

CLINICAL STUDY PROTOCOL TITLE PAGE

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

Brief Title:

Study of BGB-11417 Monotherapy in Patients With Relapsed or Refractory Mantle Cell Lymphoma

Protocol Number:

BGB-11417-201

Amendment Number:

Amendment 3.0 Global

Investigational Medicinal Products:

Sonrotoclax (BGB-11417)

Regulatory Agency Identification Number(s):

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Sponsor:

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INVESTIGATOR SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to Study BGB-11417-201 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated. This includes personnel at my site as well as personnel working in any facility where study activities are my responsibility.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable laws and regulations, the requirements of the ethics committee of record for my clinical site, and current GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients before initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site before initiating any study-specific procedures or administering investigational products to those patients.
- To maintain records of each patient's participation and all data required by the protocol in an accurate and timely manner.

Acceptance of this protocol constitutes my agreement that no confidential information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd. or one of its affiliates, unless and only to the extent required by applicable laws and regulations.

Name: <i>Last name, First name</i>	Title: <i>Title at Institution</i>	Institution: <i>Address</i>
Signature:		Date: <i>DD Month YYYY</i>

DOCUMENT HISTORY

Amendment Version Number	Approval Date	Type of Protocol Amendment
BGB-11417-201 Amendment 3.0	<i>See electronic signature</i>	Substantial
BGB-11417-201 Amendment 2.0	09 August 2023	Substantial
BGB-11417-201 Amendment 1.0	18 August 2022	Substantial
Original protocol	21 February 2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This protocol amendment 3.0 replaces protocol amendment 2.0. This amendment is considered substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament and the Council of the EU.

The primary purpose of Amendment 3.0 is to fulfill the requests received from the United States Food and Drug Administration (US FDA) and United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA). The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 9.10 Adverse Events of Special Interest (new section)	Added a new section to describe the required reporting of Hy's law cases and clinical TLS cases as adverse events of special interest.	Adding a new safety monitoring procedure across all sonrotoclax program studies to enhance patient safety
Section 7.4.1.1 Interruption or Reduction of Dose Levels During Dose Ramp-up Period. Section 7.4.1.2 Interruption or Modification of Dose Levels During Treatment With Target Dose Level Period. Section 7.5.1 Risk of Tumor Lysis Syndrome	- Updated the wording on TLS prevention in case of drug restart in case of long hold and with still active disease. - Added a standardized dose restart table in Section 7.4.1.2.	To provide additional clarification to investigators on how ramp-up should be reapplied when restarting sonrotoclax to minimize TLS risk following a long hold, based on requests received from the US FDA and UK MHRA
Section 7.2.1.2 Administration of Sonrotoclax	Updated that sonrotoclax dose will be administered with food instead of a low-fat meal once a day.	To remove limitation of fat content in food based on results of the food effect study
Section 2.1.2.3 Exploratory Objectives. Section 6.10 Patient-Reported Outcomes. Section 10.1.2.3 Exploratory Endpoints. Section 10.2.8.6 Patient-Reported Outcomes (new section)	Added PRO-CTCAE as part of patient-reported outcomes	To implement advice received from the US FDA on the MCL development program
Appendix 14 NCI PRO-CTCAE™ ITEMS - ENGLISH (new section)	Added selected questionnaires of PRO-CTCAE to assess symptomatic adverse effects expected to occur from the study treatment	

Section Number and Title	Summary of Change	Brief Rationale for Change
Title Page	- Added amendment number, regulatory agency identification number(s), approval date, and contact information. - Removed phase number, indication, sponsor medical monitor information, and protocol versions. - Updated confidentiality statement.	To align with BeiGene Global Protocol Template
Final Protocol Approval Sheet (deleted section)	Deleted the section.	
Investigator Signature Page	Updated the language.	
Document History. Protocol Amendment Summary of Changes (new sections)	Added new sections.	

SYNOPSIS

Study 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		
Study Phase:	1/2		
Indication	Relapsed or Refractory Mantle Cell Lymphoma		
Regulatory Agency Identifier Number (s):	EU CT Number: 2022-500687-35-00 US IND: 161045		
Rationale:	Mantle cell lymphoma (MCL) is an uncommon and incurable B-cell malignancy that is currently treated with combinations of cytotoxic chemotherapy and the anti-CD20 antibody rituximab. Despite the aggressive measures that can achieve a high response in treatment-naïve MCL patients, most patients experience relapse or refractory disease that ultimately results in poor outcomes, especially in those who have been previously treated with a Bruton tyrosine kinase (BTK) inhibitor. B-cell lymphoma-2 (BCL2) is a key regulator of apoptosis, aberrantly expressed in many hematologic malignancies including MCL, and plays a critical role in disease resistance to treatment. Venetoclax, the first-in-class orally bioavailable BCL2 inhibitor, demonstrated clinical activity in patients with relapsed and refractory MCL. Sonrotoclax (also known as BGB-11417) is a BCL2 inhibitor that demonstrated increased specificity and potency in preclinical models compared with venetoclax that could potentially lead to improved efficacy in patients with relapsed/refractory (R/R) MCL. The ongoing Phase 1 studies indicated that sonrotoclax is well tolerated in patients with B-cell malignancies, including MCL, and showed preliminary anti-tumor activity. This clinical trial will examine the recommended Phase 2 dose (RP2D) as well as assess efficacy, safety, and pharmacokinetics (PK) of sonrotoclax in patients with R/R MCL.		
Objectives and Endpoints			
Objectives		Endpoints	
Part 1 Primary: To determine the safety and tolerability of sonrotoclax monotherapy		Part 1 Primary: - Dose-limiting toxicity - The incidence and severity according to the National Cancer Institute-Common Terminology	

• To define the maximum tolerated dose (or maximum administered dose) and the 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	Criteria for Adverse Events v5.0 of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of sonrotoclax. • Incidence and severity of TLS-relevant events
Part 1 Secondary: • To assess the PK of sonrotoclax monotherapy • To assess the preliminary antitumor activity of sonrotoclax monotherapy in patients with R/R MCL.	Part 1 Secondary: • 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 of sonrotoclax monotherapy in patients with R/R MCL as measured by the overall response rate (ORR), duration of response, progression-free survival, time to response determined by the investigator and by the Independent Review Committee in accordance with the 2014 modification of the International Working Group on non-Hodgkin lymphoma criteria (hereafter referred as the Lugano classification), and overall survival.

Part 2 Primary: To evaluate the efficacy of sonrotoclax monotherapy at the RP2D with recommended ramp-up schedule from Part 1 in patients with R/R MCL.	Part 2 Primary: ORR as determined by the Independent Review Committee in accordance with the Lugano classification
Part 2 Secondary: - To evaluate the efficacy of sonrotoclax monotherapy in patients with R/R MCL. - To evaluate the safety and tolerability of sonrotoclax monotherapy in patients with R/R MCL	Part 2 Secondary: - Efficacy of sonrotoclax monotherapy in patients with R/R MCL as measured based on: - ORR determined by the investigator - Duration of response determined by the Independent Review Committee and by the investigator - Progression-free survival determined by the Independent Review Committee and by the investigator - Time to response determined by the Independent Review Committee and by the investigator - Overall survival - Health-related quality of life based on patient-reported outcomes - Safety and tolerability of sonrotoclax monotherapy in patients with R/R MCL as measured based on the incidence, timing, and severity of treatment-emergent adverse events and serious adverse events, clinical laboratory tests, physical examinations, and vital signs.

Trial Design	BGB-11417-201 is an open-label, multicenter, global Phase 1/2 study evaluating the efficacy and safety of sonrotoclax in patients with R/R MCL who have been treated with chemoimmunotherapy and BTK inhibitor and experienced progression on or after treatment or who are intolerant to BTK inhibitor. This study is composed of two parts (see below, Part 1 for dose escalation and safety expansion and Part 2 for efficacy expansion). After the screening period, eligible patients will receive sonrotoclax at protocol defined dose (160 mg or 320 mg) after a ramp-up period continuously until disease progression determined by the investigator (Part1) or confirmed by the Independent Review Committee (Part 2), unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Part 1: 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 starting dose is 1 mg, and the starting target dose will be 160 mg once a day for the first dose level and 320 mg if the 160 mg dose is determined to be safe. Part 1B will be a safety expansion phase with up to 2 dose cohorts, each consisting of additional patients for one target dose level (up to 12 patients at each dose level including Part 1A patients), based on the Safety Monitoring Committee recommendation and the sponsor evaluation. Part 1B is to collect more safety, PK, and other data, together with the Part 1A data, as well as the available data from Studies BGB-11417-101 and BGB-11417-102 as references, for the determination of RP2D. Part 2: Part 2 will be conducted as an open-label, single-arm, multicenter, expansion study. Sonrotoclax monotherapy will be administered at the RP2D and with recommended ramp-up schedule from Part 1 based on Safety Monitoring Committee recommendation and sponsor's evaluation. Information on the patient's disease response or progression will be assessed and analyzed by the Independent Review Committee. Safety information will also be collected for assessment of sonrotoclax safety in R/R MCL. The total duration of this study is expected to be approximately 5 years, assuming an expected enrollment duration of approximately 2 years. The sponsor has the right to terminate this study at any time.
Trial Population	The patients to be included in this study will be adult patients with histologically confirmed diagnosis of MCL by local laboratory based on the World Health Organization (WHO) 2016 classification of tumors of hematopoietic and lymphoid tissue, including demonstration of positive cyclin D1 and/or t(11;14). Patients should have received at least one line of anti-CD20-based therapy and at least one kind of BTK inhibitor therapy, but no prior BCL2 inhibitor. Last prior anticancer therapy should have failed to result in at least partial response, or patients should have documented disease progression on or after the last line of therapy, or the last line of therapy

	would have needed to be discontinued due to toxicity/intolerability despite dose justification and optimal supportive care. Patients will need to have an interval of at least 1 week since last chemotherapy or radiotherapy, at least 2 weeks since receiving any biologic or any anti-lymphoma experimental drug, at least 3 months since receiving chimeric antigen receptor cell therapy or autologous stem cell transplantation, at least 6 months since receiving an allogeneic transplant (provided no immunosuppressant remains required), or at least 2 weeks since the last treatment by cytochrome P450 3A4 moderate inhibitor or strong inhibitor or inducer (or 5 half-lives, whichever is longer) until study treatment initiation. Patients with known central nervous system involvement, with certain ongoing Grade ≥ 2 toxicities from prior anticancer therapy, with certain medical status or condition, or who are pregnant or lactating will not be eligible.
Interventions:	Part 1: sonrotoclax will be given in the form of tablets, to be taken once daily, at a range of doses in Part 1A (dose-escalation) and Part 1B (safety expansion) with a daily ramp-up schedule. Target doses planned to be utilized during this study are 160 mg and 320 mg but may be modified by Safety Monitoring Committee recommendation based on data gathered from this study. A protocol amendment will be developed if doses other than 160 and 320 mg are to be explored. Part 2: sonrotoclax will be administered at the RP2D and with recommended ramp-up schedule from Part 1.
Ethical Considerations	The effects of sonrotoclax in patients with MCL are not yet fully known. Sonrotoclax is expected to be effective in treating MCL, because venetoclax, which also inhibits BCL2, has provided clinical benefit to patients with MCL in clinical trials. Sonrotoclax demonstrated increased specificity and potency in preclinical models compared with venetoclax that could potentially lead to improved efficacy in patients with R/R MCL. To date, sonrotoclax is being tested in 6 studies in humans that are currently in progress. The safety profile is currently consistent with that known for BCL2 inhibitors. This study is designed to demonstrate efficacy and establish the safety of sonrotoclax in patients with R/R MCL. This study will be conducted in compliance with ICH GCP guidance for ethical considerations.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AESI	adverse event of special interest
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCL2	B-cell lymphoma-2
BGB-11417	sonrotoclax
BIW	twice a week
BTK	Bruton tyrosine kinase
CBC	complete blood count
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL/F	apparent total clearance of drug from plasma after oral administration
CLL	chronic lymphocytic leukemia
C _{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life 5 Dimension 5 Level Questionnaire
FDA	Food and Drug Administration
FDG	[¹⁸ F]fluorodeoxyglucose
FIH	first-in-human
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAD	maximum administered dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
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
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PGI-S	Patient Global Impression of Symptom Severity
PK	pharmacokinetic(s)
PRO-CTCAE	Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	preferred term
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R/R	relapsed/refractory
RP2D	recommended Phase 2 dose
SLL	small lymphocytic lymphoma
TLS	tumor lysis syndrome
t _{max}	time to maximum observed plasma concentration
TTR	time to response
ULN	upper limit of normal
WBC	white blood cell(s)

1. INTRODUCTION

1.1. Background Information on Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an uncommon B-cell malignancy, diagnosed in 0.51-0.55/100,000 persons per year in the United States (US), making up 6% of all non-Hodgkin lymphoma (NHL) cases, with a similar incidence rate worldwide ([Smedby and Hjalgrim 2011](#); [Wang et al 2015](#)). MCL is a cancer commonly found in older persons, with a median age at diagnosis of approximately 70 years ([Sharman et al 2017](#); [Dreyling et al 2017](#)) and a male preponderance of roughly 2.5:1 ([Barista et al 2001](#); [Smedby and Hjalgrim 2011](#)). Patients usually present with advanced disease; 70% are diagnosed in stage IV. Most commonly, there is generalized lymphadenopathy and organomegaly. Approximately 10% to 20% of patients present with bone marrow involvement, and B symptoms (fever, night sweats, and weight loss) are present in approximately 40% of patients. Extranodal involvement of the gastrointestinal tract, particularly the colon, is common ([Skarbnik and Goy 2015](#)).

Classical MCL arises from mature B cells that have undergone an (11;14) translocation with resulting overexpression of nuclear cyclin D1. The archetypal immunohistochemical profile is positive for B-cell lymphoma-2 (BCL2), CD5, and FMC7, while being negative for CD10, BCL-6, and CD23.

The Mantle Cell Lymphoma International Prognostic Index (MIPI) is composed of the parameters of the ECOG performance status, age, leukocyte count, and lactate dehydrogenase (LDH), and classifies patients into low, intermediate, and high-risk groups, with corresponding median overall survival (OS) time of 72 months, 51 months, and 29 months, respectively ([Vose 2013](#)). The histological pattern of MCL is also prognostic, with complete response (CR) rates of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for mantle-zone/nodular/diffuse patterns of 73%, 25%, and 19%, respectively, and 3-year survival rates of 100%, 50%, and 55%, respectively ([Barista et al 2001](#)). Another prognostic factor is the expression of the proliferation-associated antigen Ki-67; 60% of patients have over 10% of their tumors staining positive for Ki-67, with highly proliferative cases showing a much poorer outcome than tumors with low proliferation.

1.2. Current Treatment of Mantle Cell Lymphoma and Unmet Clinical Needs

First-line therapy for localized MCL disease includes conventional chemotherapy followed by radiotherapy. In advanced stages (stages III–IV), treatment should be determined by the patient's ability to tolerate intensive chemoimmunotherapy and their eligibility for eventual autologous stem cell transplantation (ASCT) ([Dreyling et al 2017](#)). The Nordic Lymphoma Group assessed dose-intensified R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) alternating with rituximab and high-dose cytarabine followed by ASCT and showed a median OS of greater than 10 years ([Geisler et al 2012](#)). R-CHOP alternating with R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) followed by ASCT versus R-CHOP followed by ASCT was evaluated in the MCL-Younger trial. It identified a longer time to treatment failure with a median of 9.1 years versus 3.9 years in favor of the cytarabine containing regimen, although there was no OS benefit ([Hermine et al 2016](#)). Rituximab maintenance following a rituximab-based chemoimmunotherapy induction and ASCT improves

progression-free survival (PFS) and OS and represents the current standard of care ([Le Gouill et al 2016](#)). Older patients who are not felt to be transplant candidates are generally given conventional chemoimmunotherapy with R-bendamustine (BR), VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone), R-CHOP, or lenalidomide and rituximab (R2) as high-dose cytarabine-containing regimens can be toxic in the elderly ([Kluin-Nelemans et al 2012](#); [Rummel et al 2013](#); [Robak et al 2015](#); [Flinn et al 2014](#); [Ruan et al 2015](#)).

After relapse from the front-line therapy, multiple treatment options are clinically available for relapsed/refractory (R/R) MCL patients, including bortezomib, temsirolimus, lenalidomide, ibrutinib, zanubrutinib, and acalabrutinib. Among all the approved products recently, Bruton tyrosine kinase (BTK) inhibitor provides significant efficacy (overall response rate [ORR]/CR of ibrutinib, acalabrutinib, and zanubrutinib are 68%/21%, 81%/48%, and 84%/69%, respectively). However, lack of response has been observed in one-third of the patients in the ibrutinib registration study, and 7% of the patients discontinued ibrutinib due to adverse events ([Wang et al 2013](#)). Moreover, MCL is still an incurable disease and patients ultimately relapse (median PFS: 13.9 months for ibrutinib, 22.0 months for acalabrutinib, and 22.1 months for zanubrutinib) ([Wang et al 2013](#); [Wang et al 2020](#); [Song et al 2020](#)).

