



STATISTICAL ANALYSIS PLAN

Study Protocol Number: BGB-11417-201

Study Protocol Title: A Single-Arm, Open-Label, Multicenter Phase 1/2 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of BCL2 Inhibitor BGB-11417 in Patients With Relapsed or Refractory Mantle Cell Lymphoma

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	6
1.....INTRODUCTION	8
2.....STUDY OVERVIEW	9
2.1.....Part 1: Dose Escalation and Safety Expansion	9
2.2.....Part 2: Efficacy Expansion	10
3.....STUDY OBJECTIVES	11
3.1.....Part 1: Dose Escalation and Safety Expansion	11
3.1.1.....Primary Objectives	11
3.1.2.....Secondary Objectives	11
3.1.3.....Exploratory Objectives	11
3.2.....Part 2: Efficacy Expansion	11
3.2.1.....Primary Objective	11
3.2.2.....Secondary Objectives	12
3.2.3.....Exploratory Objectives	12
4.....DEFINITION OF ESTIMANDS (PART 2).....	13
5.....STUDY ENDPOINTS.....	14
5.1.....Part 1: Dose Escalation and Safety Expansion	14
5.1.1.....Primary Endpoints	14
5.1.2.....Secondary Endpoints	14
5.1.3.....Exploratory Endpoints	14
5.2.....Part 2: Efficacy Expansion	15
5.2.1.....Primary Endpoint.....	15
5.2.2.....Secondary Endpoints	15
5.2.3.....Exploratory Endpoints	15
6.....SAMPLE SIZE CONSIDERATIONS	16
6.1.....Part 1: Dose Escalation and Safety Expansion	16
6.2.....Part 2: Efficacy Expansion	16
7.....STATISTICAL METHODS.....	17
7.1.....Analysis Sets.....	17
7.1.1.....Dose-Limiting Toxicity-Evaluable Set (Part 1A Only).....	17
7.1.2.....Safety Analysis Set (All Parts)	17

7.1.3.....	Efficacy Evaluable Set (All Parts).....	17
7.1.4.....	Pharmacokinetics Analysis Set (All Parts)	17
7.2.....	Multiplicity Adjustment.....	18
7.3.....	Data Analysis General Considerations	18
7.3.1.....	Definitions and Computations	18
7.3.2.....	Conventions	18
7.3.3.....	Handling of Missing Data.....	18
7.3.4.....	Data Integrity	19
7.4.....	Patient Characteristics	19
7.4.1.....	Patient Disposition.....	19
7.4.2.....	Protocol Deviations	19
7.4.3.....	Demographic and Other Baseline Characteristics	20
7.4.4.....	Disease History	20
7.4.5.....	Prior Anti-Cancer Therapies.....	21
7.4.6.....	Subsequent Anti-Cancer Systemic Therapies and Radiotherapy	21
7.4.7.....	Prior and Concomitant Medications	22
7.4.8.....	Medical History	22
7.5.....	Efficacy Analysis.....	22
7.5.1.....	Primary Efficacy Endpoint	22
7.5.1.1.....	Primary Estimand	22
7.5.1.2.....	Primary Analysis for Primary Estimand.....	23
7.5.1.3.....	Handling of Missing Values Not Related to Intercurrent Event.....	23
7.5.1.4.....	Sensitivity Analyses for Primary Endpoint/Estimand	23
7.5.1.5.....	Supplementary Analysis	23
7.5.2.....	Secondary and Exploratory Efficacy Endpoints (Part 1 and Part 2)	23
7.5.3.....	Subgroup Analyses	26
7.6.....	Safety Analyses	26
7.6.1.....	Extent of Exposure	27
7.6.2.....	Dose-Limiting Toxicities.....	28
7.6.3.....	Adverse Events	28
7.6.4.....	Laboratory Values	30
7.6.5.....	Vital Signs	31

7.6.6.....	Electrocardiograms (ECG)	31
7.6.7.....	Eastern Cooperative Oncology Group (ECOG) Performance Status	31
7.7.....	Pharmacokinetic Analyses	31
7.7.1.....	Part 1: Dose Escalation and Safety Expansion	32
7.7.1.1.....	Report of Pharmacokinetic Concentrations	32
7.7.1.2.....	Plots of Pharmacokinetic Concentrations	33
7.7.1.3.....	Calculation and Reporting of PK Parameters	33
7.7.2.....	Part 2: Efficacy Expansion	35
7.8.....	Other Analyses	35
8.....	INTERIM ANALYSES	36
9.....	CHANGES IN THE PLANNED ANALYSIS	37
10.....	REFERENCES	38
APPENDIX 1.	IMPUTATION OF MISSING OR PARTIALLY MISSING DATES	39
APPENDIX 2.	NON-HODGKIN'S LYMPHOMA LUGANO RESPONSE CRITERIA	42
APPENDIX 3.	NCCN--FACT FLYMSI-18 (VERSION 2).....	45
APPENDIX 4.	NCCN/FACT LYMPHOMA SYMPTOM INDEX-18 (FLYMSI-18) SCORING GUIDELINES (VERSION 2)	46
APPENDIX 5.	EUROQOL GROUP EQ-5D-5L.....	48
APPENDIX 6.	PGI-S FOR LYMPHOMA.....	51
APPENDIX 7.	PRO-CTCAE	52

LIST OF TABLES

Table 1	Censoring Rules for Analysis of Progression-Free Survival	24
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LIST OF FIGURES

Figure 1	Study Schema	9
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC _{0-t}	AUC from time 0 to the last quantifiable timepoint
Bcl-2	B-cell lymphoma-2
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CBC	complete blood count
CDE	Centre for Drug Evaluation
CI	confidence interval
CL/F	apparent total clearance of drug from plasma after oral administration
C _{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life 5 Dimension 5 Level Questionnaire
FDG	[¹⁸ F]fluorodeoxyglucose
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Review Committee
MAD	maximum administered dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index

Abbreviation	Definition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NFlymSI-18	National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PGI-S	Patient Global Impression of Symptom Severity
PK	pharmacokinetic(s)
PR	partial response
RP2D	recommended Phase 2 dose
PRO	Patient-Reported Outcomes
RD1	Ramp-up Day 1
R/R	relapsed/refractory
RWDX	Ramp-up Week X Day X
SAE	serious adverse event
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
$t_{\max}$	time to maximum observed plasma concentration
TTR	time to response
WXDX	Week X Day X

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 BGB-11417-201, entitled “A Single-Arm, Open-Label, Multicenter Phase 1/2 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of BCL2 Inhibitor BGB-11417 in Patients With Relapsed or Refractory Mantle Cell Lymphoma”. The focus of this SAP is for primary analysis specified in the study protocol.

