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BGB-3111-206 (NCT03206970)

A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects With Refractory or Relapsed Mantle Cell Lymphoma (MCL)

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-206
Study Protocol Title:	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)
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SIGNATURE PAGE

Author:

PPD

[redacted]

PPD

Approval

PPD

[redacted]

PPD

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the plasma concentration-time curve
BL	Burkitt's lymphoma
BOR	best overall response
BP	blood pressure
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
SMC	safety monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
IRC	Independent Review Committee
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
MIPI-b	Combined biologic Mantle Cell Lymphoma International Prognostic Index
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PP	per-protocol population
PR	partial response
PT	preferred term
QT	interval between the beginning of the QRS complex to the end of the T wave
RBCs	red blood cells
R/R	relapsed or refractory
SAEs	serious adverse events
SAP	statistical analysis plan
SBP	systolic blood pressure

SD	stable disease
SOC	system organ class
SOPs	standard operating procedures
SSE	significant safety event
TEAEs	treatment emergent adverse events
TTR	time to response
ULN	upper limit of normal
US	United States
WBCs	white blood cells
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the protocol BGB-3111-206 amendment 3.0 dated 25-Oct-2017 titled: *A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)*. The focus of this SAP is for the planned primary and final analyses specified in the study protocol.

The SAP version 2.0 is an amendment to the initial version of the SAP (v1.0 dated Dec 7, 2017).

2 STUDY OVERVIEW

This is a single-arm, open-label, multi-center Phase 2 study in subjects with histologically documented and confirmed MCL who have relapsed after ≥ 1 but <5 prior treatment regimen(s). The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase.

Approximately 80 subjects will be enrolled. The primary efficacy analysis will be conducted at mature data of overall response rate, no later than 6 months after the last subject received the first dose of study drug, and the final analysis will be conducted at mature data of secondary endpoints. For the primary efficacy analysis, response will be evaluated based on an Independent Review Committee (IRC) using the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria. All subjects should undergo positron emission tomography (PET) and contrast computerized tomography (CT) at screening. For patients with avid PET diseases at screening, PET and contrast CT should be repeated at Weeks 12, 24, and 48, then every 24 weeks thereafter, and before confirmation of complete remission. For subjects with non-avid PET diseases at screening, only contrast CT should be performed at Week 12 and Week 24. Contrast CT will be performed at Weeks 36 and 48 and every 24 weeks thereafter until disease progression or end of study, whichever comes first. The PET and contrast CT are required for confirmation of CR for all subjects. Endoscopy is mandatory to confirm CR for any subject with a documented history of gastrointestinal involvement. Bone marrow biopsy will be required for confirmation of CR in subjects with bone marrow tumor involvement prior to study drug.

All subjects will be followed for adverse events (AEs) for 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations. Screening evaluations can be repeated within the screening period.

Treatment phase: Subjects will receive the first dose of BGB-3111 at Cycle 1 Day 1. All subjects will be treated with 160 mg, administered orally, twice daily and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. A treatment cycle consists of 28 days.

Follow-up phase: Subjects will return 30±7 days after the last dose of study drug for safety follow-up visit. Radiological assessments will continue until documented disease progression. If a subject discontinues study drug due to reasons other than disease progression, radiological

assessments will continue until subject exhibits first progression, withdrawal of consent, death, lost to follow-up or study termination by sponsor, whichever occurs first.

Survival phase: Subjects will be followed for survival via phone contact (with subject's guardian, if applicable) every 3 months after the subject's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis.