There are minimal outcome data for patients who progress after treatment with a BTK inhibitor, and the optimal therapeutic approach has not been established. Recent retrospective analyses have reviewed several agents (including traditional chemotherapy, lenalidomide, bortezomib, and Pi3K inhibitors) in this setting. Cheah and colleagues analyzed the effects of immunochemotherapy given after ibrutinib treatment in 31 patients, showing that the ORR was 32% (CR rate, 19%); the median OS was 8.4 months; and the median duration of response (DOR) was 6 months ([Cheah et al 2015](#)). Martin and colleagues also assessed the effects of post-ibrutinib therapy. In 73 patients on their study, the ORR was 26% (CR rate, 7%) resulting in a median PFS of 1.9 months and a median OS of 5.8 months ([Martin et al 2016](#)). MCL-004 assessed a lenalidomide-based approach after ibrutinib (progressive disease, 88%; toxicity, 9%). Thirteen patients subsequently received lenalidomide; 11 patients received lenalidomide-rituximab; and 34 patients received lenalidomide plus other therapy. The ORR was 29% and the median DOR was 20 weeks ([Wang et al 2017](#)). A recent analysis from Japan real-world data reported that of 270 patients treated with BTK inhibitor, 183 (68%) patients discontinued this agent, and 108 (40%) patients subsequently received post-BTK inhibitor therapy (27% bendamustine-based, 19% bortezomib-based, and 13% cytarabine-based). The median time to treatment discontinuation of post-BTK inhibitor treatments was 1.5 months (95% CI: 1.1 to 2.0) and the median OS for post-BTK inhibitor therapies was 5.5 months (95% CI: 3.9 to 9.4) ([Rai et al 2021](#)). Another United Kingdom real-world analysis showed that of 100 patients discontinuing ibrutinib due to progressive disease, the median OS after ibrutinib treatment was only 1.4 months (95% CI: 0.6 to 2.2) ([McCulloch et al 2021](#)).

With the clinically available subsequent therapy for MCL patients post-BTK inhibitor treatment, the collated data reveal an ORR of 26% to 32%.

Patients with MCL who have been previously treated with BTK inhibitor subsequently experienced extremely poor outcomes with currently available therapy options. The development of safe and effective targeted therapy after BTK inhibitor is needed to improve the otherwise dismal outcomes of these patients.

1.3. BCL2 Inhibitor Therapy in Mantle Cell Lymphoma

Impaired apoptosis plays a central role in tumor development, tumor maintenance, and therapeutic resistance. Apoptosis can be triggered via two main pathways: the extrinsic or death-receptor-mediated pathway, and the intrinsic or mitochondrial pathway (Czabotar et al 2014). It is the intrinsic pathway that is more commonly perturbed in lymphoid malignancies. Cell death mediated through this pathway is regulated by members of a family of proteins related to BCL2, which is considered to contain three subfamilies. The pro-survival subgroup (BCL2, Bcl-xL, Bcl-W, Mcl-1, A1/Bfl-1, and possibly Bcl-B) promotes cell survival by inhibiting their pro-apoptotic relatives. The pro-apoptotic BAX/BAK-like proteins, including BOK, are the essential effectors of apoptosis, and the BH3-only proteins (BIM, PUMA, BID, BAD, NOXA, BMF, BIK, and HRK) are the initiators of apoptosis (Anderson et al 2014). In healthy cells, the pro-survival BCL2 proteins bind and inhibit BAX and BAK after they have been partially activated, impairing the ability of BAX/BAK to oligomerize and form pores to induce mitochondrial outer membrane permeabilization. The BH3-only proteins are induced transcriptionally or post-transcriptionally in response to diverse stresses and initiate apoptosis by either binding the pro-survival BCL2 proteins, thereby unleashing BAX/BAK, or by directly activating these effectors of apoptosis. The various BCL2 family proteins have differential specificity of binding to one another, resulting in a complex but ordered network of interactions governing cell fate (Roberts 2016).

High BCL2 expression is almost universal in chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), Waldenström macroglobulinemia (WM), and MCL. Aberrant expression of the BCL2 protein found in MCL was associated with deregulation of cyclin D1 (CCND1) expression caused by its translocation (Touzeau et al 2011). When BCL2 is overexpressed, the ratio of pro- and anti-apoptotic BCL2 family members is disturbed, and apoptotic cell death can be prevented. Moreover, overexpression of BCL2 protein is closely related to chemoresistance in hematological tumors. As BCL2-mediated resistance to intrinsic apoptosis is considered as a key to pathogenesis, targeting BCL2 can improve apoptosis and overcome drug resistance to cancer therapy.

Venetoclax (ABT-199) is a selective small molecule inhibitor of BCL2 protein, which was granted approval for CLL and acute myeloid leukemia. Davids and colleagues published a Phase 1 first-in-human (FIH) study of venetoclax in patients with R/R NHL (Davids et al 2017). The analysis included 106 patients (of which 28 patients had MCL, however none had received ibrutinib or lenalidomide, and 5 patients had received prior bortezomib-based therapy). Venetoclax was administered once daily until progressive disease or unacceptable toxicity at target doses ranging from 200 to 1200 mg in the dose-escalation and safety expansion cohorts. The ORR in patients with MCL was 75% whereas the estimated median PFS for the MCL population was 14 months. Venetoclax was well tolerated. The analysis determined that target daily dose of 800 mg is sufficient to consistently achieve durable response in patients with MCL. A recent real-world data outlined the efficacy of venetoclax monotherapy in a cohort of patients (N = 20) with aggressive MCL in whom BTK inhibition had failed (Eyre et al 2019). An ORR of 53% (CR rate, 18%) is encouraging and compares favorably with that for other treatments in this setting. The median time to response (TTR) on venetoclax was 48 days (range: 14 to 204 days). The median PFS was 3.2 months (95% CI: 1.2-11.3 months) and the median OS was 9.4 months (95% CI: 1.5 months-not reached). The median DOR was 8.1 months (95% CI: 2.8 to

9.8 months) and the PFS was significantly improved in venetoclax responders (median PFS: 10.7 months; 95% CI: 3.7 to 12.3 months) compared to that in nonresponders (median PFS: 1.1 months; 95% CI: 0.8 to 2.6 months; $p = 0.002$). Venetoclax monotherapy was well tolerated with maximal daily dose up to 1200 mg.

1.4. Sonrotoclax

Sonrotoclax (also known as BGB-11417) is a highly potent and selective BCL2 protein inhibitor. In vitro studies revealed that sonrotoclax strongly inhibits activity of BCL2 and BCL2-G101V (a putative resistance mutation for venetoclax) in biochemical assays. It inhibited BCL2 protein activity at much lower concentrations compared to venetoclax in biochemical and cellular assays and demonstrated better selectivity for BCL2 compared with Bcl-xL and other anti-apoptotic BCL2 family members. Consistently, sonrotoclax demonstrated better antitumor activity than venetoclax in human acute lymphocytic leukemia (ALL), MCL, and diffuse large B-cell lymphoma (DLBCL) xenograft models. The Caco-2 permeability of sonrotoclax cannot be accurately measured due to its low recovery. Similar to venetoclax, sonrotoclax is classified as either BCS Class 2 or 4 based on its poor solubility. Sonrotoclax has a favorable pharmacokinetics (PK) profile with low apparent total clearance of drug from plasma after oral administration (CL/F) in rodents and dogs. Toxicology studies showed a broad safety window and a favorable safety profile. These unique characteristics warrant further evaluation of sonrotoclax in clinical studies in patients with B-cell malignancies.

1.4.1. Summary of Relevant Nonclinical Data With Sonrotoclax

1.4.1.1. Background and Pharmacology

Sonrotoclax potently inhibited BCL2 and BCL2-G101V proteins in biochemical assays, with IC_{50} of 0.014 nM and 0.59 nM, respectively. Sonrotoclax has been developed as a highly selective inhibitor of BCL2, showing 2.00×10^3 , 1.29×10^5 , $> 7.14 \times 10^5$, and $> 7.14 \times 10^5$ folds higher selectivity, as measured by the IC_{50} , compared to Bcl-xL, Bcl-W, Mcl-1, and Bcl2A1 proteins, respectively. Selectivity of sonrotoclax was profiled in a SafetyScreen87 panel (Eurofins Panlabs Discovery Services Taiwan, Ltd.) for 87 primary molecular targets including G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors, and other non-kinase enzymes. Sonrotoclax potently inhibited BCL2 and BCL2-G101V proteins in these biochemical assays, with IC_{50} s of 0.014 nM and 0.59 nM, respectively. Activity against other BCL2 mutants (ie, D103Y, F104I) is not yet known. The cellular assays further confirmed the growth inhibition effect of sonrotoclax in BCL2 dependent ALL cell line RS4;11, but not in the Bcl-xL-dependent T-ALL cell line Molt-4. The growth inhibition was associated with a series of hallmark events of intrinsic apoptosis, including caspase activation, the externalization of phosphatidylserine at the cell membrane, and sub-G0/G1 DNA accumulation. Sonrotoclax was also shown to promote apoptosis in a variety of hematological cancer cell lines.

In PK/pharmacodynamic studies, oral administration of sonrotoclax demonstrated a clear PK/pharmacodynamic relationship in RS4;11 ALL xenografts as evidenced by increasing induction of cleaved caspase 3 levels with increasing sonrotoclax tumor concentration. Sonrotoclax was more efficacious than venetoclax in human ALL, MCL, and DLBCL xenograft models.

Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion

Preclinical PK properties of sonrotoclax were studied in mice and dogs. The compound had a low to moderate plasma clearance and volume of distribution at steady state (V_{dss}) in both preclinical species tested with moderate absolute oral bioavailability. The terminal half-life ($t_{1/2}$) after oral administration was 2.13 to 4.52 hours in mice and 3.38 to 4.37 hours in dogs. Sonrotoclax was extremely highly bound to plasma proteins in all preclinical species with mean unbound percentages (%) of less than 0.1%.

Sonrotoclax was predominantly excreted through feces in mice and dogs, with less than 0.4% of unchanged sonrotoclax excreted in urine (BGB-11417 Investigator's Brochure).

Cytochrome P450 (CYP) 3A was the major CYP isoform responsible for sonrotoclax metabolism while CYP2C8 contributed to a lesser extent. However, sonrotoclax has reversible inhibitory potential on CYP2C8 and may be a time-dependent inhibitor of CYP3A4. Sonrotoclax was not an inducer for CYP1A2, CYP2B6, and CYP3A4. The reversible and time-dependent inhibitory effect of sonrotoclax may not have functional significance in the clinic since the free fraction in human plasma protein is less than 0.1%.

Sonrotoclax was identified to be a P-gp and BCRP substrate, and it has inhibitory potential on P-gp, BCRP, OATP1B1, and OATP1B3 in a concentration-dependent manner.

1.4.1.2. Toxicology

Studies in Mice

No mortality or apparent changes were noted in ICR mice following single oral doses up to 2000 mg/kg. Test article-related mortality was noted in one mouse at the dose of 1000 mg/kg/day following 7-day repeated doses in the 14-day repeated oral dose study. Distended abdomen, abnormal respiratory sounds, stomach dilation and cecum aerification were noted in this animal.

In the 28-day repeat oral dose study in mice, no mortality or toxicologically significant changes were noted at doses up to 300 mg/kg/day. Dose-independent decreases in white blood cells (WBCs) and lymphocytes at doses ≥ 20 mg/kg/day; minimal increases in alanine aminotransferase (ALT) and/or urea at doses ≥ 100 mg/kg/day; lymphoid depletion/erythropoiesis in multiple lymphoid organs; single cell necrosis in the intestine; and increased myeloid cells in the bone marrow at doses ≥ 20 mg/kg/day were noted at the end of dosing phase. All these changes were reversible. The no observed adverse effect level (NOAEL) was considered to be 300 mg/kg/day, where the systemic exposure (based on area under the plasma concentration-time curve [AUC]) was approximately 13 times the proposed exposure in humans at a dose of 160 mg/day.

In the 13-week repeat-dose study in mice with orally administered sonrotoclax at doses up to 300 mg/kg/day, mortality was noted in 1 male at the dose of 100 mg/kg/day that was most likely caused by an opportunistic infection secondary to lymphoid depletion. Toxicological findings were similar to the 28-day repeat-dose study in mice except for more severe immunomodulatory effects and histopathology changes in the thyroid glands (follicular degeneration), adrenal glands (cortical hypertrophy), and female reproductive organs (uterine atrophy, increased vaginal mucification, ovarian cysts, and abnormal or asynchronous estrus cycling). The immunomodulatory effects noted at the dose of ≥ 100 mg/kg/day and changes in female

reproductive organs at the dose ≥ 20 mg/kg/day were considered adverse. The NOAEL was considered to be 20 mg/kg/day excluding the reproductive toxicities in females, and the maximum tolerated dose (MTD) was considered to be 300 mg/kg/day.

Studies in Dogs

No mortality or apparent changes were noted in beagle dogs following single oral doses up to 450 mg/kg.

In the 28-day repeat oral dose study in dogs, no mortality or toxicologically significant changes were noted at doses up to 100 mg/kg/day. Dose-independent decreases in WBCs, lymphocytes and lymphocyte subpopulations (total T cells, helper T cells, cytotoxic T cells and B cells), and reticulocytes at doses ≥ 6 mg/kg/day; minimal increases in total bilirubin and alkaline phosphatase at the dose of 100 mg/kg/day; increased bile in the canaliculi and hepatocellular cytoplasm in the liver at doses ≥ 30 mg/kg/day; single cell necrosis in the pancreas and decreased lymphocytes or evidence of increased single cell necrosis/lymphocyte turnover at doses ≥ 6 mg/kg/day were noted at the end of dosing phase. All these changes were reversible. The NOAEL was considered to be 100 mg/kg/day, where the systemic exposure (AUC) was approximately 15 times the proposed exposure in humans at a dose of 160 mg/day.

In the 13-week repeat-dose study in dogs with orally administered sonrotoclax, no mortality was noted in any treated animals at doses up to 100 mg/kg/day. Toxicological findings in the 13-week repeat-dose study were similar to the 28-day repeat-dose study in dogs except for more severe findings in the liver and gallbladder, and new findings in the skin, fur, and male reproductive organs at all dose levels. Histopathology findings at doses ≥ 30 mg/kg/day in the liver and gallbladder characterized by pigment accumulation in Kupffer cells, were considered adverse. In the male reproductive tract, seminiferous tubule atrophy or degeneration, Leydig cell hypertrophy, hypospermia within the lumina, atrophy and epithelial vacuolation with single cell necrosis of the epididymides, and atrophy and/or glandular dilation of prostate were noted. Changes in the testes were considered adverse. In the skin, minimal increase in melanin granule size within melanocyte cell processes were noted. The NOAEL was considered to be 10 mg/kg/day excluding the reproductive toxicities, and the highest non-severely toxic dose was considered to be 100 mg/kg/day.

1.4.1.3. Safety Pharmacology

A weak or no inhibition on hERG (human ether-à-go-go-related gene) channel was noted with an inhibition rate of 14.26% at 10 μ M sonrotoclax. No sonrotoclax-related effects on cardiovascular function (blood pressure; heart rate; PR, QRS, and QT intervals; and qualitative electrocardiogram waveforms) were noted at single doses up to 100 mg/kg in telemetry-instrumented conscious beagle dogs for 24-hour continuous monitoring.

No apparent effects on the central nervous system were noted in ICR mice following a single oral dose up to 300 mg/kg sonrotoclax by a standard functional observational battery (FOB).

Moreover, no test article-related changes in electrocardiogram (ECG) or respiratory rate were noted in beagle dogs at repeated oral doses up to 100 mg/kg/day for 28 days of treatment.

1.4.2. Summary of Relevant Preclinical Experience With Sonrotoclax

1.4.2.1. Dose Selection

Based on one-tenth of the NOAEL in mice, and one-sixth of the NOAEL in dogs, the human starting dose could be as high as 144 mg/day (BGB-11417 Investigator's Brochure). Based on preliminary results from studies BGB-11417-101 and BGB-11417-102, a 160-mg dose appears to be well tolerated in NHL patients.

As shown in [Table 1](#), the systemic exposures (AUC) at NOAEL in dogs was approximately 15-fold that of the proposed exposure in humans at 160 mg/day. Therefore, the selected dose of 160 mg/day in patients with MCL is considered appropriate.