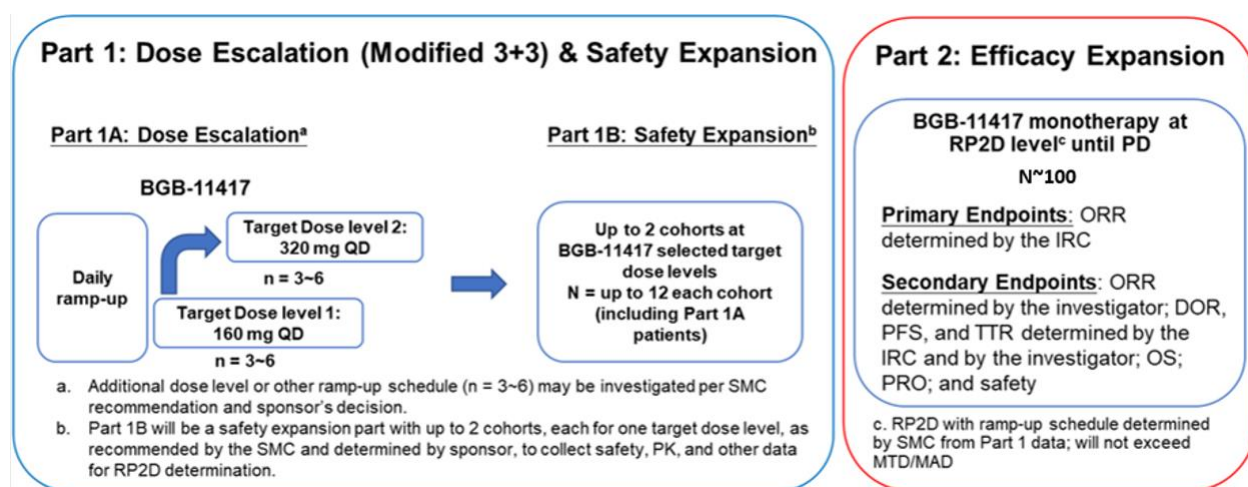
2. STUDY OVERVIEW

This single arm, open-label, multicenter Phase 1/2 study is designed to determine the recommended Phase 2 dose (RP2D), efficacy, safety, and pharmacokinetics (PK) of sonrotoclax in approximately 122 patients with R/R MCL when given as monotherapy. The primary objectives in Part 1 include the evaluation of safety, tolerability, RP2D, and ramp-up schedule of sonrotoclax monotherapy in patients with R/R MCL. The primary objective in Part 2 is to evaluate the efficacy of sonrotoclax measured by ORR determined by the IRC. Disease response will be assessed according to the Lugano classification ([Cheson et al 2014](#)). The study schema is provided in [Figure 1](#).

2.1. Part 1: Dose Escalation and Safety Expansion

Part 1 consists of Part 1A dose escalation and Part 1B safety expansion ([Figure 1](#)).

Figure 1 Study Schema



Abbreviations: DOR, duration of response; IRC, Independent Review Committee; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; patient-reported outcomes (PRO); QD, once a day; RP2D, recommended Phase 2 dose; SMC, Safety Monitoring Committee; TTR, time to response.

Note: Based on the data from Part 1, the RP2D of sonrotoclax monotherapy was determined to be 320 mg.

Part 1A will be the dose escalation phase. sonrotoclax will be investigated at a target dose level of 160 mg once a day and 320 mg once a day with a daily ramp-up schedule. The first dose level tested in the escalation part will be the target dose level of 160 mg once a day. For dose escalation, modified 3+3 principles will be followed for the determination of MTD.

The MTD is defined as the highest dose at which < 33% of the patients had experienced at least one DLT.

The DLT window will include all dose ramp-up treatment days as well as 21 days of sonrotoclax at the target dose. For the patients to have completed the DLT window, they should have received $\geq 80\%$ of the intended cumulative dose over the ramp-up period as well as $\geq 80\%$ of the intended dose over the target dose period of the applicable DLT window or have experienced a DLT.

The study plans to investigate at least 2 dose levels (160 mg and 320 mg as the target doses) with a daily ramp-up schedule. However, based on the observed PK and safety data from this study and available data from Studies BGB-11417-101 and BGB-11417-102 as references, additional dose levels or other ramp-up schedules may be investigated per the Safety Monitoring Committee recommendation and the sponsor's decision, and additional patients (approximately 3 to 6 patients for each additional dose level) could be enrolled.

Part 1B will be a safety expansion phase with up to 2 cohorts, each consisting of additional patients for one target dose level (up to 12 patients at each dose level including Part 1A patients), as recommended by the Safety Monitoring Committee and determined by the sponsor. Part 1B is to collect more safety, PK, and other data, together with the data from Part 1A, as well as the available data from BGB-11417-101 and BGB-11417-102 studies as references, for the determination of RP2D.

If the Safety Monitoring Committee recommends and the sponsor decides to explore additional dose levels or alternative ramp-up schedules, a substantial protocol modification will be submitted to health authorities and/or IRB/IEC, according to local requirements.

After the RP2D is determined and the future ramp-up schedule is recommended, further enrollment into Part 2 will commence.

2.2. Part 2: Efficacy Expansion

Part 2 will be conducted as an open-label, single-arm, multicenter, expansion study. Following establishment of a safe ramp-up schedule and RP2D in Part 1, the efficacy expansion part (Part 2) will be opened to further evaluate the efficacy of sonrotoclast.

3. STUDY OBJECTIVES

3.1. Part 1: Dose Escalation and Safety Expansion

3.1.1. Primary Objectives

- To determine the safety and tolerability of sonrotoclax monotherapy
- To define the MTD (or maximum administered dose [MAD]) and the recommended Phase 2 dose (RP2D) of sonrotoclax monotherapy for R/R MCL
- To evaluate the safety and tolerability of the ramp-up dosing schedule of sonrotoclax monotherapy in patients with R/R MCL

3.1.2. Secondary Objectives

- To assess the PK of sonrotoclax monotherapy
- To assess the preliminary antitumor activity of sonrotoclax monotherapy in patients with R/R MCL as measured by the ORR, DOR, PFS, and TTR determined by the investigator in accordance with the 2014 modification of the International Working Group on NHL criteria (hereafter referred as the Lugano classification) ([Cheson et al 2014](#)), and OS
- To assess the preliminary antitumor activity of sonrotoclax monotherapy in patients with R/R MCL as measured by the ORR, DOR, PFS, and TTR determined by the Independent Review Committee in accordance with the Lugano classification.
 - Note: The disease response assessment determined by the Independent Review Committee for patients treated in Part 1 is added in Protocol Amendment 2.0 after Part 1 has started.

3.1.3. Exploratory Objectives

- To evaluate the health-related quality of life based on patient-reported outcomes
- To evaluate the biomarker characteristics and their association with clinical outcomes to sonrotoclax monotherapy in patients with R/R MCL

3.2. Part 2: Efficacy Expansion

3.2.1. Primary Objective

- To evaluate the efficacy of sonrotoclax monotherapy at the RP2D with recommended ramp-up schedule in patients with R/R MCL as measured by the ORR as determined by the Independent Review Committee in accordance with the Lugano classification.

3.2.2. Secondary Objectives

- To evaluate the efficacy of sonrotoclax monotherapy in patients with R/R MCL, as measured by the following:
 - ORR determined by the investigator in accordance with the Lugano classification
 - DOR determined by the Independent Review Committee and by the investigator in accordance with the Lugano classification
 - PFS determined by the Independent Review Committee and by the investigator in accordance with the Lugano classification
 - TTR determined by the Independent Review Committee and by the investigator in accordance with the Lugano classification
 - OS
 - Health-related quality of life based on patient-reported outcomes
- To evaluate the safety and tolerability of sonrotoclax monotherapy in patients with R/R MCL

3.2.3. Exploratory Objectives

- To evaluate the PK of sonrotoclax in patients with R/R MCL
- To evaluate the biomarker characteristics and their association with clinical outcomes to sonrotoclax monotherapy in patients with R/R MCL
- To evaluate changes in patient reported symptom severity and patient-reported side effect burden.

4. DEFINITION OF ESTIMANDS (PART 2)

The primary clinical question of interest is to assess the efficacy of sonrotoclax as measured by ORR in patients with R/R MCL, before the patients start any new anticancer therapy or prior to disease progression.

The primary estimand is described by the following attributes:

1. Treatment of interest:

Sonrotoclax at RP2D with recommended ramp-up schedule determined from Part 1.

2. Population:

All adult patients with MCL who (1) have been treated with anti-CD20 based therapy and BTKi therapy and (2) had documented failure to achieve at least PR or documented disease progression on or after the last line of treatment, or the last line therapy needs to be discontinued due to toxicity/tolerability.

