analysis on June 2021. Biomarker analyses will not be performed for the final analysis, considering that the data collected after the interim analysis is limited to safety and does not include biomarker data.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Determining Missing and Virtual Visits Due to COVID-19

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If an in-person visit was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

NLP was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see the table below) and "Virtual" (or synonyms, see the table below). The search terms are maintained in a global lookup table and can be modified to tune the NLP model. For any comments with COVID-19 search terms, assign "Missed visit" or "Virtual visit as follows:

i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, NLP will be based on multiple records to ensure 1 unique category per subject per visit

iii. Otherwise result is missing

Examples of Search Terms for "COVID-19" and "Virtual" Used to Identify Missed and Virtual Visits

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 2. List of Laboratory Tests for Safety Summary

Serum Chemistry	Hematology
Albumin	WBC
Alkaline phosphatase	Hemoglobin
ALT	Hematocrit
Amylase	Platelet Count
AST	Basophils
BUN	Monocytes
Calcium	Eosinophils
Chloride	Neutrophils
Cholesterol	Lymphocytes
Creatinine[a]	Red Blood Cells
GGT	
Glucose[b]	
LDH	
Lipase	
Magnesium	
Phosphate	
Potassium	
Sodium	
Triglycerides	
Total bilirubin	
Total Protein	
Uric Acid	

a Both creatinine and creatinine clearance rate will be included in the safety summary. Estimated creatinine clearance rate will be calculated based on the Cockcroft-Gault formula

b If fasting status is not unknown, non-fasting criteria will be applied for toxicity grading

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Global Development Lead (GDL) eSigned	30-Jul-2024 18:48:40
PPD	Biostatistics eSigned	06-Aug-2024 23:06:37