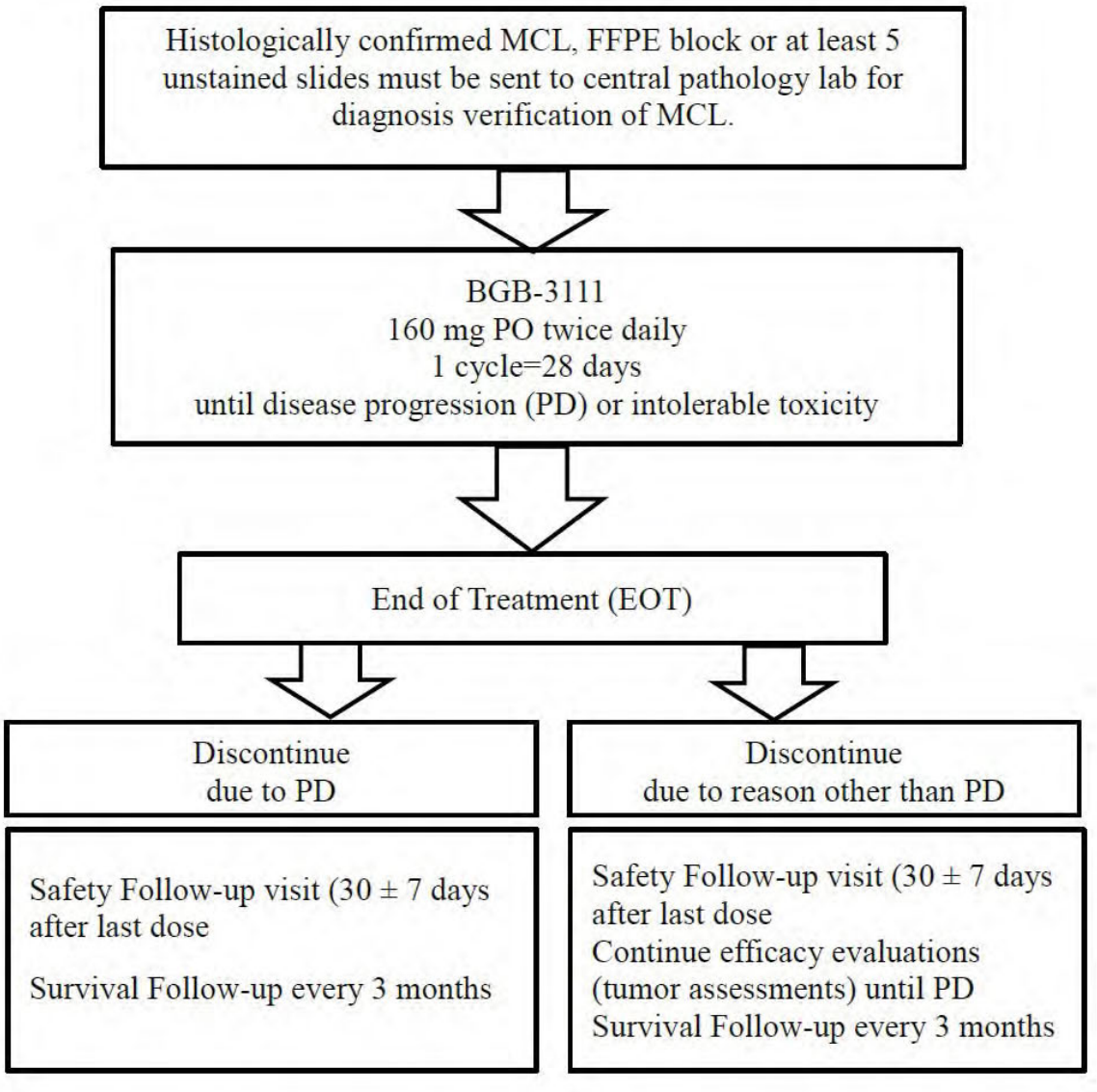

Figure 1: Study Scheme

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

To evaluate the efficacy of BGB-3111 at a dose of 160 mg orally (PO) twice daily (BID) in subjects with centrally confirmed relapsed or refractory mantle cell lymphoma (MCL) as measured by overall response rate (ORR) assessed by an Independent Review Committee (IRC) in accordance with the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson et al., 2014).

3.2 SECONDARY OBJECTIVES

To evaluate the efficacy of BGB-3111 as measured by progression free survival (PFS), time to response (TTR), and duration of response (DOR) as assessed by IRC.

To evaluate the efficacy of BGB-3111 by investigator as measured by overall response rate (ORR).

To evaluate the safety and tolerability of BGB-3111 at a dose of 160 mg PO BID in subjects with relapsed or refractory MCL.

3.3 EXPLORATORY OBJECTIVES

- CCI [redacted]

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

The primary endpoint of the study is the rate of overall response, defined as the achievement of either a partial response (PR) or complete response (CR) as determined by the Independent Review Committee (IRC) according to the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson 2014) at any time on study drug.

4.2 SECONDARY ENDPOINTS

Progression free survival (PFS) is defined as time from treatment initiation to first documentation of progression (as assessed by IRC) or death due to any cause, whichever occurs first.

Time to response (TTR) is defined as the time from treatment initiation to the first documentation of response (PR/CR as assessed by IRC) as per above response criteria.

Duration of response (DOR) is defined as the time from the first response documentation according to above response criteria to the date that progressive disease (as assessed by IRC) or death due to any cause, whichever occurs first.