3. Variable:

A binary variable to capture if a patient achieves overall response, including CR and PR, as determined by the Independent Review Committee (IRC), prior to disease progression.

4. Handling of intercurrent events:

New anticancer therapy started prior to disease progression: Patients starting any new anticancer therapy without having achieved a response before (CR or PR) will be considered as nonresponders (composite strategy).

Discontinuation of treatment prior to disease progression: response assessment after discontinuation of treatment will be counted and used for analysis (treatment policy strategy).

5. Population-level summary:

ORR

5. STUDY ENDPOINTS

5.1. Part 1: Dose Escalation and Safety Expansion

5.1.1. Primary Endpoints

- DLTs (Part 1A only)
- The incidence and severity according to the NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of sonrotoclax
- Incidence and severity of TLS-relevant events

5.1.2. Secondary Endpoints

- Derived PK parameters of sonrotoclax, including:
 - For a single dose: area under the plasma concentration-time curve from time 0 to the last measurable concentration (AUC_{last}), maximum observed plasma concentration (C_{max}), and time to reach C_{max} (t_{max}) as appropriate.
 - After steady-state: $AUC_{last,ss}$, $C_{max,ss}$, trough plasma concentration ($C_{trough,ss}$), and $t_{max,ss}$. Other PK parameters may be reported.
- Preliminary antitumor activity, determined by the investigator and by the Independent Review Committee in accordance with the Lugano classification, as measured by the following endpoints:
 - ORR, defined as the proportion of patients achieving partial response or better
 - DOR, defined as the time from first determination of response until first documentation of progression or death, whichever occurs first
 - PFS, defined as the time from start of treatment to the first documentation of disease progression or death, whichever occurs first
 - TTR, defined as the time from start of treatment to first documentation of response (PR or better)
 - OS, defined as time from the start of treatment to the date of death due to any cause

Note: The disease response assessment determined by the Independent Review Committee is added for Part 1 in Protocol Amendment 2.0 after Part 1 has started. Only Part 1 patients at the 320 mg target dose will have disease response assessed by the IRC. For patients enrolled in Part 1, treatment decisions (eg, discontinuation of study treatment due to progressive disease) will be made according to investigator's response assessment.

5.1.3. Exploratory Endpoints

- Patient-reported outcomes as measured by the NFlymSI-18

- Correlation between biomarker characteristics (eg, expression and alteration of BCL2, TP53 mutation status, Ki67 index, mutation profile) and response (eg, ORR, DOR, PFS, TTR, and OS) or resistance to sonrotoclax monotherapy

5.2. Part 2: Efficacy Expansion

5.2.1. Primary Endpoint

- ORR determined by the IRC, defined as the proportion of patients achieving partial response or better per the Lugano classification ([Cheson et al 2014](#))

5.2.2. Secondary Endpoints

- ORR determined by the investigator
- DOR determined by the IRC and by the investigator
- PFS determined by the IRC and by the investigator
- TTR determined by the IRC and by the investigator
- OS
- Patient-reported outcomes as measured by NflymSI-18 and EQ-5D-5L
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical examinations, ECG, and vital signs

5.2.3. Exploratory Endpoints

- Derived PK parameters for sonrotoclax, including steady-state C_{trough} and other pharmacokinetic parameters, if supported by data
- Correlation between biomarker characteristics (eg, expression and alteration of BCL2, TP53 mutation status, Ki67 index, mutation profile) and response (eg, ORR, DOR, PFS, TTR, and OS) or resistance to sonrotoclax monotherapy
- Changes in patient-reported lymphoma symptom severity as measured by PGI-S, and patient-reported treatment side effect burden as measured via PRO-CTCAE.

6. SAMPLE SIZE CONSIDERATIONS

The overall sample size for this study is expected to be approximately 122 patients, including 22 patients in Part 1 (enrollment completed before Protocol Amendment 2.0) and approximately 100 patients in Part 2.

6.1. Part 1: Dose Escalation and Safety Expansion

Part 1A was designed to enroll approximately 3 to 6 patients to 160 mg and 320 mg dose levels during dose escalation.

If an additional dose level and/or the ramp-up schedule were to be evaluated in Part 1A, per the SMC recommendation and sponsor's decision, additional patients (approximately 3 to 6 patients for each additional dose level) would be enrolled.

In Part 1B, up to 2 cohorts were to be expanded for safety evaluation, each consisting of additional patients at one dose level (up to 12 patients at each dose level including Part 1A patients) as recommended by the Safety Monitoring Committee and determined by the sponsor to proceed to Part 1B, to collect safety, PK, and other data for the determination of RP2D.

At the time of this document, enrollment in Part 1 was completed, with 12 patients in Part 1A (7 and 5 in 160 mg and 320 mg cohorts, and 10 patients in Part 1B (3 and 7 in 160 mg and 320 mg) and no additional dose level cohort was recommended. RP2D was determined to be the MAD, i.e., 320 mg.

6.2. Part 2: Efficacy Expansion

The sample size of approximately 100 patients is based on the power of the comparison to the historical control ORR. Assuming an ORR of 50% in the study as compared to 30% in the historical control ([Martin et al 2016](#); [Jain et al 2018](#); [Wang et al 2017](#)), the power is >0.90 with approximately 100 patients to demonstrate statistical significance at a 1-sided alpha of 0.025 using binomial exact test.

7. STATISTICAL METHODS

Analyses will be provided by study part, target dose levels and overall as appropriate.

7.1. Analysis Sets

7.1.1. Dose-Limiting Toxicity-Evaluable Set (Part 1A Only)

The DLT-evaluable Set consists of patients who meet any of following criteria:

Patients who received $\geq 80\%$ of the intended dose over the ramp-up dosing period and $\geq 80\%$ of the intended dose over the target dose period of the applicable DLT window and had sufficient safety evaluation

Patients who had a DLT event during the applicable DLT observation window

The DLT evaluable Set will be the primary analysis set used for dose escalation decision and MTD or MAD determination.

7.1.2. Safety Analysis Set (All Parts)

The Safety Analysis Set includes all enrolled patients who received ≥ 1 dose of sonrotoclax. The Safety Analysis Set will be used for safety analyses.

7.1.3. Efficacy Evaluable Set (All Parts)

The Efficacy Evaluable Set consists of all enrolled MCL patients who (1) have been treated with anti-CD20 based therapy and BTKi therapy and (2) had documented failure to achieve at least PR or documented disease progression on or after the last line of treatment, or the last line therapy needs to be discontinued due to toxicity/tolerability, and who received ≥ 1 dose of sonrotoclax. The Efficacy Evaluable Set will be used for all efficacy analyses.

7.1.4. Pharmacokinetics Analysis Set (All Parts)

The PK Analysis Set includes all patients who have ≥ 1 post dose PK sample collected according to the protocol and laboratory manual. The PK Analysis Set will be used for all PK analyses.

7.2. Multiplicity Adjustment

Not applicable.

7.3. Data Analysis General Considerations

7.3.1. Definitions and Computations

The study drug is sonrotoclax monotherapy.

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, the study day will be calculated as assessment date – the date of the 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 – the date of the first dose of study drug). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in [Appendix 1](#). Another study day in reference to the first day of target dose (W1D1) may also be calculated.

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

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

7.3.2. 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.
- P-values will be rounded to 4 decimal places. P-values that is less than 0.0001 will be presented as '< 0.0001' and p-values that is larger than 0.9999 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date the evidence was obtained rather than the associated visit date.
- 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).
- For discrete endpoints, summary statistics will include frequencies and percentages.