1.4.2.2. Interspecies Pharmacokinetics Prediction

Human CL/F was predicted using the Fu corrected-intercept-method ([Tang and Mayersohn 2005](#)). It is an empirical method using the CL/F in preclinical species as well as the rat and human plasma fraction unbound values to calculate human CL/F, and it has been shown to have good predictivity among various methods ([Ring et al 2011](#)). The predicted human CL/F of sonrotoclax is 2.7 mL/min/kg (0.16 L/h/kg). Human volume of distribution at steady state (V_{dss}) was predicted using the method developed by Oie and Tozer ([Oie and Tozer 1979](#)). This method takes the fraction unbound in plasma, the fraction unbound in tissue, plasma volume, extracellular fluid volume, and V_z/F in different animal species into consideration, and it has been demonstrated to give an accurate prediction ([Jones et al 2011](#)). The predicted human V_{dss} of sonrotoclax is 0.76 L/kg based on rat and dog data.

The predicted AUCs at the proposed doses of 160 and 320 mg for a 60 kg patient were calculated using the equation predicted AUC = targeted Dose x F/CL and data are shown in [Table 1](#). By comparison, maximum observed plasma concentration (C_{max}) and AUC from time 0 to 24 hours postdose (AUC_{0-24h}) at NOAEL were 6830 to 7480 ng/mL and 27,900 to 28,800 h ng/mL in mice (300 mg/kg/day) and 3780 to 5510 ng/mL and 31,600 to 41,300 h ng/mL in dogs (100 mg/kg/day) in the 1-month toxicity studies; all of which are much higher than the predicted AUC at the human starting dose. Based on the free drug exposures in nonclinical toxicity studies, dogs are more sensitive than mice. The safety margins for the recommended FIH doses are estimated from dog C_{max} and AUC_{0-24h} in plasma and listed in [Table 1](#). This ensures an adequate safety margin for the study. The mean observed daily AUC (1823 h ng/mL) at 160 mg/day in patients in the FIH Study BGB-11417-101 were similar with PK prediction, confirming the predicted safety margins are in good agreement with the observed PK in humans.

Table 1: Predicted AUC and Safety Margins for Oral Administration of Different Doses of Sonrotoclax in a 60-kg Patient

Dose (mg)	Predicted C_{max} (ng/mL)	Predicted AUC (h·ng/mL)	Safety margins (relative to C_{max})	Safety margins (relative AUC)
160	197	2167	19	15
320	393	4333	9.6	7.3

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum observed plasma concentration; CL/F, apparent total clearance of drug from plasma after oral administration.

Notes: Predicted CL/F = 0.16 L/h/kg, and Bioavailability = 13%. To be conservative, safety margins are based on the lower end of observed C_{max} (3780 ng/mL) and AUC_{0-24h} (31,600 h ng/mL) in male dogs.

1.4.3. Clinical Pharmacology

The FIH Study BGB-11417-101 and Study BGB-11417-102 are ongoing in patients with B-cell malignancies. The monotherapy PK of sonrotoclax is being studied in both. As of the cutoff date of 04 February 2023, preliminary PK data for sonrotoclax monotherapy from patients (n = 102) enrolled to studies BGB-11417-101 and BGB-11417-102 are available for noncompartmental analysis. The results showed that C_{max} and AUC appeared to increase in a dose-dependent manner after a single dose of 1 mg up to 160 mg as well as at steady state from 40 to 640 mg. The median time to maximum observed plasma concentration (t_{max}) is approximately 4 hours. In the noncompartmental analysis with PK data from single doses, the estimated terminal half-life of sonrotoclax is approximately 5 hours. Drug accumulation is expected to be minimal at steady state.

1.4.4. Relevant Clinical Summary from Lymphoma Patients

Detailed clinical data are available from patients with lymphoma exposed to sonrotoclax from 2 ongoing studies.

BGB-11417-101 is a global Phase 1, open-label, multicenter, dose-escalation and expansion study. Patients with NHL or CLL/small lymphocytic lymphoma (SLL) have been receiving sonrotoclax as monotherapy or in combination with zanubrutinib. BGB-11417-102 is a Phase 1, open-label, multicenter, dose-escalation study conducted in China to evaluate the safety, tolerability, PK, and preliminary antitumor activity of sonrotoclax in adult patients with mature B-cell malignancies.

1.4.4.1. Safety

A pooled analysis of monotherapy cohorts of Studies BGB-11417-101 and BGB-11417-102 was conducted to provide a comprehensive safety assessment separate from combination therapy. As of the cutoff date of 04 February 2023, 132 patients were enrolled into the 40- to 640-mg dose cohorts of sonrotoclax monotherapy in these 2 studies and were included in the Safety Analysis Set. Among them were 73 patients diagnosed with R/R NHL (non-MCL NHL), 7 patients diagnosed with R/R MCL, 14 patients diagnosed with R/R WM, and 38 patients diagnosed with CLL/SLL. Details on patient safety with sonrotoclax monotherapy are provided below for the most relevant disease types: NHL, MCL, and WM. Sonrotoclax was received at target dose

levels of 40 mg daily (3 patients), 80 mg daily (20 patients), 160 mg daily (18 patients), 320 mg daily (19 patients), and 640 mg daily (34 patients).

For patients with R/R NHL, 22 (30.1%) patients experienced ≥ 1 serious adverse event. The most commonly reported serious adverse events by preferred term (PT) were Pneumonia and Pyrexia (3 patients, 4.1% each). Six (8.2%) patients reported serious adverse events related to sonrotoclax.

For patients with R/R MCL, 2 (28.6%) patients experienced ≥ 1 serious adverse event. The serious adverse events (PTs) reported in 1 patient each included Cytomegalovirus infection reactivation, Pneumonia, Sepsis, Febrile neutropenia, Nausea, Vomiting, and Haematuria. Two (28.6%) patients reported serious adverse events related to sonrotoclax.

For patients with R/R WM, 2 serious adverse events were reported in 2 (14.3%) patients. The serious adverse events (PTs) reported in 1 patient each included COVID-19 pneumonia and Diverticulitis, and both were assessed as not related to sonrotoclax.

Of the patients with R/R NHL (73 patients), R/R MCL (7 patients), and R/R WM (14 patients) in the Safety Analysis Set, 1 patient with R/R NHL and 1 patient with R/R WM experienced treatment-emergent adverse events leading to treatment discontinuation that were not assessed as related to sonrotoclax. Five patients experienced a treatment-emergent adverse event leading to death that was not considered treatment-related: 3 patients with R/R NHL, 1 patient with R/R MCL, and 1 patient with R/R WM.

Dose-limiting toxicity (DLT) events were reported in 2 patients with R/R NHL in Study BGB-11417-102, including 1 patient in the 160 mg daily cohort (Grade 3 Bone pain) and 1 patient in the 80 mg daily cohort (Grade 3 Platelet count decreased). No action was taken with sonrotoclax as a result of both DLT events. The event of Platelet count decreased resolved, and the event of Bone pain remained unresolved. In Study BGB-11417-101, there were 2 DLT events of Grade 3 Fatigue and Grade 1 Peripheral sensory neuropathy in a patient with R/R MCL in the 80 mg monotherapy cohort. No action was taken with sonrotoclax as a result of both DLT events, which remained unresolved.

Details on the safety of patients who received sonrotoclax in combination therapy are provided in the BGB-11417 Investigator's Brochure.

1.4.4.2. Efficacy

1.4.4.2.1. Study BGB-11417-101

Study BGB-11417-101 is the FIH clinical study that evaluates the safety, PK, and efficacy of sonrotoclax as monotherapy and in combination with zanubrutinib. The efficacy endpoints of the study include ORR, DOR, TTR, and PFS as assessed by investigator, and OS.

The preliminary efficacy data for patients with lymphoma from Study BGB-11417-101 were presented at the 2022 annual meeting of the American Society of Hematology ([Soumerai et al 2022](#)). At the time of the poster data cutoff of 01 September 2022, 59 patients with NHL (including MCL and WM) had been enrolled.

In the NHL cohorts, 43 patients were treated with sonrotoclax monotherapy and 16 patients were treated with sonrotoclax in combination with zanubrutinib. In the R/R NHL cohorts (excluding

WM), 34 patients were treated at one of 5 dose levels (40 mg: n = 4, 80 mg: n = 7, 160 mg: n = 4, 320 mg: n = 9, and 640 mg: n = 11). A total of 7 patients remained on treatment and 27 patients discontinued due to disease progression (n = 27), adverse event (n = 1), or other (n = 2). There were 9 patients with R/R WM treated at one of 2 dose-levels (80 mg: n = 7, 160 mg: n = 4); 6 patients remained on treatment with 3 patients who discontinued due to disease progression (n = 2) or adverse event (n = 1). In the sonrotoclax combination with zanubrutinib, 16 patients, all with R/R MCL, were treated at one of 3 dose levels (80 mg: n = 6, 160 mg: n = 6, and 320 mg: n = 4); 13 patients remained on treatment and 3 patients discontinued due to progressive disease. In the R/R NHL cohort (without WM or MCL) of efficacy evaluable patients treated with monotherapy (n = 29), the ORR was 10% (CR: n = 1, partial response: n = 2), while in the efficacy evaluable R/R WM patients (n = 9), the ORR was 43% (partial response 43%). In the efficacy evaluable R/R MCL patients treated with sonrotoclax and zanubrutinib combination treatment (n = 9), the ORR was 78% (CR 67%, partial response 11%).

1.4.4.2.2. Study BGB-11417-102

BGB-11417-102 is a Phase 1 study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of sonrotoclax as a monotherapy in patients with B-cell malignancies (excluding MCL). The preliminary antitumor activity endpoints of the study include TTR, DOR, PFS as assessed by investigator, and OS. The preliminary efficacy data were presented at the 2022 annual meeting of American Society of Hematology (Li et al 2022). As of 11 August 2022, 48 patients had been administered with sonrotoclax, including 30 patients with R/R NHL and 18 patients with R/R CLL/SLL. Details on the efficacy of sonrotoclax monotherapy for the relevant indication of NHL are provided below.

Patients with R/R NHL had received sonrotoclax at ≤ 640 mg/d dose levels after a ramp-up period using a daily schedule. Patients had the following lymphoma types: DLBCL (16 patients), FL (7 patients), MZL (4 patients), and transformed B-cell (3 patients). The patients had a median age of 60 years, and 2 lines of prior systemic therapy (range: 1 to 7). A total of 20 out of the 30 patients with NHL discontinued the study treatment (14 due to progressive disease, 4 due to withdrawal of consent by patient, and 2 due to investigator decision). Of the 25 patients with NHL available for tumor assessment, 5 patients achieved partial response or CR: 3 patients in the 160 mg dose level, 1 patient in the 320 mg dose level, and 1 patient in the 640 mg dose level. Remission continued in 4 responders.

Details on the efficacy of sonrotoclax therapy in patients with other B-cell malignancies enrolled in Study BGB-11417-102 are provided in the BGB-11417 Investigator's Brochure.

1.5. Study Rationale

The effectiveness of BCL2 inhibition as a treatment option for patients with a variety of B-cell malignancies has been established, by approved treatments such as venetoclax. Sonrotoclax has demonstrated preclinical specificity and increased potency that could potentially lead to deeper responses in patients with MCL.

1.5.1. Rationale for Sonrotoclax Dose Finding

Preclinical data show that sonrotoclax has increased potency relative to venetoclax. Dose finding in patients with R/R MCL is warranted in order to find the optimum dose from the benefit-risk perspective.

The potency of BCL2 inhibitors results in a risk of tumor lysis syndrome (TLS) in MCL. A careful ramp-up dosing strategy is therefore required to safely reach the optimum dose.

1.5.2. Rationale for Dose Selection

[REDACTED]

1.5.3. Rationale for BGB-11417-201 Ramp-up Schedule

[REDACTED]

[REDACTED]

1.6. Benefit-Risk Assessment

As of data cutoff date of 04 February 2023, detailed safety clinical data were available from 118 lymphoma patients (including R/R MCL and other types of R/R NHL and R/R WM) exposed to sonrotoclax in either monotherapy or in combination with zanubrutinib from 2 other ongoing Phase 1 studies (BGB-11417-101 and BGB-11417-102). The preliminary results of these Phase 1 studies suggest that the sonrotoclax monotherapy is tolerable in patients with R/R NHL at doses up to the 640 mg level and using weekly or daily ramp-up schedules. DLTs have been rare and do not appear dose-dependent. The risk of TLS appears limited and manageable with few laboratory cases resolved with simple symptomatic measures and no clinical TLS cases to date. Transient neutropenia has been the most common $\geq$ Grade 3 treatment-emergent adverse event. Substantial decreases in ALC have been seen in patients with CLL during ramp-up, as well as objective responses in monotherapy in patients with R/R NHL indicating good potential of antitumor activity.

No BCL2 inhibitors have been approved for MCL at the time of this amendment. From clinical experience with existing drugs in this therapeutic class (BCL2 inhibitors) for the approved indications, the most common adverse reactions ($\geq 20\%$) of any grade were neutropenia/neutrophil count decreased, diarrhea, nausea, anemia, fatigue, and upper respiratory tract infection. The most frequently reported serious adverse reaction ($\geq 2\%$) unrelated to disease progression were pneumonia and febrile neutropenia ([Venclexta prescribing information 2021](#)). The main adverse reaction of note is TLS which, when present, usually occurs early during drug initiation. It is anticipated that patients may experience TLS, gastrointestinal tract upset, neutropenia, and infections while taking sonrotoclax. Patients enrolled in this study will be closely monitored for these and other potential adverse events.

Patients receiving BCL2 inhibitors as a monotherapy or in combination have shown clinical benefit in a wide range of disease types, including CLL/SLL ([Davids et al 2018](#); [Stilgenbauer et al 2018](#); [Kater et al 2019](#)), acute myeloid leukemia, multiple myeloma (MM), and NHL ([Zelenetz et al 2019](#)) in addition to MCL ([Tam et al 2018](#)) and WM ([Tam et al 2020](#)). Recent real-world data outlined the efficacy of venetoclax monotherapy in 20 patients with R/R MCL in whom BTK inhibition had failed ([Eyre et al 2019](#)). An ORR of 53% (CR rate: 18%) is encouraging and compares favorably with that of other treatments in this setting.

Based on the available safety and preliminary efficacy data for patients enrolled in Part 1 of this study, the benefit-risk assessment was consistent with that of the other more advanced studies described above.

Based on the preclinical pharmacology and preliminary clinical data of sonrotoclax, as well as the clinical safety and efficacy of venetoclax, the risk-benefit ratio of sonrotoclax treatment in R/R MCL post-BTK inhibitor is expected to be favorable.

1.7. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards and the applicable regulatory requirements (eg, Regulation [EU] No. 536/2014).

Approved Date 13.06.2024

2. STUDY OBJECTIVES

2.1. Study Objectives

2.1.1. Part 1: Dose Escalation and Safety Expansion

2.1.1.1. 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

2.1.1.2. 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.

2.1.1.3. 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

2.1.2. Part 2: Efficacy Expansion

2.1.2.1. Primary Objective

- To evaluate the efficacy of sonrotoclax monotherapy at the RP2D with recommended ramp-up schedule from Part 1 in patients with R/R MCL as measured by the ORR as determined by the Independent Review Committee in accordance with the Lugano classification.

2.1.2.2. 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
 - DOR determined by the Independent Review Committee and by the investigator
 - PFS determined by the Independent Review Committee and by the investigator
 - TTR determined by the Independent Review Committee and by the investigator
 - 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

2.1.2.3. 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.

2.2. Definition of Primary Estimand for 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 BTK inhibitor therapy and (2) had documented failure to achieve at least partial response 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 objective response, including CR and partial response, as determined by the Independent Review Committee, prior to disease progression.

4. Handling of intercurrent events:

New anticancer therapy started prior to disease progression: Patients starting any new anticancer therapy without achieving an objective response (including CR and partial response) before will be considered as non-responders (composite strategy).

Discontinuation of treatment and no new anticancer therapy started 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

3. STUDY DESIGN

3.1. Summary of Study Design

This single arm, open-label, multicenter Phase 1/2 study is designed to assess the RP2D, efficacy, safety, and PK of sonrotoclax in patients with R/R MCL. 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 ORR determined by the Independent Review Committee. Disease response will be assessed according to the Lugano classification. The primary analysis will be conducted at least 6 months after the last patient received the first dose. The study schema is provided in [Figure 1](#).

Screening evaluations will be performed within 28 days before the first administration of sonrotoclax.

The treatment period starts with the first day of sonrotoclax administration (ie, Ramp-up Week 1 Day 1) and continues until the last dose has been administered. Patients will receive sonrotoclax continuously until disease progression determined by the investigator (Part 1) or confirmed by the Independent Review Committee (Part 2), unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first.