ORR as assessed by the investigator: defined as the achievement of either a PR or CR as assessed by the Investigator at any time on study drug.

Incidence and severity of treatment-emergent adverse events according to Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03).

Incidence, severity, and causation of adverse events leading to study drug discontinuation.

4.3 EXPLORATORY ENDPOINTS

- CCI

5 SAMPLE SIZE CONSIDERATIONS

Approximately 80 subjects will be enrolled. The sample size calculation was mainly based on the level of precision of the estimated ORR. For an observed ORR of 70%, the 95% exact CI is (58.7%, 79.7%) with 80 subjects. Assuming ORR of 70% in the trial as compared to 40% in the historical control, using a binomial exact test, the power is >0.99 with 80 subjects to demonstrate statistical significance at a 1-sided alpha of 0.025.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

The Safety Population includes all subjects who received any dose of study treatment. All safety analyses will be based on the safety population.

The Revised Safety Population includes subjects with pathologically confirmed MCL among those in the Safety Population. The population is also the primary efficacy evaluable population.

The Per-protocol (PP) Population includes subjects who received any dose of the study drug and had no major protocol deviations. Criteria for exclusion from the PP will be determined and

documented before the database lock for the primary analysis. This may be used as a supplementary to the primary analysis of the primary endpoint if more than 15% of the Revised Safety population have major protocol deviations.

CCI

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

Treatment duration: The treatment duration will be calculated as (date of the last dose of study drug – date of first dose of study drug + 1).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected on/before the first dose of study drug.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for prior/concomitant medications/procedures, subsequent anti-cancer therapies, adverse events and deaths. Specific rules for handling of missing or partially missing dates for prior/concomitant medications/procedures, subsequent anti-cancer therapies, adverse events, and deaths are provided in Appendix A.

By-visit summary of variables with missing data will use only non-missing data, not imputed one, unless otherwise specified. Unscheduled visits will not be included in by-visit summaries.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

Not applicable.

6.2.6 Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Subject Disposition

The number (percentage) of subjects treated (i.e. safety population), with centrally confirmed pathology (i.e. revised safety population), discontinued from study drugs and discontinued from the study will be summarized. The primary reason for end of treatment (study drug discontinuation) and end of study will be summarized.

Survival status (alive, death, or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

6.3.2 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. Major protocol deviations will be summarized for all patients in the safety population. They will also be listed by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the safety population. Continuous variables include age, weight, and vital signs; categorical

variables include sex, age group (<65 vs. ≥65), and ECOG-PS. A listing of demographic and other baseline characteristics will be provided.

6.3.4 Disease History and Characteristics

The number (percentage) of subjects reporting a history of disease and characteristic, as recorded on the CRF, will be summarized. Disease characteristics include time since first diagnosis of MCL (month), disease stage, MCL international prognostic index (MIPI)/Combined biologic MCL international prognostic index (MIPI-b) (low, intermediate, high, derived based on CRF and central lab data), Ki-67-postive cell percentage categories (based on central lab pathology), blastoid histology (yes vs no, based on CRF), and confirmation of MCL by central pathology (yes vs no, by central lab report). A listing of disease history will be provided.

6.3.5 Prior Anti-Cancer Drug Therapies

The number of prior anti-cancer drug therapies and prior anti-cancer radiotherapy will be summarized. The therapies with the same line of regimen are counted as one prior therapy/surgery.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes, and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term by phase in the safety population. Prior medications are defined as medications that started before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose or or initiation of a new anti-cancer therapy. A listing of prior and concomitant medications will be provided.

6.3.7 Medical History

Medical History will be coded using MedDRA (version 19.0 or newer). The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by MedDRA system organ class (SOC) and preferred term (SOC) based on the safety population. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

All efficacy analyses will be based on the Revised Safety population. The primary endpoint of ORR will also be analyzed using the safety population and the per-protocol population (if necessary) as supplementary to the primary analysis.

6.4.1 Primary Efficacy Endpoint

<u>Overall Response Rate (ORR) by IRC</u>

The primary analysis of ORR will be based on the PET-based assessments by the Independent Review Committee (IRC) following the 2014 modification of the International Working Group in NHL criteria. ORR is defined as the proportion of subjects achieving a best overall response of CR or PR.

A point estimate and a 2-sided Clopper-Pearson 95% confident interval (CI) of ORR will be provided. A binomial exact test will be performed to test against the null hypothesis H_0: ORR=0.40 using the significant level of 0.025 (1-sided). Best overall response (BOR) is defined as the best response recorded from the start of BGB-3111 until data cut or start of new anti-cancer treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for ORR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, stable disease [SD], and progressive disease [PD]) will be presented.