7.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for prior/concomitant

medications/procedures, subsequent anti-cancer therapies, adverse events, deaths, disease diagnosis and prior systemic anticancer therapy. Specific rules for the handling of missing or partially missing dates are provided in [Appendix 1](#).

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included. Unscheduled visits will not be included in by-visit summaries.

7.3.4. 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.

7.4. Patient Characteristics

7.4.1. Patient Disposition

The summary of patient disposition will be based on all patients enrolled. The following patient disposition information will be summarized:

- Number of enrolled patients
- Number (%) of treated patients
- Number (%) of treated patients who remain on treatment
- Number (%) of treated patients who discontinued treatment
- Reasons that patients discontinued treatment
- Number (%) of treated patients who remain in the study
- Number (%) of treated patients who discontinued from the study
- Reasons that patients discontinued from the study

Study follow-up time will be defined as the time from date of first dose to date of death or end of study (whichever occurs earlier) for patients who have discontinued from the study, or the database cutoff date for ongoing patients. Treatment follow-up time is defined as the time from the date of first dose to the date of end of treatment for patients who have discontinued from the treatment, or the database cutoff date for ongoing patients. Study and treatment follow-up time will be summarized descriptively.

7.4.2. Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patient.

7.4.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set, including the following variables:

- Age (continuously and by categories [<65 versus ≥ 65])
- Sex
- Race
- Ethnicity
- Region
- Country
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Baseline vital signs (height, weight, temperature, systolic blood pressure, diastolic blood pressure, heart rate or pulse rate)
- ECG
- Neutrophils absolute count
- Platelets count
- Hemoglobin
- Creatinine
- Creatinine clearance estimated by the Cockcroft-Gault equation
- Aspartate aminotransferase (AST)
- Alanine transaminase (ALT)
- Total bilirubin
- Hepatitis C virus (HCV) antibody
- Hepatitis B core antibody (HBcAb)
- Hepatitis B Surface Antigen (HBsAg)

A listing of demographic and baseline characteristics data will be provided.

7.4.4. Disease History

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized in the safety analysis set.

Disease characteristics include:

- Time since first diagnosis of MCL to first dose (month)
- Number (%) of patients with prior radiotherapy
- Number (%) of patients with prior stem cell transplant

- Relapsed versus refractory disease status to last prior systemic therapy
- Stage at study entry
- Bulky disease
- Histology classification
- Ki-67 IHC status
- Ki-67 percent positive
- TP53 mutation status
- MCL international prognostic index (MIPI)
- MIPI-b
- Extranodal disease at study entry
- Baseline bone marrow involvement
- Confirmed gastrointestinal involvement

A listing of disease history will be provided.

7.4.5. Prior Anti-Cancer Therapies

The following information related to prior anti-cancer therapy will be summarized for the Safety Analysis set:

- Number (%) of patients with prior systematic therapy for cancer
- Number of lines of prior therapies and number of lines of prior therapies categorized as 1, 2, 3, etc.
- Prior systemic anticancer medications
- Best overall response to last prior line therapy
- Time from the end of last therapy to first dose date (months)
- Reason last line therapy ended

A listing of prior anti-cancer drug therapies will be provided.

7.4.6. Subsequent Anti-Cancer Systemic Therapies and Radiotherapy

Subsequent anti-cancer systemic therapy or radiotherapy is defined as any non-protocol systemic therapy or radiotherapy for MCL with a start date on or after the date of the first dose.

Number (percentage) of patients receiving subsequent anti-cancer systemic therapies or radiotherapy will be summarized in the safety analysis set. Subsequent anti-cancer systemic therapy by regimen will also be summarized. Listings of subsequent systemic anti-cancer therapies and radiotherapy will be provided.

7.4.7. Prior and Concomitant Medications

Prior medications are defined as medications that started before the first dose of study drug. 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 and/or up to 30 days after the patient's last dose, or the initiation of a new anti-cancer therapy which happens earlier.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes of the version currently in effect at BeiGene at the time of database lock. They will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the safety analysis set. A listing of prior and concomitant medications will be provided.

7.4.8. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) of the version currently in effect at BeiGene at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class (SOC) and preferred term (PT) in the safety analysis set. A listing of medical history will be provided.

7.5. Efficacy Analysis

Response assessments will be determined by the investigator and by the IRC per the Lugano classification ([Cheson et al 2014](#)).

Efficacy analyses will be provided by study part and target dose levels as appropriate. Efficacy analysis may also be provided by pooling patients from Part 1 and Part 2 at the same target dose level. All efficacy analyses will be based on the Efficacy Evaluable Set.

For the Centre for Drug Evaluation (CDE) registration in China, the efficacy analysis in Part 2 will be conducted excluding the patients whose efficacy data were presented to the CDE during the consultation meeting. The patients whose efficacy data were presented to the CDE during the consultation meeting will be excluded from the hypothesis testing for ORR for the CDE registration in China.

The primary efficacy analysis will be conducted approximately 12 months after the last patient enrolled. In addition, to initiate CDE registration in China, the efficacy analysis at approximately 6 months after the last patient enrolled will be conducted.

7.5.1. Primary Efficacy Endpoint

7.5.1.1. Primary Estimand

Primary estimand is defined in Section [4](#).

7.5.1.2. Primary Analysis for Primary Estimand

The primary efficacy endpoint of Part 2 is ORR, defined as the proportion of patients who achieve CR or PR, as determined by the IRC review. ORR in the historical control is assumed to be approximately 30% based on recent trials ([Martin et al 2016](#); [Jain et al 2018](#); [Wang et al 2017](#)). The ORR in this study is estimated to be 50%, which is deemed a clinically meaningful improvement.

The null hypothesis to be tested is:

$$H_0: \text{ORR} \leq 30\%$$

against the alternative:

$$H_1: \text{ORR} > 30\%$$

Binomial exact test will be used to evaluate ORR. The test against H_0 will be performed at a 1-sided significance level of 0.025. If the H_0 can be rejected, it will be concluded that sonrotoclax rules out a historical control of 0.3 ORR at the significance level. The number and proportion of patients who achieve the overall response will be summarized. Associated 2-sided 95% Clopper Pearson CI of ORR will be calculated.

7.5.1.3. Handling of Missing Values Not Related to Intercurrent Event

Patients without any post-baseline response assessment (regardless of the reason) will be considered as nonresponders.

7.5.1.4. Sensitivity Analyses for Primary Endpoint/Estimand

Not planned.

7.5.1.5. Supplementary Analysis

Not planned.

7.5.2. Secondary and Exploratory Efficacy Endpoints (Part 1 and Part 2)

All analyses apply to both Part 1 and Part 2 unless otherwise stated.

ORR by Investigator

ORR by investigator will be analyzed using the same statistical methods as ORR by IRC. Concordance of ORR by IRC and by investigator will be analyzed.

ORR by IRC (Part 1 only)

The number and proportion of patients who achieve the overall response will be summarized. Associated 2-sided 95% Clopper Pearson CI of ORR will be calculated.

Duration of Response by IRC

DOR is defined as the time from the first response to the first documentation of disease progression or death due to any cause, whichever occurs first. DOR will be summarized only for patients who have achieved an overall response of at least PR. The Kaplan-Meier method will be used to estimate the distribution of DOR, including the median and event free rate at selected timepoints such as 6, 9, and 12 months. The two-sided 95% CIs for median and other quartiles of DOR will be generated using Brookmeyer and Crowley method ([Brookmeyer and Crowley, 1982](#)), whereas the two sided 95% CI for event free rate at landmark timepoints will be generated using Greenwood's formula ([Greenwood, 1926](#)). Duration of follow-up for DOR will be estimated by reverse Kaplan Meier method. Kaplan-Meier curves for DOR will also be generated. The censoring rules for DOR will follow the PFS censoring rules.