All patients who permanently discontinue study drug will remain in the study and have a Safety Follow-up Visit. The Safety Follow-up Visit occurs approximately 30 days (± 7 days) after the last dose of sonrotoclax or before the initiation of a new anticancer therapy, whichever occurs first.

Patients who discontinue study drug due to reasons other than disease progression will remain on study entering the long-term follow-up stage and should be followed up according to the tumor assessment schedule until disease progression; initiation of a new anticancer therapy; patient withdrawal of consent, death, or is lost to follow-up; or until termination of the study by the sponsor, whichever occurs first.

Patients who discontinue study drug and have disease progression, or who initiate new anticancer therapy, will enter survival follow-up. During survival follow-up, patients will be contacted every 6 months by telephone to assess survival status and subsequent therapies for MCL, until withdrawal of consent, death, loss to follow-up, or until the study terminates, whichever occurs first.

3.1.1. Part 1: Dose Escalation and Safety Expansion

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

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. A minimum of 3 patients will be initially enrolled per dose level.

- If none of the first 3 evaluable patients enrolled at a given dose level experience a DLT, dose escalation may proceed.

- If 1 of the first 3 evaluable patients enrolled at a given dose level experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
- If less than one-third of the evaluable patients enrolled at a given dose level experiences a DLT (eg, DLTs in < 2 of 6 patients), escalation will proceed to the next higher dose level.
- If a DLT is observed in at least one-third of patients (eg, 2 or more in 6 patients or less), the MTD will have been exceeded and dose escalation will be stopped. Additional patients (for a minimum of 6 evaluable patients) will be assessed for DLTs at the preceding dose level (if a minimum of 6 evaluable patients had not already been assessed at that dose level).

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.

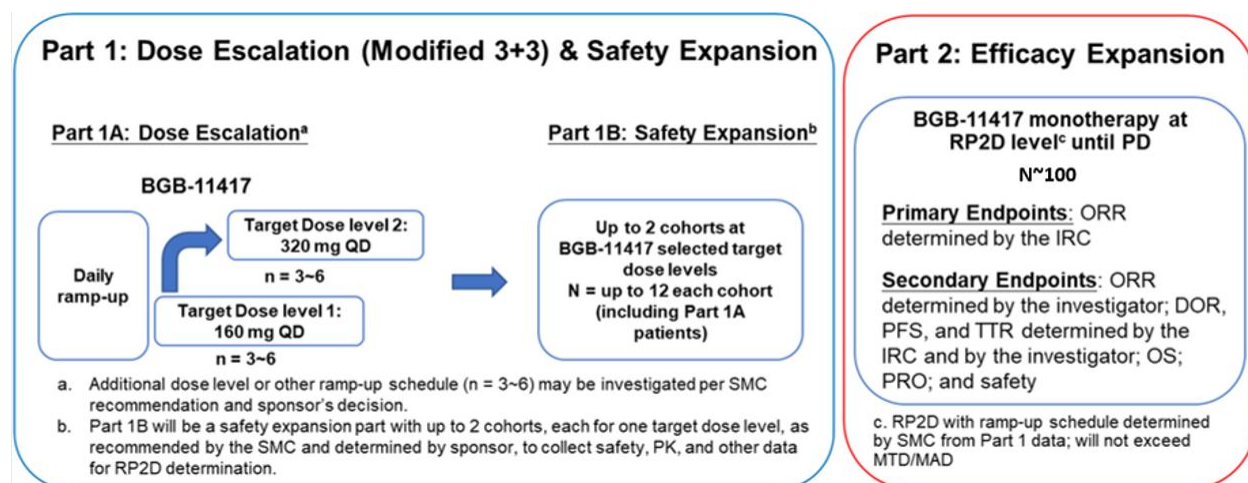
If the Safety Monitoring Committee recommends and the sponsor decides to explore additional dose levels or alternative ramp-up schedules, a substantial protocol modification will be submitted to health authorities and/or IRB/IEC, according to local requirements.

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

3.1.2. Part 2: Efficacy Expansion

Part 2 will be conducted as an open-label, single-arm, multicenter, expansion study. Sonrotoclax monotherapy will be administered at the RP2D and with recommended ramp-up schedule from Part 1 (Figure 1). Details of the ramp-up schedule for Part 2, which was recommended after Safety Monitoring Committee review of Part 1, are provided in Section 3.2.3.

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; PRO, patient-reported outcomes; 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.

A Safety Monitoring Committee consisting of study investigators and sponsor study members will review data from each dose level in each dose-escalation and safety-extension cohort (see Section 11.1). The Safety Monitoring Committee will assess the tolerability and safety of each dose level and its associated ramp-up schedule and advise on the opening of subsequent doses levels and new cohorts. When an MTD or MAD is established, the Safety Monitoring Committee will review the totality of data including safety, PK, and activity data to recommend an RP2D before Part 2 of the study will open. It is possible that after reviewing the totality of data for a given dose level, an RP2D may be selected before an MTD or MAD is reached. The Safety Monitoring Committee will also periodically review aggregated safety data from all patients and the criteria for interruption of patient enrollment in the study as specified in Section 10.6.2.

3.2. Study Treatment

3.2.1. Medicinal Product Approval Status

Sonrotoclax is the only investigational medicinal product (IMP) that will be used in this study and has not yet been approved for the treatment of MCL in any country. No auxiliary medicinal products as defined by Article 2(8) of Regulation (EU) 536/2014 will be used in this study.

3.2.2. Part 1: Dose Escalation and Safety Expansion

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, or another target dose level, or with a different ramp-up schedule per the Safety Monitoring Committee recommendation and sponsor's decision.

Part 1B will be a safety expansion phase with up to 2 cohorts, each consisting of additional patients, for one target dose level, as recommended by the Safety Monitoring Committee and determined by the sponsor. Part 1B will collect more safety, PK, and other data, together with the

Part 1A data, as well as the available data from Studies BGB-11417-101 and BGB-11417-102 as references, for the determination of RP2D.

Once an RP2D and the ramp-up schedule are established, Part 2 will open to further explore its efficacy.

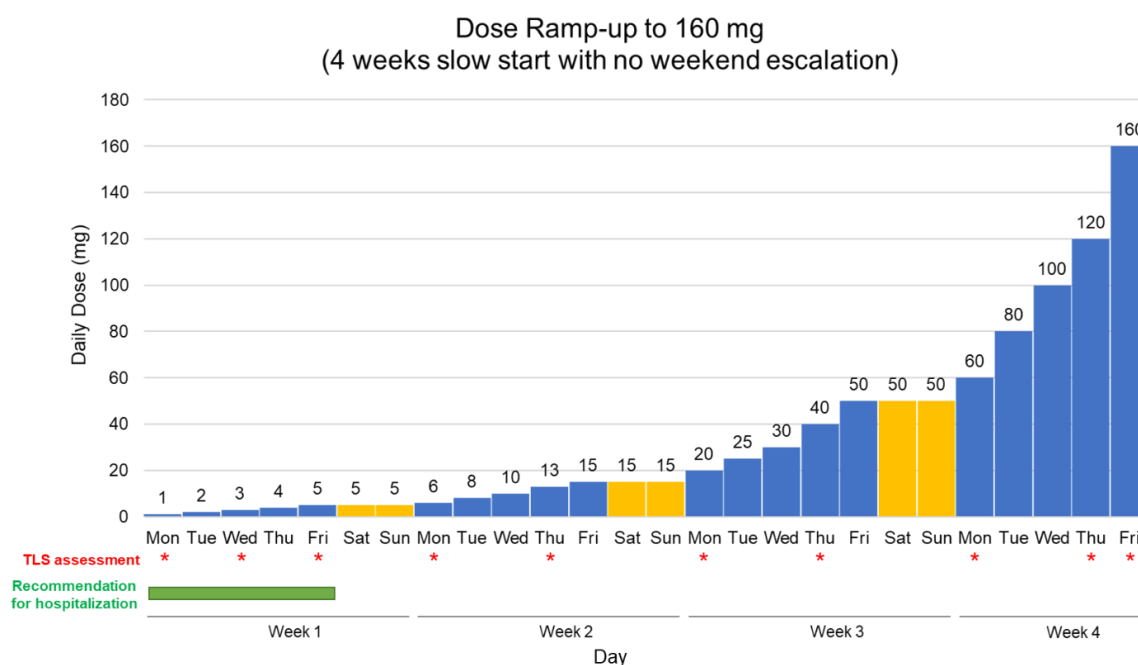
3.2.2.1. Ramp-up Schedules for Part 1

Patients treated with BCL2 inhibitors can face an increased risk of TLS, influenced both by the patient's disease type and the patient's individual risk of TLS based on tumor burden and renal function. In MCL, an increased risk of TLS is expected because of the high level of activity of BCL2 inhibitors. To mitigate this risk, patients will utilize dose ramp-up.

In Part 1 of this study a daily ramp-up schedule will be used, whereby the dose may be increased in small amounts each day until the target dose is reached. The daily ramp-up schedule to target dose 160 mg and 320 mg is presented in [Figure 2](#) and [Figure 3](#), respectively. The number of days of dosing ramp-up will vary depending on the target dose (see [Appendix 4](#) for the details).

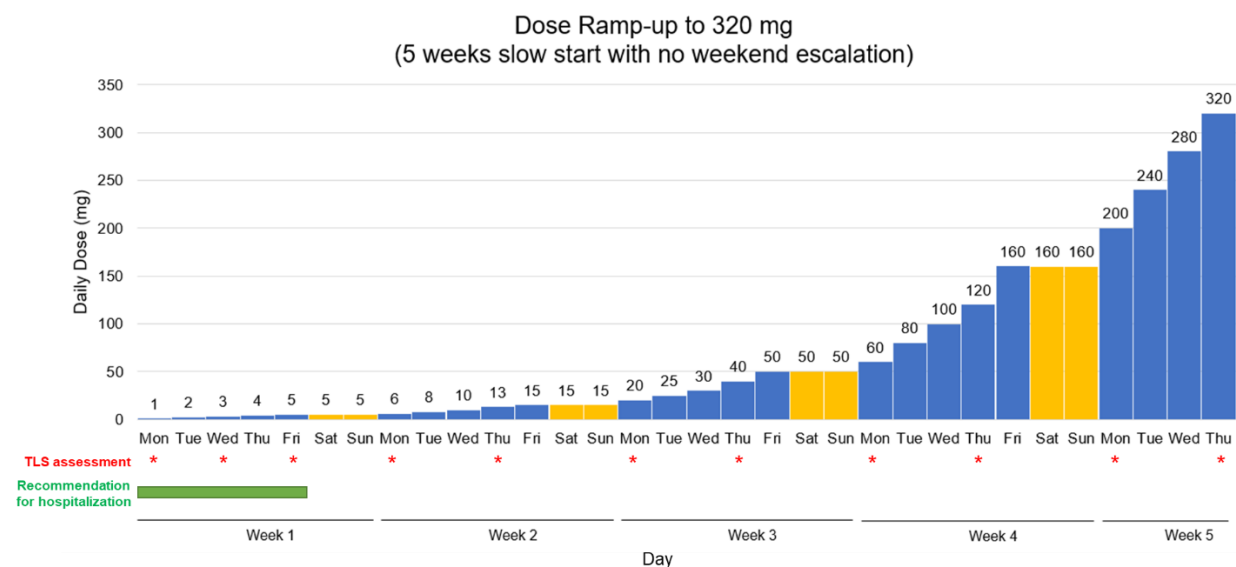
In reviewing the ramp-up schedule, the Safety Monitoring Committee will assess clinical data, including TLS-relevant laboratory data and occurrence of TLS events.

Figure 2: Daily Ramp-up Schedule for 160-mg Target Dose



Abbreviation: TLS, tumor lysis syndrome.

Figure 3: Daily Ramp-up Schedule for 320-mg Target Dose



Abbreviation: TLS, tumor lysis syndrome.

3.2.2.2. Dose-Limiting Toxicities

DLTs will consist of the following events without a clear alternative cause other than study drug and will be assessed and graded per the guidelines in Section 9.1.2. For patients meeting inclusion/exclusion criteria but also exhibiting any of the below DLT-qualifying events at baseline: the toxicity must worsen by at least one grade during the DLT window to be considered a DLT. Refer to Section 7.4.1 for the details of dose interruption, modification, and discontinuation of sonrotoclax in patients who experience DLTs.

Hematologic Toxicity

- Grade ≥ 3 febrile neutropenia
- Grade ≥ 3 thrombocytopenia lasting > 7 days or resulting in clinically significant bleeding (ie, Grade ≥ 3 bleeding event or central nervous system bleeding of any grade)
- Any Grade ≥ 4 hematological toxicity, with the following exceptions:
 - Grade 4 neutropenia lasting ≤ 7 days with or without treatment
 - Grade 4 lymphopenia
 - Grade 4 leukopenia

Nonhematologic Toxicity

- Any Grade ≥ 3 nonhematologic toxicity with the following exceptions:
 - Laboratory TLS as defined by the Howard criteria (Howard et al 2011, Howard et al 2018) that resolves ($\leq$ Grade 1 or baseline) in ≤ 3 days. Laboratory TLS will be considered in determination of the ramp-up dose and the schedule and will be

included in the overall dose-finding decisions by the Safety Monitoring Committee but will not be considered a DLT.

Note: Clinical TLS as defined by the Howard criteria is considered a DLT.

- Individual TLS-related laboratory adverse events (ie, hyperuricemia, hyperphosphatemia, hyperkalemia, and/or hypocalcemia) that resolve ($\leq$ Grade 1 or baseline) in ≤ 3 days with or without treatment
- Grade 3 gastrointestinal toxicity (ie, nausea, vomiting, diarrhea) that resolves to $\leq$ Grade 2 following therapeutic intervention in ≤ 7 days
- Asymptomatic biochemical laboratory abnormalities that resolve ($\leq$ Grade 1 or baseline) in ≤ 7 days with or without supportive care (eg, electrolyte abnormalities responsive to supplementation)

3.2.2.3. Dose-Limiting Toxicity Window

The DLT window will include all dose ramp-up treatment days as well as 21 days of sonrotoclast at the target dose.

For the patient to have completed the DLT window they should have received $\geq 80\%$ of the intended dose during the ramp-up period and $\geq 80\%$ of the intended dose during the target dose period of the applicable DLT window or have experienced a DLT. If a patient does not reach this threshold before the DLT window ends for reasons other than a DLT, the patient will be considered not evaluable for DLT purposes and will be replaced.

3.2.2.4. Ramp-up Schedule Evaluation

Assessment of a ramp-up schedule can be conducted when all patients at that target dose level complete all ramp-up steps and are at the target dose for ≥ 7 days; and could be conducted simultaneously with DLT evaluation at Safety Monitoring Committee meeting. To evaluate the tolerability of the ramp-up schedule, the Safety Monitoring Committee will review the following data on all patients treated with ≥ 1 ramp-up dose:

- Clinical TLS events (Section 7.5)
- Laboratory TLS events (Section 7.5)
- Available PK data
- TLS-relevant clinical chemistry laboratory data, including:
 - Phosphorus
 - Potassium
 - Uric acid
 - Calcium
 - Serum Creatinine
- Hematology data
- Any other available relevant data that may further provide context to the above

After reviewing the above data, the Safety Monitoring Committee may recommend enrolling additional patients or modification of the ramp-up schedule (eg, removal or addition of ramp-up doses).

In addition to optimizing the ramp-up schedule, the schedule of TLS laboratory monitoring and required hospitalizations may also be optimized and modified.

3.2.2.5. Choosing the Maximum Tolerated Dose or Maximum Administered Dose

The MTD is defined as the highest dose at which < 33% of the patients had experienced at least one DLT. If all evaluated dose levels demonstrate an observed incidence of DLT in < 33% of patients, the MTD has not been reached, and the highest dose level evaluated will be considered as MAD.

3.2.2.6. Choosing a Recommended Phase 2 Dose

The RP2D is the dose ultimately chosen for Part 2. This dose will not be higher than the MTD or MAD but may be lower. The Safety Monitoring Committee reviewed all available applicable PK, safety, and preliminary antitumor activity data at the cut-off date of 11 May 2023, and recommended the 320 mg dose as the RP2D of sonrotoclax; the sponsor agreed with this recommendation.

3.2.2.7. Inpatient Dose Escalation

Patients on the lower dose level (ie, 160 mg dose) who have a suboptimal response, as determined by the investigator following disease assessment, may be allowed to increase their dose to a higher dose level (ie, 320 mg dose) that has subsequently been declared tolerable. Dose escalation prior to identifying the RP2D requires approval from the medical monitor. These patients will be required to follow appropriate ramp-up steps to reach the new dose level, including any necessary prophylaxis and monitoring, using a plan that is approved by the medical monitor. Once the RP2D is identified, patients on lower levels may increase to the RP2D at the investigator's discretion using a plan approved by the Safety Monitoring Committee.