6.4.2 Secondary Efficacy Endpoints

Progression Free Survival (PFS)

PFS is defined as the time (in weeks) from the date of first study dose to disease progression or death of any cause, whichever occurs first:

PFS=(The earlier of disease progression or death date – the date of first study dose +1)/7.

PFS will be based on the IRC assessments. PFS as assessed by investigator will also be analyzed as sensitivity analysis.

Kaplan-Meier methodology will be used to estimate the median and other quantiles of PFS and it 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time. Two-sided 95% CIs of median and other quantiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer, 1982; Klein 1997) with log-log transformation. PFS rates at selected landmark time points (e.g. 6-month) will be provided and corresponding 95% confidence intervals will be calculated based on the Greenwood's formula (Kalbfleisch 1980) with log-log transformation.

The duration of the follow-up for PFS will be determined by reverse Kaplan-Meier method (Schemper 1996).

PFS will be right-censored based on rules provided in Table 1. These conventions are modified based on the May 2007 FDA Guidance for Industry: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (FDA, 2007).

Note that the frequency of disease assessments is every 12 weeks in the first 48 weeks and every 24 weeks thereafter. Therefore, missing more than one disease assessment will be interpreted as

gaps longer than 24 weeks in the first 48 weeks or gaps longer than 48 weeks thereafter for censoring purposes of PFS.

Table 1. Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessments	Date of the first dose	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first disease assessment showing with documented disease progression	Progressed
3	Alive without documented disease progression at the time of data cut-off or withdrawal from study (including lost-to-follow-up without disease progression)	Date of last disease assessment	Censored
4	New anticancer treatment started before documented disease progression or death	Date of last disease assessment prior to or on date of new anticancer treatment	Censored
5	Death before first disease assessment	Date of death	Progressed
6	Death or progression after more than one missed scheduled disease assessment	Date of last disease assessment without documented disease progression before missed tumor assessments	Censored

Duration of Response (DOR)

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). Censoring rule for DOR will follow PFS censoring rule. Kaplan-Meier curve will be used to estimate median and other quantiles and 95% confidence intervals for duration of response. DOR will be based on the IRC assessments, DOR as assessed by investigators will be analyzed as sensitivity analysis.

Time to Response (TTR)

Time of response for responders (CR or PR) is defined as the time interval between the first dose and the date of the earliest qualifying response. TTR will be summarized by sample statistics such as mean, median and standard deviation for responders only. TTR will be based on the IRC assessments, TTR as assessed by investigators will be analyzed as sensitivity analysis.

Overall Response Rate (ORR) by Investigator

Analysis of ORR based on the PET-based assessments by the investigators will be performed using the same methods described for the analysis of ORR as assessed by IRC.

6.4.3 Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups, as appropriate (i.e. when there is sufficient number of subjects in the subgroup, otherwise relevant subgroups may be combined): sex, age group (<65 vs. ≥65), disease stage, ECOG-PS (o vs. ≥1), prior line of therapy for MCL (<3 vs. ≥3), MIPI/MIPI-b (low, intermediate, high), Ki-67-positive cell percentage categories, and blastoid histology (yes vs. no). Within group values (rates for ORR/medians for PFS, DOR, TTR) will be presented in forest plots.

6.4.4 Exploratory Efficacy Endpoints

CCI [redacted]

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety population. The study will set up a Safety Monitoring Committee (SMC). The SMC will monitor safety data according to the SMC charter (Appendix C) periodically throughout the study.

Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including AEs, laboratory values, vital signs, and physical examination and ECG findings.

6.5.1 Extent of Exposure

Extent of exposure to the study drug will be summarized descriptively with respect to the following:

- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered
- Duration of exposure (days): defined as the duration (in days) from the date of the first dose to the last dose of the study drug

- Total dose received per subject (mg): defined as the cumulative dose of the study drug during the treatment period of the study

- Actual dose intensity (mg/day): defined as the total dose (in mg) received by a subject divided by the duration of exposure (in day)

- Relative dose intensity: defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity.

The number (percentage) of subjects requiring dose reductions, dose interruption, dose missed, and drug discontinuation due to AEs will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized by categories.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

The number (percentage) of subjects with treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized by SOC and PT. TEAEs with grade 3 or above will also be summarized by PT in descending order.