DOR by Investigator

DOR by investigator will be analyzed using the same statistical methods as DOR by IRC.

Progression-Free Survival by IRC

PFS is defined as the time from treatment initiation to the first documentation of disease progression or death due to any cause, whichever occurs first. PFS will be analyzed using the same methods as the DOR analysis, but for all patients in the Efficacy Evaluable Set.

The PFS censoring rule will follow FDA Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" ([FDA, 2018](#)).

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	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
3	New anticancer treatment started before documented disease progression or death	Date of last disease assessment prior to date of new anticancer treatment	Censored
4	Death before first disease assessment	Date of death	Event
5	Death or progression after two or more missed consecutive scheduled disease assessment	Date of last disease assessment without documented disease progression before missed tumor assessments	Censored

Progression-Free Survival by Investigator

PFS by investigator will be analyzed using the same statistical methods as PFS by IRC.

Time to Response by IRC

TTR is defined as the time from treatment initiation to the first documented response. TTR will be summarized for responders only using sample statistics, such as sample mean, median, and standard deviation.

Time to Response by Investigator

TTR by investigator will be analyzed using the same statistical methods as TTR by IRC.

Overall Survival

OS is defined as the time from treatment initiation to death due to any causes. OS will be analyzed using the same methods as the PFS analysis except for the censoring rules. Patients who are known to be alive as of their last known status will be censored at their last date known alive.

NFlymSI-18, EQ-5D-5L, PGI-S and PRO-CTCAE

NFlymSI-18 is a patient-reported outcomes (PRO) questionnaire that is developed to measure lymphoma specific symptoms and/or treatment-related concerns in patients with advanced lymphoma. The NFlymSI-18 includes 18 separate questions (items) in four scales: “disease related symptoms – physical,” “disease related symptoms – emotional,” “treatment side effects,” and “function and wellbeing,” with the recall period of 1 week (the past week). Higher scores indicate better health-related quality of life (HRQoL). A sample questionnaire is provided in [Appendix 3](#). NFLYMSI-18 scoring guidelines are provided in [Appendix 4](#).

The NFlymSI-18 total and scales scores and their change from baseline will be summarized descriptively (eg, mean [standard deviation], median, range) for all assessment timepoints in Parts 1 and 2. For Part 2 only, a mixed model for repeated measures (MMRM) will be used to estimate the mean change from baseline for NFlymSI-18 subscales of “disease related symptoms – physical” and “treatment side effects”, the key PRO endpoints. The least square mean change from baseline at the key clinical cycles (i.e., assessment timepoints Week 8, Week 16, and Week 28) post baseline will be provided.

The EQ-5D-5L comprises a descriptive module and a Visual Analogue scale (VAS). The descriptive module comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. Higher scores indicate lower quality of life. The EQ VAS measures respondent’s self-rated health status on a 0 to 100 scale, with 100 = ‘the best health you can imagine’ and 0 = ‘the worst health you can imagine’. Higher scores on VAS indicate higher health status. A sample questionnaire is provided in [Appendix 5](#).

The EQ-5D-5L visual analogue scale score at each assessment timepoint and changes from baseline will be summarized descriptively (e.g. mean, standard deviation, median, Q1, Q3, minimum, maximum) in Part 2.

PGI-S Lymphoma asks the severity of the lymphoma symptoms within the past week on 5 level Likert score: (1) Not at all, 2) Mildly, 3) Moderately, 4) Very, 5) Extremely, with higher scores showing the worse symptoms. A sample questionnaire is provided in [Appendix 6](#).

The PGI-S score at each assessment timepoint and changes from baseline will be summarized descriptively (eg, mean [standard deviation], median, range) in Part 2.

The PRO-CTCAE measurement system was developed by NCI as a companion to the CTCAE. It was designed to improve the validity, reliability, and precision with which symptomatic adverse effects of treatment are evaluated in patients with cancer in clinical studies. The PRO-CTCAE item library consists of 124 discrete items representing 78 symptomatic adverse events that are common in oncology and are included in the CTCAE. PRO-CTCAE, in this study, consists of 4 items that are most relevant to the study drugs' side effects: nausea, vomiting, diarrhea, and fatigue. Responses are provided on a 5-point Likert scale, and the recall period is 7 days. A sample of PRO-CTCAE is provided in [Appendix 7](#).

The PRO-CTCAE score at each assessment timepoint and change from W8D1 will be summarized descriptively (eg, mean [standard deviation], median, range) in Part 2.

7.5.3. Subgroup Analyses

Primary endpoint (ORR by IRC) and selected secondary endpoint (ORR by investigator) will be summarized descriptively in the specified subgroups, as appropriate (i.e., when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined): sex, age group (<65 vs. ≥65), region, race, ECOG performance status (0 vs. ≥1), prior line of therapy (<3 vs. ≥3), relapsed or refractory, reason last prior therapy ended (treatment completed, progressive disease, toxicity, other), disease stage (Stage I, Stage II, Stage III, Stage IV), bulky disease (Yes vs. No), histology classification (classic, pleomorphic, blastoid, unknown, other), Ki-67 positive percentage groups, TP53 mutation (detected vs. undetected), MIPI, MIPI-b, baseline extranodal disease, bone marrow involvement, and gastrointestinal involvement. Within-group summary statistics (e.g., ORR with their 95% CIs) will be presented in forest plots. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

7.6. Safety Analyses

Safety will be assessed by monitoring and recording all AEs graded by the [NCI CTCAE v5.0](#). Laboratory values (CBC, serum chemistry, coagulation, and urinalysis), vital signs, physical examinations, and ECG findings will also be used to assess safety. Descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data in the Safety Analysis Set.

The safety analyses may be conducted by study part, target dose level, and overall population as appropriate in the Safety Analysis Set.

7.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized:

- Duration of exposure (months): defined as the duration from ramp-up Day 1 (RD1) to the last dose date of the study drug.
- Duration of exposure (months) at target dose: defined as the duration from the final ramp-up day at the target dose (W1D1) to the last dose date of the study drug.
- Duration of exposure (months) at ramp-up: defined as the time from Ramp-Up Day 1 (RD1) to the final ramp-up day at the target dose (W1D1) for patients who reach the target dose, or from Ramp-Up Day 1 (RD1) to the last study drug dose date for patients who do not reach the target dose.
- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.
- Total dose received per patient (mg) at target dose: defined as the cumulative dose of the study drug from W1D1 to the last dose date of the study drug.
- Total dose received per patient (mg) at ramp-up: defined as the cumulative dose of the study drug from Ramp-Up Day 1 (RD1) to the final ramp-up day at the target dose (W1D1) for patients who reach the target dose, or from Ramp-Up Day 1 (RD1) to the last study drug dose date for patients who do not reach the target dose.
- Actual dose intensity (mg/day): defined as the total dose received by a patient divided by the duration of exposure (days).
- Actual dose intensity (mg/day) at target dose: defined as the total dose received by a patient starting from W1D1 divided by the duration of exposure (days) starting from W1D1.
- Actual dose intensity (mg/day) at ramp-up: defined as the total dose received by a patient at ramp-up divided by the duration of exposure (days) at ramp-up.
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity is defined as the planned dose by a patient divided by the duration of exposure.
- Relative dose intensity (%) at target dose: defined as the ratio of the actual dose intensity starting from W1D1 and the planned dose intensity starting from W1D1.
- Relative dose intensity (%) at ramp-up: defined as the ratio of the actual dose intensity at ramp-up and the planned dose intensity at ramp-up.