Any significant safety events occurring in these patients (eg, TLS events or events that would meet the definition of a DLT) will be reviewed by the Safety Monitoring Committee and incorporated into decision-making about the safety of target doses and ramp-up schedules.

3.2.3. Part 2: Efficacy Expansion

Following establishment of a safe ramp-up schedule and RP2D in Part 1, the efficacy expansion part will be opened to further evaluate the efficacy of sonrotoclax.

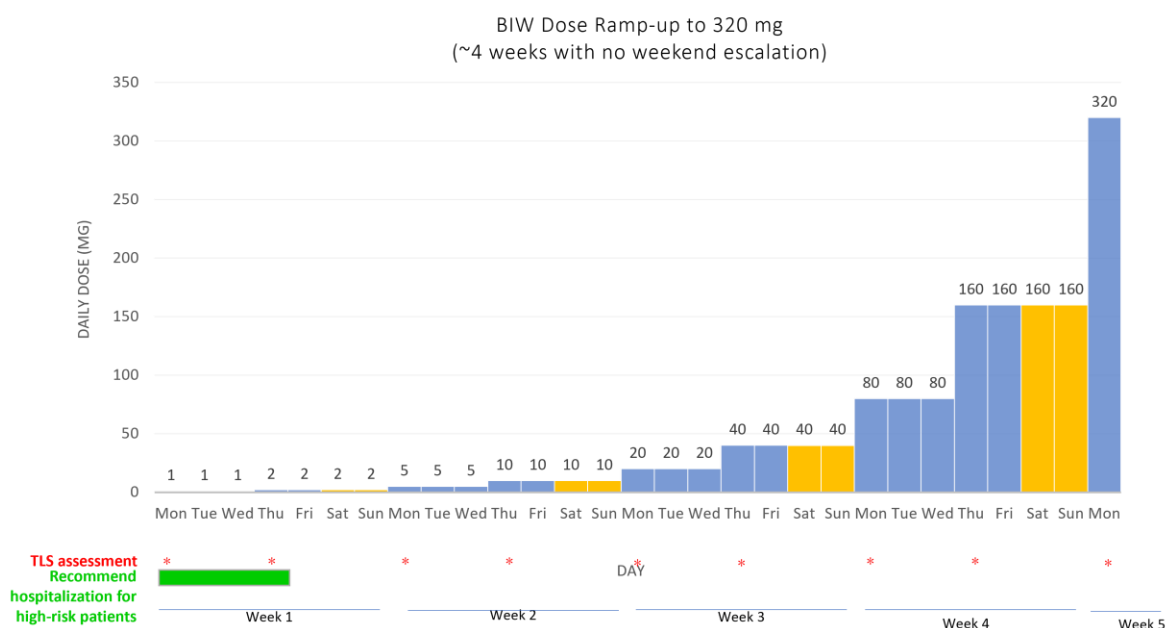
Based on data from Part 1, the RP2D of sonrotoclax monotherapy was determined to be 320 mg. The Safety Monitoring Committee also assessed the daily ramp-up schedule as safe and agreed to further simplify it for patients through the BIW dose ramp-up schedule presented in [Figure 4](#), whereby the treatment dose per day is doubled BIW, with TLS monitoring on those days when the dose is increased. Patients who have consented to Protocol Amendment 2.0 or above before their first dose of study drug will follow the BIW ramp-up dosing schedule ([Figure 4](#)). All other patients in Part 2 will follow the daily ramp-up dosing schedule ([Figure 3](#)).

The Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits may be removed in the future, as recommended by the Safety Monitoring Committee and based on the review of safety data of the first approximately 15 patients dosed with the BIW ramp-up schedule. The Safety Monitoring Committee will review that the following observations are met:

- No more than one patient with a laboratory TLS treatment-emergent adverse event
- No clinical TLS treatment-emergent adverse event
- No serious TLS treatment-emergent adverse event

In the event the Safety Monitoring Committee recommends that the Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits can be omitted, patients subsequently reaching these weeks in their ramp-up schedule will attend monitoring visits according to the reduced schedule as outlined in [Appendix 4](#), unless the investigator evaluates a persistent TLS risk.

Figure 4: Twice-a-week Dose Ramp-up Schedule for 320 mg Target Dose



Abbreviations: BIW, twice-a-week; TLS, tumor lysis syndrome.

3.3. Duration of Study

The total duration of this study is expected to be approximately 5 years, assuming an expected enrollment duration of approximately 2 years. The sponsor has the right to terminate this study at any time.

At the time this study ends, patients who will continue to benefit from study treatment in the opinion of the investigator may have access to a long-term extension study.

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient must meet all the following inclusion criteria to be considered eligible for participation in this study:

1. Provision of signed and dated written informed consent prior to any study-specific procedures, sampling, or analyses.
2. Age 18 years or older.
3. Histologically local lab confirmed diagnosis of MCL based on the World Health Organization (WHO) 2016 classification of tumors of hematopoietic and lymphoid tissue (Swerdlow et al 2016), including demonstration of positive cyclin D1 and/or t(11;14).
4. Patients should have received
 - i. at least one line of appropriate anti-CD20 based immune or chemoimmunotherapy (eg, R-CHOP will be considered as appropriate for young patients who could tolerate intensive therapy, and BR or rituximab combined with BTK inhibitor will be considered as appropriate for older patients or patients with comorbidities precluding intensive therapy and ASCT)
 - ii. and at least one kind of covalent or non-covalent adequate BTK inhibitor therapy (as monotherapy or in combination with other anticancer agents).
5. Documented failure to achieve at least partial response or documented disease progression on or after the last line of treatment, or the last line therapy need to be discontinued due to toxicity/tolerability despite dose justification and optimal supportive care. Refer to Appendix 10 for the definition of treatment intolerance.
6. Presence of measurable disease, defined as ≥ 1 nodal lesion that is > 1.5 cm in longest diameter, or ≥ 1 extranodal lesion that is > 1 cm in longest diameter.
7. Availability of archival tissue confirming diagnosis of MCL, or willing to undergo fresh tumor biopsy.
8. ECOG performance status of 0 to 2.
9. Adequate organ function defined as:
 - a. Absolute neutrophil count (ANC) $\geq 1000/\text{mm}^3$ (or $\geq 750/\text{mm}^3$ for patients with bone marrow involvement of lymphoma) within 7 days before the first study dose (without growth factor support)
 - b. Platelets $\geq 75,000/\text{mm}^3$ (or $\geq 50,000/\text{mm}^3$ for patients with bone marrow involvement of lymphoma) within 7 days before the first study dose (without growth factor support or transfusion)
 - c. Creatinine clearance ≥ 50 mL/min as estimated by either the Cockcroft-Gault or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations or via 24-hour urine collection

- d. AST/serum glutamic oxaloacetic transaminase, and ALT/serum glutamic pyruvic transaminase $\leq 3.0 \times$ upper limit of normal (ULN)
 - e. Serum total bilirubin $\leq 2 \times$ ULN (for patients in the United States: $\leq 1.5 \times$ ULN) (unless documented Gilbert's syndrome)
10. Women of childbearing potential must have a negative serum pregnancy test ≤ 7 days before the first dose of study drug and must be reconfirmed negative by urine or serum pregnancy test on the date of first dose prior to dosing. Female patients of childbearing potential must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of sonrotoclax.
 11. Male patients are eligible if abstinent, vasectomized, or if they agree to the use of barrier contraception in combination with other methods described in [Appendix 14](#) during the study treatment period and for ≥ 90 days after the last dose of sonrotoclax.
 12. Ability to provide written informed consent and ability to understand and comply with the requirements of the study.
 13. For France only: Patients must be registered with the French social security ("affiliation à la Sécurité Sociale").

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study:

1. Known central nervous system involvement by lymphoma.
2. Prior malignancy other than MCL within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer.
3. Prior exposure to a BCL2 inhibitor (eg, venetoclax/ABT-199).
4. Prior ASCT within the last 3 months; or prior autologous chimeric antigen receptor-T cell therapy within the last 3 months; or prior allogeneic stem cell transplant within the last 6 months or currently has an active graft-vs-host disease requiring the use of immunosuppressants.
5. Receipt of the following treatment at the time indicated before the first dose of study drug:
 - a. Corticosteroid given with antineoplastic intent, but a short course (≤ 7 days) of systemic corticosteroid treatment for control of lymphoma related symptoms or BTK inhibitor withdraw flare is allowed prior to the first dose of study drug provided it is tapered off within 5 days after initiation of study treatment.
 - b. Any biologic and/or immunologic-based therapy(ies) including experimental therapy(ies) for lymphoma within 2 weeks prior to the first dose of study drug.
 - c. Systemic chemotherapy or radiation therapy within 1 week prior to the first dose of study drug.
6. Ongoing Grade ≥ 2 toxicity from prior anticancer therapy (except for alopecia, ANC, and platelets. For ANC and platelets, please follow inclusion criterion #9).

7. Clinically significant cardiovascular disease including the following:
 - a. Myocardial infarction within 6 months before screening
 - b. Unstable angina within 3 months before screening
 - c. New York Heart Association class III or IV congestive heart failure
 - d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
 - e. QT interval corrected based on Fridericia's formula (QTcF) > 480 msec (for patients in the United States: ≥ 470 msec)
 - f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
 - g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening
8. Known infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
 - a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU/mL), and if they are willing to undergo monitoring for HBV reactivation.
 - b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (< 15 IU/mL), and if they are willing to undergo monitoring for HCV reactivation.
9. Active fungal, bacterial and/or viral infection requiring systemic therapy.
10. Unable to swallow tablets or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
11. Receiving any treatment with a moderate CYP3A4 inhibitor or strong CYP3A4 inhibitor or inducer within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of sonrotoclax, or requiring long-term use of strong CYP3A4 inhibitors or inducers.
12. Major surgery within 4 weeks of the first dose of study drug.
13. Vaccination with a live vaccine within 4 weeks prior to the first dose of study drug.

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. A non-live coronavirus disease 2019 (COVID-19) vaccine may be administered if recommended per local practice.
14. Pregnant or lactating women.
15. History of hypersensitivity to excipient(s) of the sonrotoclax tablet.
16. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results.

5. STUDY ORGANIZATION

The structure and organization of the study are summarized below.

5.1. Study Visit Schedule

Scheduled study visits are outlined in the Schedule of Assessments ([Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)). The study visit schedule is relative to the first dose of study drug (ie, Ramp-up Week 1 Day 1). Subsequent visits should maintain this schedule regardless of any drug holds. Acceptable windows around these visits are indicated in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). Study drug supply (Section 7.1.2) and dispensation (Section 7.1.4) must be considered when scheduling study visits. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2. Screening and Enrollment

After signing the consent form, a patient may delay the first screening procedure for up to 14 days. After the first screening procedure, all other screening procedures must be performed within 28 days of the first administration of study drug. The site investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

Repeating screening procedures or tests are allowed once if the patient did not previously meet the inclusion and exclusion criteria or if the patient needed to have a documented result within the protocol-specified screening window.

Patients who have screen failed may rescreen after approval from the medical monitor.

Computed tomography (CT) scans, positron emission tomography (PET)-CT scans, and bone marrow aspirate/biopsy completed as part of the standard of care after the discontinuation of last line anti-MCL therapy and ≤ 42 days before the first dose may be used for screening if they fulfil all the protocol requirements.

5.3. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include, but are not limited to, vital signs/focused physical examination, ECOG performance status, adverse event review, concomitant medications and procedures review, radiological assessments, and hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the investigator's assessment as appropriate, and the results of these tests should be entered on the unscheduled visit electronic case report form (eCRF).

5.4. Treatment Period

The treatment period starts with the first day of sonrotoclax administration and continues until the last dose has been administered.

5.4.1. End of Treatment

Patients must permanently discontinue study drug(s) for any one of the following reasons:

- Disease progression, determined by the investigator in Part 1 or confirmed by the Independent Review Committee in Part 2 (see [Appendix 8](#))
 - Patients who may continue to benefit from study drug after disease progression may remain in the study upon the investigator's discussion with the medical monitor or designee. Patients that remain in the study will continue to follow the required assessments during the treatment phase.
- Adverse event(s) requiring permanent treatment discontinuation as defined in Section [7.4.1](#).
- Any study drug interruption lasting > 28 days for any reason (exceptions may be possible after discussion with the medical monitor)
- Start of alternative anticancer therapy to treat MCL, or start of therapy for secondary malignancy that would interfere with assessment of safety and efficacy of study treatment
- A positive pregnancy test
- Patient withdraws consent. Patients may voluntarily withdraw consent from treatment at any time. Withdrawal of consent to the study drug does not require discontinuation from the study: even with treatment discontinued, a patient may remain on study to continually gather survival information.
- Investigator decision
- Lost to follow-up
- Other (must specify)

5.5. Post-treatment Period

After the permanent discontinuation of study drug, patients will then enter the post-treatment period.

5.5.1. Safety Follow-up Visit

All patients who permanently discontinue study drug will have a Safety Follow-up Visit approximately 30 days after the last dose of study drug or before the initiation of a new anticancer therapy, whichever occurs first. This visit will include the collection of adverse events and serious adverse events that may have occurred after the patient was permanently discontinued from study drug. For the follow-up of adverse events and serious adverse events, see Section [9.1.2.2](#). Refer to the Schedule of Assessments ([Appendix 1](#)) for the assessments to be performed at the Safety Follow-up Visit.

5.5.2. Long-term Follow-up

Patients who permanently discontinue study drug for reasons other than disease progression (eg, toxicity) or death will continue to undergo Long-term Follow-up tumor assessments

according to Section 6.8 and the Schedule of Assessments (Appendix 1), until the patient experiences disease progression, starts a new anticancer therapy, withdraws consent, is lost to follow-up, dies, or until the study is terminated, whichever occurs first.

If a patient had already transitioned to tumor assessments interval of every 24 weeks or yearly when the treatment was discontinued, the response assessment may continue to follow the same visit frequency in Long-term Follow-Up until the documented disease progression.

If the patient refuses to return for these visits or is unable to do so, every effort should be made to contact them or the patient's guardian by telephone to determine the patient's disease status and survival.

5.5.3. Survival Follow-up

Patients who discontinue study drug and have progressed, or initiate a new anticancer therapy, will enter survival follow-up. During survival follow-up, patients will be contacted every 6 months by telephone to assess survival status and subsequent therapies for MCL until withdrawal of consent, death, loss to follow-up, or until the study is terminated, whichever occurs first.

5.6. End of Study for an Individual Patient

Reasons for complete withdrawal from the study (including treatment and all follow-up visits) will be the following circumstances:

- Patient withdraws consent
- Death
- Study termination by sponsor
- Lost to follow-up
- Other (must specify)

Patients may voluntarily withdraw consent from the study at any time.

5.7. Lost to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow-up during the study to complete study-related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up.

5.8. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, or is lost to follow up.

Alternatively, if the sponsor decides to terminate the study, the end of study is after completion of the last patient's last visit.

Approved Date 13.06.2024

6. STUDY ASSESSMENTS AND PROCEDURES

Assessments and procedures required during the study are detailed below. Please refer to [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) for the timing of these assessments and procedures.

6.1. Informed Consent

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the Informed Consent Form (ICF) will be given to the patient to read, and the patient must have adequate time to understand and ask questions.

Study site personnel must obtain a signed informed consent before any study-specific procedures are conducted unless the procedures are part of the routine standard of care and must document the informed consent process in the patient's clinical record. Informed consent may be obtained up to 14 days before the 28-day screening period, the screening window will start with the first protocol-required screening procedure. Consent must be obtained using the most current version of the form approved by the IRB/IEC.

Screening procedures or tests may be repeated if certain eligibility criteria were not met or if a test had to be performed within the protocol-specified screening window.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before enrollment, study site personnel should document the screen failure in the patient's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

6.2. Confirmation of Eligibility

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

6.3. Medical and Cancer History

Review any medical and cancer history any time after obtaining informed consent during screening. Clinically significant medical history findings (ie, previous diagnoses, diseases, or surgeries) not pertaining to the study indication, started before signing the informed consent, and being considered relevant for the patient's study eligibility will be collected and captured in the eCRF. "Clinically significant" is defined as any events, diagnoses or laboratory values requiring treatment, follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Other background information is to be collected including staging and sites of disease (including bone marrow involvement). Prior medications/significant non-drug therapies will also be collected.

Other baseline characteristic information will be collected as relevant to the patient's disease, including but not limited to components of the respective clinical prognostic indices for MCL (MIPI and Percentage of Ki-67 positive cells).

The MIPI will be calculated based on the baseline values of age, ECOG performance status, LDH as quotient to the ULN, and the WBC count per 10^6 L ([Hoster et al 2008](#); [Hoster et al 2014](#)).