Subject data listings of all AEs, SAEs, treatment-related AEs, grade 3 or above AEs, AEs that led to death and AEs that led to treatment discontinuation will be provided.

6.5.3 Laboratory Values

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for selected laboratory parameters and their changes from baseline will be summarized by visit.

Laboratory parameters that are graded in NCI CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Subject data listings of selected laboratory parameters will be provided.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subjects and visits.

6.5.5 Electrocardiograms (ECG)

Electrocardiogram assessments will be performed at the Screening visit. Descriptive statistics for baseline ECG parameters will be presented together with other baseline variables.

6.5.6 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized. ECOG scores will be summarized by visit.

6.6 CCI [redacted]

[redacted]

6.7 OTHER ANALYSES

Not applicable.

7 INTERIM ANALYSIS

Not applicable.

8 CHANGES IN THE PLANNED ANALYSIS

The primary efficacy analysis will be conducted no later than 6 months after the last subject received the first dose of study drug. In protocol amendment 3 and SAP v1.0, it was specified that the primary analysis will be performed 12 months after the last subject received the first dose of study drug. As a result, the interim analysis as planned in SAP v1.0 is omitted from this version of the SAP.

9 REFERENCES

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10 APPENDIX

Appendix A: Missing Data Imputation Rule

In general, missing or partial dates will not be imputed as data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

A.1 Prior/Concomitant Medications/Procedures

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

A.2 Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first day of the month

- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If end date is completely missing, do not impute.

A.3 Deaths

In case only the day of a death date is missing, the death will be assumed to be on the 1st date of the month if the last date of subject known to be alive is earlier that the 1st date of the month, otherwise the death date will be assumed to be on 1 day after the last date of subject known to be alive.

A.4 Subsequent Anti-cancer Therapies

If the start date of a subsequent anti-cancer therapy is missing, the start date will be assumed to be on the 1st date of the month.

Appendix B: Non-Hodgkin's Lymphoma LUGANO Response Criteria

For assessment of Non-Hodgkin's lymphoma LUGANO response criteria, positron emission tomography [PET] should be performed in cooperation with diagnostic contrast computed tomography [CT] simultaneously or in different procedures. The PET-CT should be used for response assessment in fluorodeoxyglucose (FDG)-avid histologies (using the 5-point scale provided in the footnote of the table below); CT is preferred for low or variable FDG avidity, in accordance with 2014 modification of the International Working Group on Non-Hodgkin's Lymphoma Criteria (Cheson, 2014).

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response)[d]
Complete Response	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass[b,c] on 5-point scale (5-PS)	All of the following: target nodes/nodal masses must regress to ≤ 1.5 cm in LDi, no extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response)[d]
Partial Response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and no new or progressive lesion At interim, these findings suggest disease response At end of treatment, these findings indicate residual disease	All of the following: ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with biopsy or an interval scan	Not applicable
No response or stable disease	Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment, no new or progressive lesion	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Unmeasurable lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Response	Site	PET-CT (metabolic response)	CT (radiologic response)[d]
Disease Progression	Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	One of the following in PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline If not prior splenomegaly, must increase by at least 2 cm from baseline
	Unmeasurable lesion	None	New or clear progression of preexisting unmeasurable lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under-treatment).
b Refer to PET 5-point scale (5-PS).
c It is generally accepted that in Waldeyer's ring or high physiological uptake or spleen/bone marrow activated (eg, by chemotherapy or myeloid colony stimulating factor) extranodal sites, uptakes may be greater than normal mediastinum and/or liver. In this situation, if uptake of initial involvement site is no greater than surrounding normal tissues, even if the tissue has high physiologic uptake, complete molecular remission (CMR) can also be concluded.
d False positive result of PET scan related to infection or inflammation may be observed. Biopsy for involvement site is still the gold standard for new or persistent pathological changes.
PET 5-point scale:
1. no uptake above background
2. uptake ≤ mediastinum
3. uptake > mediastinum, but < liver
4. uptake moderately > liver
5. uptake markedly higher than liver and/or new lesions
X new areas of uptake unlikely to be related to lymphoma

Abbreviations: CMR, complete molecular remission; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transvers diameter of a lesion; PET, positron emission tomography; PPD, cross product of the longest transvers diameter of a lesion and perpendicular diameter; 5-PS, 5-point scale; SDi, shortest axis perpendicular to the longest transvers diameter of a lesion; SPD, sum of the product of the perpendicular diameters for multiple lesions.

Appendix C: Safety Monitoring Committee Charter

Appendix D: Independent Review Charter