The number (percentage) of patients with dose modification (including reduction and interruption) will be summarized with the respective reasons. The days on which the first dose reduction/interruption occurs will be summarized. Frequency of dose reduction/interruption will be summarized descriptively. Duration of dose interruption (days) will be summarized descriptively. Patient data listings will be provided for all dosing records, and for the above calculated summary statistics.

7.6.2. Dose-Limiting Toxicities

Number and percentage of patients with DLT events will be summarized by dose level based on the DLT-evaluable Set.

7.6.3. Adverse Events

AEs will be graded by the investigators using the [NCICTCAE v5.0](#). The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (of the version referenced at BeiGene at the time of database lock) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A TEAE is defined as an AE that had 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 the last dose of sonrotoclax or initiation of a new anticancer therapy, whichever comes first. Beyond 30 days after the last dose of study drug, AE with the same group ID of any TEAE should be considered as a treatment-emergent event. AE with both start date and end date missing will be counted as TEAE. AE with start date missing and end date after the date of first dose of study drug will also be considered as TEAE. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

An overview of patients with at least one TEAE will be presented with the incidence of:

- Patients with at least 1 TEAE
- Patients with at least 1 TEAE with grade 3 or higher
- Patients with at least 1 Serious TEAE
- Patients with at least 1 TEAE leading to death
- Patients with at least 1 TEAE leading to death, with a start date within 8 weeks of the first dose
- Patients with at least 1 TEAE leading to treatment discontinuation
- Patients with at least 1 TEAE leading to treatment discontinuation, with a start date within 8 weeks of the first dose
- Patients with at least 1 TEAE leading to dose modification, including dose interruption and dose reduction
- Patients with at least 1 treatment-related TEAE
- Patients with at least 1 treatment-related TEAE with grade 3 or higher
- Patients with at least 1 treatment-related Serious TEAE
- Patients with at least 1 treatment-related TEAE leading to death

- Patients with at least 1 treatment-related TEAE leading to treatment discontinuation
- Patients with at least 1 treatment-related TEAE leading to dose modification, including dose interruption and dose reduction

The incidence of following TEAEs and Serious TEAEs will be reported by SOC and PT (and by worst grade if specified), sorted by decreasing frequency of SOC and PT (a patient with multiple occurrences of the same event within a SOC and PT will be counted only once by the worst grade according to [NCI CTCAE v5.0](#)):

- TEAE (any grade) by SOC/PT and by SOC/PT/worst grade
- TEAE with grade 3 or higher by SOC/PT
- Serious TEAE by SOC/PT
- TEAE leading to death by SOC/PT
- TEAE leading to treatment discontinuation by SOC/PT
- TEAE leading to treatment modification by SOC/PT
- Treatment-related TEAE by SOC/PT
- Treatment-related TEAE with grade 3 or higher by SOC/PT
- Treatment-related Serious TEAE by SOC/PT
- Treatment-related TEAE leading to death by SOC/PT
- Treatment-related TEAE leading to treatment discontinuation by SOC/PT
- Treatment-related TEAE leading to treatment modification by SOC/PT

The incidence of following TEAEs will be reported by PT:

- TEAE (any grade)
- TEAE with grade 3 or higher
- Serious TEAE
- TEAE leading to death
- TEAE leading to treatment discontinuation
- TEAE leading to dose modification
- Treatment-related TEAE

TEAEs of particular interest include anemia, thrombocytopenia, neutropenia, infection (with a subcategory of opportunistic infections), and tumor lysis syndrome (reported AE). For each AEPI category, an overview of patients with at least one TEAE of particular interest will be presented with the incidence of:

- Patients with at least 1 TEAE of particular interest
- Patients with at least 1 TEAE of particular interest with grade 3 or higher

- Patients with at least 1 Serious TEAE of particular interest
- Patients with at least 1 TEAE of particular interest leading to death
- Patients with at least 1 TEAE of particular interest leading to treatment discontinuation
- Patients with at least 1 TEAE of particular interest leading to dose modification, including dose interruption and dose reduction

The incidence of following TEAEs of particular interest and Serious TEAEs of particular interest will be reported by Category and PT:

- TEAE of particular interest (any grade) by Category/PT
- TEAE of particular interest with grade 3 or higher by Category/PT
- Serious TEAE of particular interest by Category/PT
- TEAE of particular interest leading to death by Category/PT
- TEAE of particular interest leading to treatment discontinuation by Category/PT
- TEAE of particular interest leading to dose interruption by Category/PT
- TEAE of particular interest leading to dose reduction by Category/PT

Time to first TEAE of particular interest and time to resolution on the first Grade 3 or higher TEAE of particular interest will be summarized. Exposure adjusted incidence rate of TEAEs of particular interest and exposure adjusted incidence rate of TEAEs of particular interest with grade 3 or higher will be summarized as well.

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be provided.

Listings of all AEs, treatment-related AEs, Serious AEs, AEs leading to treatment discontinuation, AEs leading to treatment discontinuation with a start date within 8 weeks of the first dose, AEs leading to treatment modification, AEs leading to death, and AEs leading to death with a start date within 8 weeks of the first dose will be provided. Listings of TEAEs of particular interest will be provided for each category. A listing of AEs that were started within 24 hours of the laboratory TLS for patients with ≥ 2 post-dose metabolic abnormalities within 24 hours of each other will be provided. A listing of AEs that were started within 24 hours of the reported TLS event for patients with reported TLS will be provided.

7.6.4. Laboratory Values

Clinical laboratory (e.g., CBC, serum chemistry, and urinalysis) values will be evaluated for each laboratory parameter. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report. Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in [NCI CTCAE v5.0](#) 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.

Potential drug induced liver injury will be summarized.

Laboratory tumor lysis syndrome abnormality will be summarized. Time to first onset of laboratory tumor lysis syndrome abnormality and time to resolving on the first laboratory tumor lysis syndrome and will be summarized.

Box-whisker plots will be generated for parameters of interest.

Patient data listings of selected list of lab parameters will be provided.

7.6.5. Vital Signs

Descriptive statistics for vital sign parameters (e.g., systolic and diastolic blood pressures, heart rate, body temperature) and changes from baseline will be presented by visit.

Shift tables assessing the toxicity grade of systolic and diastolic blood pressures at baseline versus worst toxicity recorded post-baseline will be presented.

Box-whisker plots will be generated for actual value and change from baseline for systolic and diastolic blood pressure.

7.6.6. Electrocardiograms (ECG)

A 12-lead electrocardiogram (ECG) will be performed locally in triplicate at screening and at the Safety Follow-up Visit for all patients and as clinically indicated at other timepoints. At each timepoint, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval.

Actual value and change from baseline for the ECG parameters (QT interval, heart rate, and QTcF interval) will be summarized.

The number and percentage of patients satisfying the following QT and QTcF conditions at any time post-baseline will be summarized:

- >450 , >480 , or >500 msec
- ≤ 30 msec increase from baseline, >30 and ≤ 60 msec increase from baseline, or >60 msec increase from baseline

7.6.7. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

7.7. Pharmacokinetic Analyses

The analysis set for patients with PK samples will contain all patients who had at least one post-dose PK sample collected according to the protocol and laboratory manual. Concentration and PK parameters of sonrotoclax will be summarized and listed for Part 1 and Part 2 separately. Population PK analyses of PK data from this study, and other studies, may be conducted as

appropriate, and the results of such analysis will be reported separately from the clinical study report.

Exposure-response (efficacy and safety endpoints) analysis may be carried out if supported by sufficient data and the results of such analyses will be reported separately from the clinical study report.