MIPI score will be calculated according to the following formula:

MIPI score = $0.03535 \times \text{age (years)} + 0.6978$ (if ECOG performance status > 1, otherwise 0) + $1.367 \times \log_{10}(\text{LDH/ULN}) + 0.9393 \times \log_{10}(\text{WBC count per } 10^6\text{L})$

Percentage of Ki-67 positive cells should be collected wherever possible, based on central pathology report. When available, MIPI-b score will also be calculated for purposes of descriptive prognostic features ([Hoster et al 2008](#)).

MIPI-b formula = $0.03535 \times \text{age (years)} + 0.6978$ (if ECOG performance status > 1, otherwise 0) + $1.367 \times \log_{10}(\text{LDH/ULN}) + 0.9393 \times \log_{10}(\text{WBC count per } 10^6\text{L}) + 0.02142 \times \text{Ki-67 (\%)}$

Information will also be collected regarding childbearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (eg, physical examination, vital signs, ECOG performance status, hematology and blood chemistry, urinalysis, pregnancy test, echocardiogram or multiple gated acquisition [MUGA] scan, and ECG). For further details on eligibility assessments, see [Appendix 1](#).

6.4. Demographic Data

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the European Medicine Agency (EMA) and US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

6.5. Study Drug Dispensation

Sonrotoclax will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. Instructions are to be provided for dosing, storage, and the return of all bottles (used and unused) at future visits.

6.6. Pharmacokinetics

Blood will be collected to characterize the PK of sonrotoclax (and possible major metabolites). See [Appendix 2](#) and [Appendix 3](#) for sampling schedules.

The time of sonrotoclax administration on all days with PK collection must be recorded in the eCRF (including the administration prior to predose PK collection and any other situations where dosing occurred outside the clinic). On the days with PK collection, administration of study drug must occur under the supervision of the investigator (or designee) after the predose PK sample is obtained. PK samples will only be collected from sites that are able to adequately follow the sampling, handling, and processing procedures outlined in the Laboratory Manual.

For each sample, the actual time of collection will be captured to the nearest minute in the eCRF and recorded in the database.

Details concerning handling of the PK plasma samples, including labeling and shipping instructions, will be provided in the Laboratory Manual for this study. Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma concentration of sonrotoclax (and possible major metabolites) using a validated method.

6.7. Safety Assessments

Safety assessments are to be done at timepoints indicated in [Appendix 1](#). For patients in Part 2 after Protocol Amendment 2.0 is implemented, Week 2 Day 1 and Week 3 Day 1 visits will not be performed.

6.7.1. Cardiac Function

An assessment of left ventricular ejection fraction will be performed at screening and documented per [Appendix 1](#), and may be performed at other visits as medically indicated. Note: An echocardiogram, MUGA scan, or a gated heart pool scan (GHPS) are all acceptable.

6.7.2. Physical Examination and Vital Signs

Physical examination includes an assessment of body systems according to the standard of care at the study site and as clinically indicated by symptoms at timepoints indicated in [Appendix 1](#). Progressive disease assessed by physical examination (eg, lymphadenopathy) must be confirmed radiologically, either by a CT or PET-CT scan.

Targeted physical examination for response assessment is described in Section [6.8.2](#).

Height (cm) is determined at screening only. Weight will be monitored as indicated in [Appendix 1](#).

Vital signs include sitting blood pressure, heart or pulse rate, and body temperature. Vital signs will be monitored as indicated in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#).

6.7.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed as indicated in [Appendix 1](#). [Appendix 7](#) will be used to assess performance status.

6.7.4. Electrocardiogram

All ECG recordings will be performed using a standard, high-quality, high-fidelity digital electrocardiograph. To minimize postural variability, ECG recordings must be performed after the patient has been resting in a supine position for ≥ 5 minutes. When coinciding with blood draws and other procedures (eg, vital sign measurements) at the same timepoint, ECG assessment should be performed before these procedures. Circumstances that may induce changes in heart rate, including environmental distractions (eg, television, radio, etc) should be avoided as much as possible.

For safety monitoring purposes, the investigator should review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Perform ECG at screening (locally) and at the Safety Follow-up Visit (locally). During the treatment period, perform as clinically indicated (see [Appendix 1](#)). At screening and at the Safety Follow-up Visit, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval.

6.7.5. Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within the screening window. Concomitant medications should be collected as indicated in [Appendix 1](#). NOTE: during the survival follow-up phase, only information on new anticancer therapy will be collected.

6.7.6. Adverse Events Review

Record adverse events that occurred during screening in the medical history case report form and in the patient's source document. The adverse event reporting period is defined in Section [9.4.1](#). Serious adverse events that occur from the time of signing of informed consent will be reported to the sponsor as per Section [9.4.1](#).

All adverse events and serious adverse events will be followed according to guidance in Section [9.1.2.2](#). The accepted regulatory definition for an adverse event is provided in Section [9.1](#). Important additional requirements for reporting serious adverse events are explained in Section [9](#).

6.8. Efficacy Assessments

Procedures and assessments related to the assessment of efficacy of study drug are detailed below and are to be done at timepoints indicated in [Appendix 1](#). For patients in Part 2 after Protocol Amendment 2.0 is implemented, Week 2 Day 1 and Week 3 Day 1 visits will not be performed.

6.8.1. Response Assessment

Assessments of MCL status during the study will include disease-related symptoms; targeted physical examination of lymph nodes, liver, spleen, and skin; bone marrow examination (only in case of CR and with bone marrow involvement at baseline); PET-CT and CT scan with contrast of chest, abdomen, pelvis, and neck if clinically indicated; endoscopy if clinically indicated; and PROs. “Clinically indicated” should be interpreted as follows: the corresponding procedure is required if there is a presence or suspicion of an affection of the body region by the disease (eg, a finding from targeted physical examination or on another previously performed procedure of an [¹⁸F]fluorodeoxyglucose [FDG]-avid focus detected in that particular region). If a CT scan of the neck was performed at baseline and showed evidence of the disease, a CT scan of the neck will be required at post-baseline assessments. Response assessments should be performed at 8 weeks (study day 56 ± 7 days) and 16 weeks (study day 112 ± 7 days) after the first dose of study drug (ie, Ramp-up Week 1 Day 1), then every 12 weeks up to one year, then every 24 weeks for 2 years, and yearly thereafter until disease progression, initiation of a new anticancer therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever comes first. The response assessments may be performed within a ± 7-day window of the scheduled date. In the event of a treatment interruption, disease assessments are to continue per the Schedule of Assessments ([Appendix 1](#)).

Response will be determined by the Independent Review Committee and investigator based on the Lugano Classification ([Cheson et al 2014](#); [Appendix 8](#)).

For patients who permanently discontinue study treatment before disease progression or start of a new anticancer therapy, tumor assessments (including imaging) will continue until disease progression determined by the investigator (Part 1) or confirmed by the Independent Review Committee (Part 2), or the start of a new anticancer therapy.

Clinical suspicion of progressive disease at any time will require a radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.

In Part 2, for patients with suspected disease progression, study sites should immediately notify the Independent Review Committee by completing the suspected progressive disease notification form. Study sites should also ensure that all imaging scans are submitted to the Independent Review Committee portal and that relevant clinical data are entered into the electronic data capture (EDC) system. Once the Independent Review Committee receives the scans and relevant clinical data, the review will be conducted expeditiously. While the Independent Review Committee is conducting the review, patients should remain on study treatment until disease progression is confirmed by the Independent Review Committee.

6.8.2. Targeted Physical Examination for Response Assessment

Targeted physical examination for response assessment involves examination of systems associated with clinical signs and symptoms, such as the lymph nodes, abdomen, and skin. Targeted physical examination for response assessment will be performed as indicated in [Appendix 1](#) and may be performed within a ± 7-day window of the scheduled date.

6.8.3. Response-Relevant Imaging

All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's course on the study.

In Part 2, all PET-CT, CT, and magnetic resonance imaging (MRI) scans obtained during the study will be collected and reviewed by a central imaging vendor identified to this trial. De-identified copies of all scans must be provided to the sponsor or designee (eg, central imaging vendor).

The response-relevant imaging may be performed within a ± 7 -day window of the scheduled date.

6.8.3.1. Computed Tomography Scan

Patients will undergo contrast-enhanced CT scans of chest, abdomen, pelvis, and neck if clinically indicated. CT will be performed at screening, at 8 weeks (study day 56 ± 7 days) and 16 weeks (study day 112 ± 7 days) after the first dose of study drug (ie, Ramp-up Week 1 Day 1), then every 12 weeks up to one year, then every 24 weeks for 2 years, and yearly thereafter until disease progression, initiation of a new anticancer therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. For patients with a contraindication to receiving intravenous contrast for CT scan (eg, contrast allergy or other medical contraindication, such as renal insufficiency), an MRI scan may be used in place of a CT scan. For patients being assessed via MRI scans, a non-contrast chest CT scan is acceptable and preferred in place of a chest MRI scan to evaluate the lung parenchyma ([Appendix 1](#)). The same imaging technique (ie, CT or MRI scan) should be used consistently throughout a patient's time on the study.

6.8.3.2. Positron Emission Tomography-Computed Tomography Scan

All patients will undergo PET or combined PET-CT scans at screening. For patients with FDG-avid disease, PET-CT scan should be repeated at 8 weeks (study day 56 ± 7 days) and 16 weeks (study day 112 ± 7 days) after the first dose of study drug (ie, Ramp-up Week 1 Day 1; [Appendix 1](#)). Afterwards, a PET scan is only required for confirmation of complete and partial response determined by CT scan or if clinically indicated (including confirmation of disease progression in case of absence of any clinical symptoms or ambiguous CT-based assessment). The CT portion of the PET-CT should be used in lieu of a CT with contrast only if the CT portion of the PET-CT has been performed with diagnostic quality, adheres to the specified slice thickness/scan parameters, and intravenous contrast is administered. Otherwise, separate PET-CT and CT scans (see Section [6.8.3.1](#)) should be done.

A CR should be confirmed by PET-CT scan for patients who had FDG-avid disease during screening, as required by the response assessment criteria. Patients who had non-FDG-avid disease at screening confirmed by the Independent Review Committee will be followed by CT-based assessments alone.

6.8.4. Bone Marrow Examination for Response Assessment

An assessment of disease infiltration in the bone marrow is required at screening (unless already documented in peripheral blood) and for confirmation of CR in patients with bone marrow involvement of lymphoma at baseline. Bone marrow examination for response assessment may be performed within the $\pm$ 7-day window of the scheduled date.

See Section 6.9 for details.

6.8.5. Endoscopy

Endoscopy with biopsy may be performed (optional) at screening for patients with gastrointestinal involvement of their MCL. Patients who had an endoscopy performed during the screening period which confirmed gastrointestinal involvement will require an endoscopy to confirm CR. Endoscopy may be performed within a $\pm$ 7-day window of the scheduled date.

6.8.6. Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms (B symptoms) (Hallek et al 2008) (unexplained fever of $> 38^{\circ}\text{C}$ for 3 consecutive days; unexplained, recurrent drenching night sweats; or unexplained loss of $> 10\%$ body weight within the previous 6 months) will be evaluated as specified per the Schedule of Assessments (Appendix 1) and may be performed within a $\pm$ 7-day window of the scheduled date.

6.8.7. Patient-Reported Outcomes

Patient-reported outcomes for response assessment are specified in Section 6.10.

6.9. Bone Marrow Examination and Tumor Tissue Collection

A bone marrow examination at screening is required to evaluate lymphoma involvement unless bone marrow involvement was already proven by cytological and phenotypical documentation of circulating lymphoma cells at screening. If the bone marrow is involved at screening/baseline, a post-baseline bone marrow assessment will be required in case of suspected CR.

6.9.1. Sample Collection Guidance

Bone Marrow Aspirate/Biopsy

When multiple biopsy samples are needed from the same visit for multiple purposes, they should be split from the same sample whenever possible. Please follow standard practice for your site.

Bone marrow biopsy and aspirate are required during screening to assess bone marrow involvement of lymphoma. If a patient has had a bone marrow examination performed after the discontinuation of last line anti-MCL therapy and within 42 days prior to the first dose of study drug (ie, Ramp-up Week 1 Day 1), a repeat bone marrow biopsy/aspirate is not required during the Screening Period. Post baseline, repeat bone marrow biopsy and aspirate are required if imaging results demonstrate a CR in patients with bone marrow involvement of lymphoma at baseline.

The screening and repeat bone marrow aspirate/biopsy sample must be analyzed by a local pathologist for assessment of lymphoma involvement in the marrow. Only when lymph node/extra nodal lesion biopsy sample is not available, the bone marrow biopsy sample collected for pathology confirmation and biomarker examination as the substitution needs to be sent to a central laboratory.

Tumor Tissue Samples

Archival tumor tissue will be sent to a central laboratory, to confirm the pathology diagnosis of MCL, and for the biomarker examination. It is not required that the archival tissue sample be sent before treatment. The eligibility of the MCL diagnosis will be determined based on the review of pathology report from a local laboratory. If archival tissue is not available, patients must undergo a fresh tumor biopsy prior to enrollment for confirmation of diagnosis.

For all tumor tissue samples, lymph node or extra nodal lesion biopsy samples are required. A bone marrow biopsy sample is acceptable only if it has disease involvement and if it is not feasible to get the biopsy sample from other tumor sites, otherwise lymph node or extra nodal lesion biopsy sample is required.

For baseline tumor tissue samples, a site can submit any of the following to a central laboratory:

- A formalin-fixed, paraffin embedded (FFPE) block with tumor tissue (preferred; if multiple blocks are available, the most recent one is preferred)
- Approximately 17 unstained slides (slides from most recent collected block is preferred)

Optional biopsy samples will also be taken from patients at disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism (written informed consent is required prior to fresh tumor biopsy). If feasible, any follow-up biopsy samples should be ideally taken from the same tumor lesion as the screening biopsy sample.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For fresh biopsy specimens, acceptable procedures include excisional or core needle biopsies for deep tumor tissue, or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. The needle used for biopsies should be ≥ 18 gauge in diameter and ≥ 1 cm in length. Please follow standard practice for your site.

6.10. Patient-Reported Outcomes

Patient-reported outcomes will continue to be assessed until a patient discontinues treatment due to progressive disease (confirmed by the Independent Review Committee for Part 2); the last patient-reported outcomes are to be collected at the last response evaluation visit when disease progression is determined. If a patient discontinues treatment for reasons other than disease progression and enters the long-term follow-up period, patient-reported outcomes will continue to be assessed until disease progression, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first. Assessment of patient-reported outcomes may be performed within a ± 7 -day window of the scheduled date. Patients enrolled in Part 1 will be asked to complete the National Comprehensive Cancer Network-Functional Assessment of

Cancer Therapy Lymphoma Symptom Index-18 (NFlymSI-18) per the Schedule of Assessments ([Appendix 1](#)). Patients enrolled in Part 2 will be asked to complete the NFlymSI-18, the European Quality of Life 5 Dimension 5 Level Questionnaire (EQ-5D-5L), the Patient Global Impression of Symptom Severity (PGI-S) for lymphoma, and Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) per the Schedule of Assessments ([Appendix 1](#)).

NFlymSI-18

The NFlymSI-18 is a patient-reported outcome questionnaire that is developed to measure disease-specific symptoms and/or treatment-related concerns in patients with advanced lymphoma ([Hlubocky et al 2013](#)). It is a copyrighted instrument, which has been translated and validated in over 35 languages and is used commonly in more lymphoma trials. 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). A sample questionnaire is provided in [Appendix 11](#) as an example only.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome ([EuroQol Group 1990](#); [Herdman et al 2011](#)). Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale (VAS) to general health state on a scale from “the worst health you can imagine” to “the best health you can imagine.” A sample questionnaire is provided in [Appendix 12](#) as an example only.

PGI-S

PGI-S for lymphoma is a one item question measuring overall severity of lymphoma symptoms in the past 7 days (past week). Scores are based on a 5-level Likert scale from “Not at all” to “Extremely” with higher score showing more severity. A sample questionnaire is provided in [Appendix 13](#) as an example only.

PRO-CTCAE

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 14](#).

6.11. Biomarkers

Tissue and blood samples for biomarker assessment will be collected as stated in [Appendix 1](#). Requirements of tumor tissue and bone marrow samples, including those used for biomarkers purposes, are outlined in Section [6.9](#).

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the Laboratory Manual for details of sample handling. If leftover and extra samples are still available after biomarker analysis for this study, they will be retained/archived/saved for future research and may be used upon consent.