7.7.1. Part 1: Dose Escalation and Safety Expansion

7.7.1.1. Report of Pharmacokinetic Concentrations

Plasma concentration-time data will be summarized and displayed by dose level and nominal time in both tabular and graphical form. Individual concentration data will be listed including the dose level, relative time to dosing, actual sample collection time. The number of patients with non-missing plasma concentration, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] % associated to the geometric mean will be included in the descriptive statistics summary.

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. The concentration and time data will be listed individually and summarized by treatment/dose group using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.
- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term “BLQ” with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ is treated as missing data, and the time point is ignored in the computations.
- BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).
- If a concentration at a given time point is missing it shall be reported as a missing value. Missing values may be defined in a bioanalytical source as “NS” (no sample), “NR” (no result), “IS” (insufficient sample), etc. If missing data are not identified in the bioanalytical source (i.e., the record is missing), the reporting convention of “NS” shall be utilized.

If the calculated mean concentration is zero, and SD and geometric CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

7.7.1.2. Plots of Pharmacokinetic Concentrations

Concentration versus time data will be plotted individually (using actual time) and summarized (using nominal time) graphically using arithmetic mean ($\pm$ SD) plots by visit/dose group, respectively. Each plot will be showed in linear (i.e., original) scale and semi-logarithmic scale of time. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on both linear scale but not shown in log-linear scale.

7.7.1.3. Calculation and Reporting of PK Parameters

PK parameters of sonrotoclax will be derived using standard noncompartmental analysis (NCA) methods and will be computed using Phoenix™ WinNonlin® Version 8.2 or higher (Certara, NJ, USA). Actual dose and blood draw times will be used to calculate the PK parameters. Other PK parameters may be calculated if supported by the data. The PK parameter estimates for a single dose (Ramp-up Week1 Day 1) profile includes but is not limited to the following. Other PK parameters may be calculated if supported by the data.

Parameter (Units)	Definition	Method of Determination
AUC_{0-t} (ng·h/mL) *	Area under the concentration versus time curve from time 0 to t hour	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{last} (ng·h/mL)	AUC from time zero to time of last quantifiable concentration	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{inf} (ng·h/mL)	AUC from zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (ng/mL)	Maximum observed drug concentration during a dosing interval	Reported value
T_{max} (h)	Time to reach C_{max}	Actual elapsed time for observed C_{max}
$t_{1/2}$ (h)	Apparent terminal elimination half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL/F (L/h)	Apparent drug clearance	Calculated as $Dose/AUC_{inf} \cdot F$, where F is the fraction of dose absorbed
V_z/F (L)	Apparent volume of distribution during the terminal phase	Calculated as $CL/F/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve

* AUC_{0-t} will be only calculated in patients who had last quantifiable concentration at nominal 8 hours post-dose.

The PK parameter estimates at steady state (Week4 Day1) included but not limited to the following.

Parameter (Units)	Definition	Method of Determination
$AUC_{0-t, ss}$ (ng·h/mL) *	Area under the concentration versus time curve from time 0 to t hour at steady state	Calculated using the linear up/log down variant of the trapezoidal rule
$AUC_{last, ss}$ (ng·h/mL)	AUC from time zero to time of last quantifiable concentration at steady state	Calculated using the linear up/log down variant of the trapezoidal rule
$C_{max, ss}$ (ng/mL)	Maximum observed drug concentration during a dosing interval at steady state	Reported value
$C_{4h, ss}$ (ng/mL)	Observed concentration at 4-hour nominal timepoint at steady state	Reported value

$C_{\text{trough, ss}}$ (ng/mL)	Observed drug concentration at predose nominal time point at steady state	Reported value
$T_{\text{max, ss}}$ (h)	Time to reach C_{max} at steady state	Actual elapsed time for observed C_{max} .
$T_{\text{last, ss}}$ (h)	Time of the last quantifiable concentration at steady state	Actual elapsed time for observed the last quantifiable concentration

* $AUC_{0-t, \text{ss}}$ will be only calculated in patients who had last quantifiable concentration at nominal 8 hours post-dose.

The parameters C_{max} , T_{max} , T_{last} , C_{4h} , and C_{trough} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, T_{max} will be assigned to the first occurrence of C_{max} .

Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

Where possible, the following diagnostic parameters of the plasma PK analysis will be calculated and listed, but not summarized:

- Interval: The time interval (hours) of the log-linear regression used to determine λ_z
- n: Number of data points included in the log-linear regression analysis to determine λ_z (a minimum of 3 points will be used)
- Adjusted Rsq: Coefficient of determination for calculation of λ_z . If adjusted Rsq is less than 0.80, then λ_z and related parameters will not be reported.
- %AUC_{extrap}: Percentage of AUC obtained by extrapolation; if greater than 20% then AUC_{0-inf} and related parameters will not be reported.

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%.
- For in-text tables, Geometric mean (geometric CV%) will be the default method of reporting PK parameters. T_{max} should be presented as median, range (minimum, maximum), when presenting the summary statistics. $t_{1/2}$ should be presented as arithmetic mean, range (minimum, maximum).
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.
- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g. AUC range from 10 to 10,000 ng.h/mL and C_{max} range from 1 to 1000 ng/mL.

In this scenario, for reporting PK parameters such as AUC and $C_{\max}$, the following guidance is provided for rounding:

- If the numerical value is below 100 then one decimal place may be used e.g. 0.1 or 99.9.
- For values ranging from >100, whole numbers should be used e.g. 100 or 9999.
- If > 10,000 the clinical pharmacologist may decide on changing units e.g. from $\mu\text{g/ml}$ to mg/ml .
- For reporting times e.g. for $T_{\max}$, T_{last} , or $t_{1/2}$, if <1 h use 2 decimals; time up to 24 h should be reported to one decimal place e.g. 23.5 h, time >24 h should be rounded to nearest whole number e.g. 105 h.

7.7.2. Part 2: Efficacy Expansion

The PK concentration data collected sparsely at pre-dose and post-dose will be tabulated and summarized by visit and time point. Descriptive statistics will include the number of patients with non-missing plasma concentration, means, standard deviations, coefficient of variation [CV%], median, minimum, maximum, geometric mean [GeoMean], and geometric coefficient of variance [GeoCV%]. A listing will include relative time to dosing, actual sample collection time and time deviation from the relative time point. For the sparse PK profile of BGB-11417, PK parameters such as C_{trough} at steady state will be summarized.

Additional PK parameters may be calculated if deemed appropriate. Estimates for these parameters will be tabulated and summarized (eg, n, mean, standard deviation, coefficient of variation [CV%], median, minimum, maximum, geometric mean [GeoMean], and geometric coefficient of variance [GeoCV%]).

Correlation between PK and biomarker endpoints may be explored as appropriate. Results of these analyses, such as exposure-response (efficacy or safety endpoints) analysis, may be carried out if supported by data.

7.8. Other Analyses

Additional exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

8. INTERIM ANALYSES

No interim analysis is planned.

9. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

10. REFERENCES

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APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

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

1. Prior/Concomitant Medications/Procedures

When the start date or end date of 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 the start date of 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 the end date of 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 medication is completely missing, do not impute. If the imputed date for medication end date > death date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

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 the 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 $\neq$ 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 $\neq$ month and year of treatment start date, then set to first day of the month
- If year of the start date is missing or start date is completely missing, do not impute.

If the end date of an AE 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 the end date is completely missing, do not impute.

If the imputed AE end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

3. Deaths

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01 Jan or the last date of a patient known to be alive + 1, whichever is later.
- If only day is missing, the death will be assumed to be on the first day of the month or the last date of a patient known to be alive +1, whichever is later.