Tumor tissue (FFPE) block or unstained slides must be sent to a central laboratory for confirmation of MCL diagnosis and examinations of other biomarkers. Biomarker assessments will include, but are not limited to, expression of BCL2 family members, BCL2 alteration, apoptosis markers, disease risk factors status such as TP53 mutation, Ki67 index, and gene mutation/expression profiling. (Note: For sites from the China mainland, tissues will be obtained to test the expression of BCL2 family members [BCL2, Bcl-xL, MCL-1], BCL2 alteration [copy number gain, amplification, translocation, and mutation], disease risk factors [Ki-67 expression, TP53 mutation], gene mutation/expression profiling.)

6.11.1. BCL2 Expression and Disease Risk Factors

Tumor tissue samples collected at screening will be used to assess BCL2 family member expression by immunohistochemistry (IHC). Ki-67 index at screening will be evaluated by IHC in MCL.

6.11.2. TP53 Mutation and Mutation Profiling

Tumor tissue samples collected at screening will be used to assess mutations of TP53 and other hematologic malignancy related genes by next-generation sequencing (NGS).

6.11.3. Mechanism of Resistance and Activation

Blood samples will be collected at screening, time of the first response (immediately or at the next scheduled site visit), and at disease progression (immediately or at the next scheduled site visit). Blood-based biomarker analysis (such as DNA/ctDNA sequencing, ctDNA amount) will be performed to explore the association with the response, resistance, and prognosis to sonrotoclax.

An optional biopsy will also be taken during the study from accessible tumor sites in patients who have confirmed disease progression; these biopsies are done to explore genetic alterations, BCL2 family member expressions (BCL2, Bcl-xL, MCL-1) associated with drug resistance. A separate written patient consent is required for fresh tumor biopsies.

6.12. Laboratory Assessments

Samples for protocol-specified laboratory assessments will be collected and tested locally unless otherwise specified. Additional laboratory assessments, including laboratory values required within a short timeframe on dosing days to determine drug dosage, and unscheduled laboratory

tests ordered by the investigator as necessary for patient monitoring, will be performed locally and entered into the eCRF. Hepatitis B and C testing may also be assessed locally if the local laboratory is able to perform the test to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C respectively); otherwise, the results must be confirmed by the central laboratory.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels are provided in the Laboratory Manual.

Clinical chemistry, complete blood count (CBC), coagulation, urinalysis, and serum immunoglobulin samples will be tested at the timepoints specified in the Schedule of Assessments ([Appendix 1](#)) and may also be performed as medically necessary. Laboratory assessments should be done before the first study drug administration unless otherwise specified. Select screening blood tests performed ≤ 72 hours before the first study drug administration do not need to be repeated on the first day of study drug administration, but laboratory tests for TLS monitoring may still be required for safety monitoring purposes (eg, TLS monitoring, see [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)). For patients in Part 2 after Protocol Amendment 2.0 is implemented, Week 2 Day 1 and Week 3 Day 1 visits will not be performed.

6.12.1. Hematology

A CBC with differential is required to be performed as indicated in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). A CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, WBC count with differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

6.12.2. Clinical Chemistry

Serum chemistry is required to be performed as indicated in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). Serum chemistry includes sodium, potassium, chloride, bicarbonate or carbon dioxide, glucose, blood urea nitrogen (or urea), creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, aspartate aminotransferase (AST), LDH, alkaline phosphatase, uric acid, and lipase (at screening only). An increase in serum aminotransferase to $> 3 \times$ ULN should be followed by repeat testing within 48 to 72 hours of ALT, AST, alkaline phosphatase, and total bilirubin to confirm the abnormalities and to determine if they are increasing or decreasing.

6.12.2.1. Tumor Lysis Syndrome-Relevant Laboratory Assessments

Note that the following clinical chemistry tests are relevant to TLS monitoring (see Section [7.5](#)) and will be required at regular intervals at select timepoints as indicated per [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#):

- Potassium
- Phosphorus
- Uric acid
- Calcium

- Serum creatinine

Some timepoints may request both clinical chemistry and TLS-relevant laboratory assessments. In such cases, a single clinical chemistry assessment may suffice for both as long as it includes the required tests listed above.

6.12.3. Serum Immunoglobulins

Quantitative serum immunoglobulins (IgA, IgG, IgM) will be measured at screening, Week 1 Day 1, then every 12 weeks during the treatment phase, and at the Safety Follow-up Visit as specified in [Appendix 1](#). Quantitative assessment of serum immunoglobulins may be performed within the ± 7-day window of the scheduled date.

6.12.4. β2-Microglobulin

A β2-microglobulin assessment made after discontinuation of last line anti-MCL therapy and ≤ 42 days before the first dose of study drug (ie, Ramp-up Week 1 Day 1) may be used in lieu of screening. If one is not available, a sample should be collected during screening for this assessment.

6.12.5. Coagulation

The coagulation profile includes prothrombin time, which will also be reported as international normalized ratio, and activated partial thromboplastin time.

6.12.6. Hepatitis B and C Testing

Eligibility Testing

Viral hepatitis B and C serologic markers and viral load (if applicable) will be tested at screening. HBV testing will include HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb). In addition, HBV DNA will be assessed by polymerase chain reaction (PCR) in patients with negative results for HBsAg but positive results for HBcAb (regardless of HBsAb status). HCV testing will consist of HCV antibody plus HCV RNA by PCR in patients with positive results for HCV antibody.

Hepatitis B and C testing may be performed by a local laboratory if the laboratory is able to perform the test to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C, respectively); otherwise, the results must be confirmed by the central laboratory.

Patients with positive HBsAg, detectable HBV DNA, or detectable HCV RNA are not eligible.

[Table 2](#) describes how the results for HBV and HCV testing at screening relate to study eligibility.

Table 2: Eligibility and Monitoring of Patients With HBV and/or HCV Infection

Screening assessment	Meets inclusion criteria	To be excluded
HBV	HBsAg (-) and HBcAb (-)	HBsAg (+)

Screening assessment	Meets inclusion criteria	To be excluded
	HBsAg (-) and HBcAb (+) HBV DNA “Not detected” Assess HBV DNA by PCR every 4 weeks ($\pm$ 7 days) (or every 12 weeks [$\pm$ 7 days] for patients receiving prophylactic antiviral therapy)	HBsAg (-) and HBcAb (+) HBV DNA detected
HCV	Antibody (-) or Antibody (+) HCV RNA “Not detected” Assess HCV RNA by PCR every 4 weeks ($\pm$ 7 days)	Antibody (+) HCV RNA detected

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction.

Monitoring

Patients who are HBsAg negative, HBcAb positive, and with undetected HBV DNA and not on prophylactic antiviral treatment must have their HBV DNA assessed by PCR every 4 weeks from the first dose of study drug (ie, Ramp-up Week 1 Day 1) until Safety Follow-up. Afterwards, the monitoring should continue every 12 weeks for 12 months. HBV DNA assessment by PCR may be performed within the $\pm$ 7-day window of the scheduled date. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. Patients treated prophylactically with antivirals should undergo testing of HBV DNA by PCR every 12 weeks instead of 4 weeks. If HBV DNA is found to be $\geq$ 100 IU/mL, then study drug(s) should be held, and antiviral therapy initiated. If HBV DNA is $\geq$ 20 IU/mL but $<$ 100 IU/mL, then HBV DNA should be rechecked by PCR in $\leq$ 2 weeks. If the repeat level is again $\geq$ 20 IU/mL, then study drug should be held, and antiviral therapy initiated. Resumption of study drug in patients whose HBV reactivation resolves must be discussed with, and approved by, the medical monitor in consultation with physician with expertise in managing hepatitis B.

Patients positive for HCV antibody but with undetected HCV RNA must have HCV RNA assessed by PCR every 4 weeks from the first dose of study drug (ie, Ramp-up Week 1 Day 1) until Safety Follow-up. Afterwards, the monitoring should continue every 12 weeks for 12 months. HCV RNA assessment by PCR may be performed within the $\pm$ 7-day window of the scheduled date. If HCV RNA is detected ($\geq$ 15 IU/mL), then study drug should be held, and antiviral therapy initiated. Resumption of study drug in patients whose HCV reactivation resolves must be discussed with and approved by the medical monitor in consultation with physician with expertise in managing hepatitis C.

The medical monitor or designee should be informed of any suspected hepatitis B or hepatitis C reactivation.

6.12.7. Pregnancy Test

For screening purposes, a serum pregnancy test will be performed $\leq$ 7 days before the first dose of study drug (ie, Ramp-up Week 1 Day 1) for women of childbearing potential. Any female patient who is pregnant will not be eligible for the study.

In addition, exclusion of patients due to pregnancy will need to be confirmed on the date of first dose (ie, Ramp-up Week 1 Day 1) before dosing, through a laboratory-based highly sensitive urine or serum pregnancy test. Urine or serum pregnancy tests will be performed at baseline, Ramp-up Week 5 Day 1 (if 320 mg), Week 1 Day 1, Week 4 Day 1, and then every 4 weeks during the treatment period. For patients at the 320 mg dose level under the daily dose ramp-up schedule and for patients in the BIW dose ramp-up scheme, pregnancy tests for Ramp-up Week 5 Day 1 and Week 1 Day 1 can be combined. This will require additional visits after Week 24. If there are more than 4 ramp-up weeks for a patient, additional testing will be required to ensure a minimum of 1 pregnancy test every 4 weeks. Pregnancy tests must be continued every 4 weeks for ≥ 90 days after the last dose of study drug and may be performed within the ± 7 -day window of the scheduled date. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Patients will start the first dose only with a negative test result. Patients with a positive result from a serum test will be ineligible to start dosing.

Any patient with a positive serum pregnancy test result will immediately and permanently discontinue study treatment.

6.12.8. HIV Testing

Patients with HIV infection are excluded from the study. HIV testing will be performed during screening unless previous HIV test results from ≤ 4 weeks prior to screening are available.

6.12.9. Urinalysis

Urinalysis is required to be performed at screening as indicated in [Appendix 1](#). Urinalysis will include pH, glucose, proteins, ketones, and specific gravity.

7. STUDY TREATMENT

7.1. Study Treatment Preparation and Dispensation

7.1.1. Packaging and Labeling

Sonrotoclax film-coated tablets will be provided in a child-resistant, high-density polyethylene bottle with a desiccant, induction seal, and bottle label.

The contents of the label will be in accordance with all applicable local regulatory requirements.

7.1.2. Study Drug Supply

Sonrotoclax will be supplied by the sponsor.

7.1.3. Handling and Storage

The study drugs will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. The study drugs must be kept at the temperature conditions specified on the labels.

7.1.4. Study Drug Dispensation

Study drugs must be dispensed and administered as described below. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug.

All study drugs will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual.

For dispensation of study drug provided by the sponsor, please ensure that the bottle number(s) and/or batch number listed in Interactive Response Technology (IRT) system matches with what is being given to the patient, if applicable.

7.1.5. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study

drug received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

Patients will be requested to bring their unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and administered to the patient and all dose changes including the reason for dose changes during the study must be recorded in the appropriate eCRF.

7.1.6. Disposal and Destruction

Please refer to the Pharmacy Manual for details regarding disposal and destruction.

During or after completion of the study, following drug inventory reconciliation by the monitor, the study site will destroy or return all unused, partially used, or used study drug supplies. The inventoried supplies can be destroyed on-site according to institutional policies, after receiving written sponsor approval. Alternatively, inventoried supplies can be returned to the depot for destruction.

7.2. Dosage and Administration

The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Patients will be requested to bring their unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

7.2.1. Sonrotoclax

Sonrotoclax will be administered to all patients enrolled.

7.2.1.1. Dose Selection of Sonrotoclax

Sonrotoclax will be administered at a range of doses in Part 1A (dose-escalation) and Part 1B (safety expansion) (Section 3). Doses planned to be utilized during this study are 160 mg and 320 mg but may be modified by Safety Monitoring Committee recommendation based on data gathered from this study.

In Part 2, sonrotoclax will be administered at the RP2D and with recommended ramp-up schedule from Part 1 (Section 3.2.3). Based on all available data from Part 1, the RP2D of sonrotoclax monotherapy was determined to be 320 mg.

7.2.1.2. Administration of Sonrotoclax

Sonrotoclax doses will be achieved by orally administering 1-mg, 5-mg, 20-mg, or 80-mg film-coated tablets. Each dose will be administered with food once a day. The available PK data in the food effect study showed high interpatient PK variability in the fasting state, with significantly low exposure observed in some individuals. Dosing with food (both low-fat and high-fat meals) reduced the interpatient PK variability while increasing the exposure, with a range of increase in C_{max} and AUC of 30% to 100% compared with that in the fasting state. There was no significant PK difference in patients dosed with low-fat and high-fat meals. Sonrotoclax film-coated tablets should not be broken or chewed at any time. On the day of PK blood sampling, study drug administration for patients will occur at the center after the predose

blood sampling has occurred under the supervision of the investigator or his/her designee. The investigator or his/her designee must instruct the patient not to self-administer the study drug prior to the site visit on those days.

Patients will be advised that if a dose of the study drug is not taken at the scheduled time, they should take the missed dose as soon as they remember, ensuring that the dose is taken within 8 hours of the missed dose with food. Otherwise, patients should skip the missed dose (during ramp-up, consult [Appendix 4](#) for guidance on missed doses). An extra dose of the study drug should not be taken to make up for the missed dose.

7.2.1.3. Sonrotoclax Ramp-up

A ramp-up schedule is defined as the sonrotoclax dosing schedule a patient utilizes to gradually reach or “ramp-up” to the intended target dose and schedule. For example, if a patient’s intended target dose is 160 mg daily, the ramp-up schedule would consist of all doses needed to reach the dose of 160 mg daily.

The daily ramp-up schedule will be utilized in Part 1. Patients will gradually increase the dose of sonrotoclax approximately daily until the target dose is reached (see [Figure 2](#) and [Figure 3](#), which give examples of 160-mg and 320-mg target doses, respectively). It will begin with 1 mg on Ramp-up Week 1 Day 1 and then continue with the dose increments noted in [Figure 2](#) and [Figure 3](#). Initially, the daily ramp-up will consist of dose escalations on weekdays only, with approximately 30% daily dose increases (modified to enable dosing with available tablets). Patients will stop ramp-up at the target dose level to which they have been assigned. The final ramp-up day at the target dose will be labeled as Week 1 Day 1. The ramp-up schedule covering all dose levels up to 320 mg is detailed in [Appendix 4](#).

The ramp-up schedule of sonrotoclax in Part 2 will be determined based on the data from Part 1. Patients who have consented to Protocol Amendment 2.0 or above before their first dose of study drug will follow the BIW ramp-up dosing schedule. All other patients in Part 2 will follow the daily ramp-up dosing schedule.

The BIW ramp-up schedule will begin with 1 mg on Ramp-up Week 1 Day 1 and then continue with the dose increments noted in [Figure 4](#) (in Section [3.2.3](#)) until the RP2D in Part 2 is reached. The final ramp-up day at the target dose will be assigned as Week 1 Day 1.

The Safety Monitoring Committee may recommend the removal of the Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits in the BIW ramp-up schedule, as outlined in Section [3.2.3](#). If the ramp-up schedule and/or doses are to be modified further during study conduct following regular safety data review (eg, based on TLS events, laboratory results, and other clinical assessments) by the Safety Monitoring Committee, the health authorities and/or IRB/IECs will be notified and a protocol amendment submitted according to local requirements.

7.2.1.4. Duration of Treatment

Once patients begin sonrotoclax treatment, they should continue until an event requiring treatment discontinuation occurs (see Section [5.4.1](#)).

7.3. Overdose

Any dose of study drug in excess of the amount specified per the patient's intended dose and schedule is considered to be an overdose. Adverse events associated with an overdose or incorrect administration of study drug will be recorded in the Adverse Event eCRF. Any serious adverse events associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via the serious adverse event reporting process as described in Section 9.6.1. There is no specific antidote for sonrotoclax. In an event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

7.4. Dose Interruption and Modification

7.4.1. Sonrotoclax

7.4.1.1. Interruption or Reduction of Dose Levels During Dose Ramp-up Period

If a dose hold occurs during dose ramp-up, the ramp-up may continue the same dose regimen prior to dose hold after resolution of the toxicity. Repeated dose holds during ramp-up could refer to Section 7.4.1.3 and Section 7.4.1.4, and could be discussed with the medical monitor.

Sonrotoclax should be interrupted if the patient is not able to attend required site visits during the dose ramp-up period (eg, due to unexpected events, such as public health or humanitarian emergencies). Sonrotoclax may be restarted once the patient is able to resume attending site visits. The investigator should consult with the medical monitor in case of prolonged interruption or if a dose hold occurs early in the dose ramp-up. For patients who have had a drug interruption lasting > 7 days during the ramp-up, the restart dose must be at least one dose level lower than the last dose given prior to the interruption (Table 4), except for the initial dose of 1 mg. If the study drug was interrupted for ≤ 7 days, sonrotoclax may be restarted at the same dose level as before the hold or at one dose level lower per investigator's discretion based on a TLS risk assessment (including tumor burden status) and depending on whether the hold occurs early in the dose ramp-up.