4. Subsequent Anti-cancer Therapies

If the start date of a subsequent anti-cancer therapy is incomplete or missing, impute as follows:

- If both month and day are missing, then set to January 1st
- If only day is missing, then set to first day of the month
- If the subsequent anti-cancer therapy is collected from CRF “post-treatment discontinuation anti-cancer systemic therapy” or “post-treatment discontinuation anti-cancer procedure” page, and the imputed date is $\leq$ the last dosing date, then set to last dosing date + 1

If stop date of a subsequent anti-cancer therapy 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 the imputed stop date > min (death date, study discontinuation date, data cutoff date), then set to min (last known alive date, study discontinuation date, data cutoff date)

If year of the start date/stop date is missing, do not impute.

5. Disease Diagnosis

If a disease diagnosis date 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 a diagnosis date is completely missing, do not impute.

6. Prior Systemic Therapy

If a prior systemic therapy start/stop date or disease progression date is partially missing, impute as follows:

- If start date of a prior systemic therapy 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 the imputed start date $\geq$ first dose date then set to first dose date – 1
- If end date of a prior systemic therapy 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 the imputed end date $\geq$ first dose date, then set to first dose date -1

APPENDIX 2. 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 et al, 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
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: $\geq 50\%$ 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 $\times$ 5 mm as the default value When no longer visible, 0 $\times$ 0 mm For a node > 5 mm $\times$ 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

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response) ^d
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
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 $\leq$ 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; LD_i, 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; SD_i, shortest axis perpendicular to the longest transvers diameter of a lesion; SPD, sum of the product of the perpendicular diameters for multiple lesions.

Temporary withholding of sonrotoclax (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

APPENDIX 3. NCCN--FACT FLYMSI-18 (VERSION 2)

Below is a list of statements that other people with your illness have said are important.
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

			Not at all	A little bit	Some- what	Quite a bit	Very much
D R S- P	GP1	I have a lack of energy.....	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	Leu1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
	BMT6	I get tired easily	0	1	2	3	4
	BP1	I have bone pain.....	0	1	2	3	4
	HI8	I have trouble concentrating	0	1	2	3	4
	GF5	I am sleeping well.....	0	1	2	3	4
D R S- E	C6	I have a good appetite.....	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
	BR M9	I have emotional ups and downs.....	0	1	2	3	4
	Leu4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4
	Leu5	I feel uncertain about my future health.....	0	1	2	3	4
T S E	GP2	I have nausea	0	1	2	3	4
	N3	I worry about getting infections.....	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
F W B	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)
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03 March 2010

APPENDIX 4. NCCN/FACT LYMPHOMA SYMPTOM INDEX-18 (FLYMSI-18) SCORING GUIDELINES (VERSION 2)

- Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
 2. Perform reversals as indicated, and sum individual items to obtain a score.
 3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
 4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

<u>Scale</u>	<u>Item Code</u>	<u>Reverse item?</u>		<u>Item response</u>	<u>Item Score</u>
FLymSI-18	GP1	4	-	_____	= _____
	GP4	4	-	_____	= _____
Total	C2	4	-	_____	= _____
	LEU1	4	-	_____	= _____
<i>Score range: 0-72</i>	BMT6	4	-	_____	= _____
	BP1	4	-	_____	= _____
	HI8	4	-	_____	= _____
	GF5	0	+	_____	= _____
	Ca6	0	+	_____	= _____
	GE6	4	-	_____	= _____
	BRM9	4	-	_____	= _____
	LEU4	4	-	_____	= _____
	LEU5	4	-	_____	= _____
	GP2	4	-	_____	= _____
	N3	4	-	_____	= _____
	GP5	4	-	_____	= _____
	GF3	0	+	_____	= _____
	GF7	0	+	_____	= _____

Sum individual item scores: _____

Multiply by 18: _____

Divide by number of items answered: _____ = **FLymSI-18 score**

<u>Subscale</u>	<u>Item Code</u>	<u>Reverse item?</u>		<u>Item response</u>	<u>Item Score</u>
FLymSI-DRS-P	GP1	4	-	_____	= _____
	GP4	4	-	_____	= _____
(Disease Related	C2	4	-	_____	= _____
	LEU1	4	-	_____	= _____
Symptoms-Physical)	BMT6	4	-	_____	= _____
	BP1	4	-	_____	= _____
<i>Score range: 0-36</i>	HI8	4	-	_____	= _____
	GF5	0	+	_____	= _____
	Ca6	0	+	_____	= _____

Sum individual item scores: _____

Multiply by 9: _____

Divide by number of items answered: _____ = **FLymSI-DRS-P score**

<u>Subscale</u>	<u>Item Code</u>	<u>Reverse item?</u>	<u>Item response</u>	<u>Item Score</u>
FLymSI-DRS-E (Disease Related Symptoms-Emotional)	GE6	4 -	_____	= _____
	BRM9	4 -	_____	= _____
	LEU4	4 -	_____	= _____
	LEU5	4 -	_____	= _____
Score range: 0-16				

Sum individual item scores: _____

Multiply by 4: _____

Divide by number of items answered: _____ = **FLymSI-DRS-E score**

FLymSI-TSE (Treatment Side Effects)	GP2	4 -	_____	= _____
	N3	4 -	_____	= _____
	GP5	4 -	_____	= _____
Score range: 0-12				

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____ = **FLymSI-TSE score**

FLymSI-F/WB (Function/ Well-Being)	GF3	0 +	_____	= _____
	GF7	0 +	_____	= _____
Score range: 0-8				

Sum individual item scores: _____

Multiply by 2: _____

Divide by number of items answered: _____ = **FLymSI-F/WB score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

APPENDIX 5. EUROQOL GROUP EQ-5D-5L



Health Questionnaire

English version for the UK

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Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

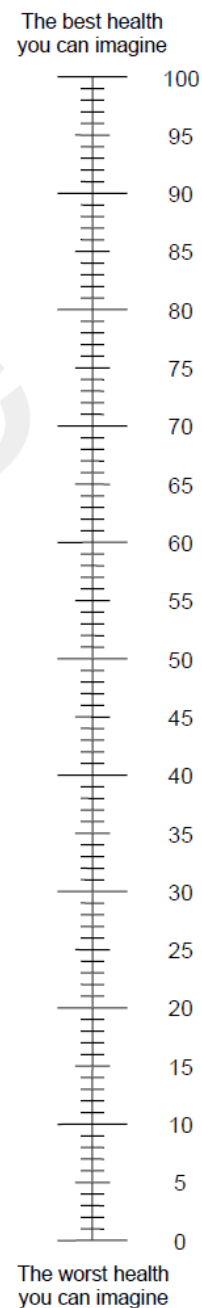
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



APPENDIX 6. PGI-S FOR LYMPHOMA

Patient Global Impression of Symptom Severity (PGI-S) Lymphoma

During the past week, how severe were your lymphoma symptoms (e.g., fatigue, pain, lumps, or swellings, etc.)

- ☐ Not at all
- ☐ Mildly
- ☐ Moderately
- ☐ Very
- ☐ Extremely

APPENDIX 7. PRO-CTCAE

Item Library Version 1.0

Lymphoma Treatment Side-Effect Items

As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days:

9. PRO-CTCAE™ Symptom Term: Nausea				
a. In the last 7 days, how OFTEN did you have NAUSEA?				
☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very Severe

10. PRO-CTCAE™ Symptom Term: Vomiting				
a. In the last 7 days, how OFTEN did you have VOMITING?				
☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very Severe

15. PRO-CTCAE™ Symptom Term: Constipation				
a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very Severe

16. PRO-CTCAE™ Symptom Term: Diarrhea				
a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

53: PRO-CTCAE™ Symptom Term: Fatigue				
a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				

53: PRO-CTCAE™ Symptom Term: Fatigue				
☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the National Cancer Institute at the National Institutes of Health in Bethesda, Maryland, USA. The use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

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