7.4.1.2. Interruption or Modification of Dose Levels During Treatment With Target Dose Level Period

The guidelines set forth in Table 3 should be followed for dose interruption or modification of sonrotoclax for hematologic (Section 7.4.1.3) or nonhematologic (Section 7.4.1.4) toxicities.

Table 3: Sonrotoclax Dose Reduction Levels During the Treatment Period at Target Dose Level

Toxicity occurrence	Sonrotoclax dose level prior to toxicity	Sonrotoclax dose upon resumption of dosing
First	Target dose	Target dose
Second ^a	Target dose	50% of the target dose
Third	50% of the target dose	25% of the target dose
Fourth	25% of the target dose	Discontinue sonrotoclax

^a The first instance of Grade 4 nonhematologic toxicity should begin with the guidance given for “Second” toxicity occurrence: see Section 7.4.1.4.

Sonrotoclax may be restarted upon resolution of toxicity per the investigator’s discretion if held for up to 28 consecutive days. If, in the investigator’s opinion, it is in the patient’s best interest to restart treatment after 28 days, then written approval must be obtained from the medical monitor. For patients who have had a dosing interruption lasting > 7 days and who have significant active disease present, the restart dose must be at least one dose level lower than the last dose given prior to the interruption (Table 4). All appropriate TLS prophylaxis measures should also be resumed before restarting the dose (refer to Section 7.5.2). Individual cases must be discussed with the medical monitor before patients restart after a drug hold > 7 days.

Table 4: Dose to Restart Sonrotoclax After a Dose Interruption Longer Than 7 Days

Dose at time of interruption (mg)	Highest restart dose (mg)*
1 mg	1 mg
2 mg	1 mg
5 mg	2 mg
10 mg	5 mg
20 mg	10 mg
40 mg	20 mg
80 mg	40 mg
160 mg	80mg
320 mg	160 mg
*The investigator may restart at a lower dose than noted above.	

7.4.1.3. Dose Reductions of Sonrotoclax and Drug Holds for Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness.

Hematologic toxicities

- Grade $\geq$ 3 febrile neutropenia
- Grade $\geq$ 3 thrombocytopenia that results in clinically significant bleeding
- Any Grade $\geq$ 4 heme toxicity with the following exceptions:
 - Grade 4 neutropenia lasting $\leq$ 7 days with or without treatment
 - Grade 4 lymphopenia
 - Grade 4 leukopenia

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to Grade $\leq$ 1 or baseline.

If the same event reoccurs, patients will restart at 50% decrease of the dose level upon recovery of the toxicity to Grade ≤ 1 or baseline. A maximum of 2 dose reductions will be allowed. Patients with Grade ≥ 3 thrombocytopenia associated with significant bleeding requiring medical intervention will be discussed with the medical monitor.

Re-escalation to the intended cohort dose may be allowed under certain circumstances after discussion with the medical monitor.

Any hematologic toxicities beyond the above-mentioned conditions determined by the investigators as requiring sonrotoclax dose interruptions or reductions need to be discussed with the medical monitor.

7.4.1.4. Dose Reductions of Sonrotoclax and Drug Holds for Nonhematologic Toxicity

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness.

- All instances of hepatic laboratory abnormalities meeting Hy's law criteria
 - ALT or AST $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN without initial findings of cholestasis and after excluding other potential causes.
- Any $\geq$ Grade 3 nonhematologic toxicity with the following exceptions:
 - TLS-related laboratory adverse events (ie, hyperuricemia, hyperphosphatemia, hyperkalemia, and/or hypocalcemia) that resolve before the next dose, with or without treatment.
 - Grade 3 gastrointestinal (GI) toxicity (ie, nausea, vomiting, diarrhea) unless unresponsive to treatment ≥ 3 days
 - Asymptomatic biochemical laboratory abnormalities that resolve in ≤ 7 days

For the first instance of Grade 4 nonhematologic toxicity that is not clearly related to underlying disease, immediately follow the "Second Occurrence" guidance (restarting sonrotoclax at 50% decreased dose level) in [Table 3](#) and continue from there for subsequent instances. In such instances, rechallenge to the original starting dose may be possible only after consultation and approval from the medical monitor.

For the first occurrence of nonhematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to Grade ≤ 1 or baseline.

If the same event reoccurs, patients will restart at 50% decreased dose level upon recovery of the toxicity to Grade ≤ 1 or baseline. A maximum of 2 dose reductions will be allowed.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see [Section 6.12.6](#).

Any nonhematologic toxicities beyond the above-mentioned conditions determined by the investigators as requiring sonrotoclax dose interruptions or reductions need to be discussed with the medical monitor.

7.5. Tumor Lysis Syndrome

TLS is an oncologic emergency that is caused by rapid tumor cell lysis leading to a release of large amounts of potassium, phosphate, and nucleic acids into systemic circulation.

TLS can be separated into laboratory TLS and clinical TLS as defined by [Howard et al 2011](#) and [Howard et al 2018](#) (see [Table 5](#)).

Table 5: Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic abnormality	Criteria for classification of laboratory tumor lysis syndrome ^a	Criteria for classification of clinical tumor lysis syndrome ^a
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L) in adults or > 6.5 mg/dL (2.1 mmol/L) in children	
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 4.5 mg/dL (1.12 mmol/L) ^b	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury ^c	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value > 1.5 times the upper limit of the age appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of < 0.5 mL/kg/hr for 6 hours

Source: [Howard et al 2011](#), [Howard et al 2018](#)

^a In laboratory TLS, 2 or more metabolic abnormalities must be present during the 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

^b The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x (4 – albumin in grams per deciliter).

^c Acute kidney injury is defined as an increase in the creatinine level of ≥ 0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical TLS.

7.5.1. Risk of Tumor Lysis Syndrome

The risk of TLS in an individual patient is a continuum related to the tumor burden found in each patient. Therefore, the tumor burden will affect the hospitalization and monitoring requirements applicable to a given patient on this study. Renal dysfunction should also be considered as a factor and may warrant additional prophylaxis and monitoring for a given patient. The risk of TLS persists when patients restart the study drug after an interruption, particularly if their disease still remains active based on investigator's assessment (see Section 7.4.1).

7.5.1.1. Patients With Low Tumor Burden

Patients with a low tumor burden are defined as those with an absence of high TLS risk features. A patient with a low tumor burden may follow the increased monitoring and hospitalization guidelines for those with a high tumor burden/renal dysfunction at the discretion of the investigator.

7.5.1.2. Patients With High Tumor Burden

Patients with a high tumor burden are at higher risk for TLS. Patients considered to have a high tumor burden include those meeting any of the following criteria:

- High tumor burden, defined as any of the following:
 - Any lymph node ≥ 10 cm in longest transverse diameter of a lesion (LDi)
 - Both of the following:
 1. Any lymph node LDi ≥ 5 cm
 2. Absolute lymphocyte count (ALC) $\geq 25 \times 10^9/L$
 - Detectable circulating lymphoma cells

Lymph node size used to classify the tumor burden category must be determined by imaging.

Patients felt to have other disease characteristics putting them at high risk for TLS may be treated as high risk at the discretion of the investigator.

7.5.1.3. Patients With Renal Dysfunction

Renal dysfunction (creatinine clearance < 80 mL/min) may also increase the risk of clinically relevant TLS independent of tumor burden. Regardless of tumor burden, patients with a creatinine clearance ≤ 80 mL/min should be monitored closely when the dose of sonrotoclax is increased. Additional prophylaxis and monitoring of these patients should be considered.

7.5.2. Mitigation and Monitoring of Tumor Lysis Syndrome

To mitigate and detect the occurrence of TLS during this study, TLS prophylaxis, patient hospitalization, and regular laboratory monitoring are employed. The need for such measures will vary depending on the tumor burden and renal function.

The schedule for these measures is summarized in [Appendix 2](#) and [Appendix 3](#).

[Appendix 4](#) provides additional guidance on dosing and study visits for each ramp-up schedule.

Ramp-up schedules and associated laboratory monitoring may be revised by the Safety Monitoring Committee.

7.5.2.1. Hydration

Oral hydration should include 1.5-2 L/day beginning 24 to 48 hours before the first dose of sonrotoclax and continuing until ≥ 24 hours after the first dose on Ramp-up Week 1 Day 1.

As applicable, intravenous hydration should include 150-200 mL/hour beginning at hospital admission until 24 hours after the first dose of sonrotoclax.

On other ramp-up days, adequate hydration (eg, 6 to 8 glasses of water per day) is recommended.

Investigators could provide the hydration treatment per institutional standards.

7.5.2.2. Antihyperuricemic Prophylaxis

For all patients, antihyperuricemic treatment should be given 2-3 days before the first dose of sonrotoclax (ie, Ramp-up Week 1 Day 1) and continue until ≥ 7 days after reaching the target dose. Allopurinol administered at 300 mg daily is the default prophylaxis treatment for patients unless otherwise noted. Patients allergic to allopurinol must use another uric acid reducer.

For patients with a high tumor burden, rasburicase may be given before the initial dose or dose increment, unless there is a medical contraindication. This should be strongly considered if the baseline uric acid level is elevated compared to local laboratory normal reference ranges. For patients with a contraindication to rasburicase (such as G6PD deficiency), the TLS risk-mitigation plan should be reviewed by the medical monitor. Rasburicase should also be considered early for any patient who has increasing uric acid levels following treatment.

7.5.2.3. Hospitalization

Hospitalization is not mandatory but recommended for high-risk patients from Ramp-up Week 1 Day 1 up to Ramp-up Week 1 Day 5. Patients could be discharged from the hospital on Ramp-up Week 1 Day 5 (for daily dose ramp-up schedule) or Ramp-up Week 1 Day 4 (for BIW dose ramp-up schedule), after the review of the TLS laboratory assessments at 4 hours postdose. If hospitalization is not suitable, the patients still need to schedule site visits, at least on Ramp-up Week 1 Day 1, Ramp-up Week 1 Day 3, and Ramp-up Week 1 Day 5 for patients following the daily dose ramp-up schedule, or at least on Ramp-up Week 1 Day 1 and Ramp-up Week 1 Day 4 for patients following the BIW dose ramp-up schedule, and follow the TLS monitoring guidance in [Appendix 2](#) and [Appendix 3](#).

Hospitalization should be considered if the patient is exhibiting signs or symptoms that may be related to TLS (eg, TLS-related laboratory abnormalities), or the patient has a high tumor burden or renal dysfunction factors that lead to a high risk of TLS. Hospitalization may be used where needed per the investigator's discretion. Elective hospitalization is not a serious adverse event.

7.5.2.4. Tumor Lysis Syndrome-Related Laboratory Monitoring

TLS-related tests (Section [6.12.2.1](#)) will be monitored pre- and postdose at all study visits including administration of sonrotoclax, with timed postdose assessments as indicated in

[Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). This schedule may be adjusted per the Safety Monitoring Committee based on data gathered during the study.

Results of these laboratory tests should be sent immediately and reviewed before the patient leaves the clinic or receives any additional drug. Predose laboratory test results do not need to be reviewed prior to dosing in the following conditions:

- Patient is no longer in dose ramp-up.
- The prior TLS laboratory test results (from ≤ 7 days prior to dosing) have been reviewed.

For all patients, a 4-hour TLS laboratory test (or any later set of TLS laboratory tests) must be conducted and reviewed before the patient is released from the clinic.

7.5.3. Treatment of Tumor Lysis Syndrome

Any patient who develops clinically relevant TLS-related laboratory abnormalities or fulfills Howard Criteria for laboratory or clinical TLS must have treatment held until the abnormalities have resolved. Patients should be well-hydrated. Good urine output should be maintained using diuretics, if required.

Management recommendations are provided in [Appendix 9](#), but patients should be treated according to institutional guidelines.

If any of the laboratory abnormalities in [Appendix 9](#) occur during the first dose of sonrotoclax (including the first dose of a ramp-up schedule), the guidelines below should be followed:

- Patient should be hospitalized for monitoring and the investigator notified (note: a rapidly rising serum potassium level is a medical emergency).
- No additional sonrotoclax doses should be administered until the issue resolves.
- Nephrologist (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous fluids should be initiated at a rate of ≥ 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesia, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine immediately.
- Vital signs should be taken at time of all blood draws or any intervention.

7.6. Precautions

For information on warnings and precautions for sonrotoclax, refer to the BGB-11417 Investigator's Brochure.

7.6.1. Neutropenia and Febrile Neutropenia

Neutropenia is a common toxicity seen in patients with lymphoid and myeloid malignancies who have received multiple prior therapies and can result from bone marrow infiltration of their underlying disease or reduced bone marrow reserves after therapy ([Lustberg 2012](#)). Neutropenia may also be induced or exacerbated in these patients due to an on-target pharmacological effect of sonrotoclax. Patients with clinically significant neutropenia may be susceptible to serious infections and corrective treatments may be required. Febrile neutropenia is a common complication of cancer therapy that can be life-threatening.

Pre-clinical studies of sonrotoclax did not show an increased risk of neutropenia.

As of 04 February 2023, neutropenia shift from baseline was reported in patients with B-cell malignancies who received sonrotoclax monotherapy in all indications without an observed dose relationship. Treatment-related treatment-emergent adverse events of Neutropenia and Febrile neutropenia were reported. Changes in neutrophils should be closely monitored and cautioned for signs of infections. Refer to the current BGB-11417 Investigator's Brochure for more information.

7.6.2. Phototoxicity

The molar extinction coefficient of sonrotoclax was $> 1000 \text{ L mol}^{-1}\text{cm}^{-1}$ between 290 nm and 472 nm. Based on the photochemical properties of sonrotoclax and ICH S10, the risk of phototoxicity is considered possible. Investigators should advise patients to take measures, such as avoiding direct sunlight and using ultraviolet (UV) protection (eg, using sunscreen and wearing hats and long sleeves), from the first dose of sonrotoclax (ie, Ramp-up Week 1 Day 1) until 48 hours (> 5 half-lives) after the last dose of sonrotoclax.

8. PRIOR AND CONCOMITANT THERAPY

8.1. Prior Therapy

Patients must meet all applicable eligibility criteria (Sections 4.1 and 4.2) including those related to prior therapy.

Prior anticancer therapies for the treatment of MCL should be carefully documented in the appropriate eCRF form.

8.2. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the eCRF with indication and dates of administration.

8.2.1. Permitted Medications

The following treatments are allowed:

- Blood product transfusions and growth factor support per standard of care and institutional guidelines
- Limited or replacement corticosteroids for indication(s) other than B-cell malignancy
 - Intermittent use of systemic corticosteroids is allowed if it is for short durations (< 2 weeks) to treat condition(s) not related to the B-cell malignancy (eg, to treat a flare of chronic obstructive pulmonary disease).
 - A short course (≤ 7 days) of systemic corticosteroid treatment (at doses ≤ 20 mg/day prednisone equivalent) for control of lymphoma-related symptoms or BTK inhibitor withdrawal flare is allowed prior to the first dose of study drug (ie, Ramp-up Week 1 Day 1) provided it is tapered off within 5 days after initiation of study treatment.
 - After consultation with and approval by the medical monitor, adrenal replacement therapy is allowed.
Note: Adrenal replacement is the only allowed chronic use of systemic corticosteroids.
- Therapy to reduce symptoms per standard of care and institutional guidelines

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are predisposed to opportunistic infections because of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including *Pneumocystis jirovecii* pneumonia, prophylaxis should be considered as per institutional standards.

Prophylactic measures against infection (eg, for the prevention of bacterial, viral, or fungal infections) and/or for the prevention of hepatitis B infection reactivation may be used per institutional standards.

8.2.2. Prohibited or Restricted Medications

Patients should not receive other anticancer therapies (eg, cytotoxic, biologic, or immunotherapy) while on treatment in this study. Other anticancer therapies should not be administered until disease progression is determined by the investigator (for Part 1) or confirmed by the Independent Review Committee (for Part 2).

Warfarin or other vitamin K antagonists are not allowed while the patient is receiving sonrotoclax. The investigator should discuss the use of other anticoagulant therapies including, but not limited to, heparin, low-molecular weight heparin, Factor Xa inhibitors, or direct thrombin inhibitors, with the medical monitor.

Live vaccines are prohibited throughout study treatment until > 30 days after the end of study treatment. A non-live COVID-19 vaccine may be administered if recommended per local practice.

8.3. Potential Interactions Between the Study Drugs and Concomitant Medications

8.3.1. Sonrotoclax Drug-Drug Interactions

Based on available nonclinical metabolism data, the primary metabolic pathway for sonrotoclax involves the CYP3A isoform. Administration of sonrotoclax with moderate CYP3A inhibitors or with strong CYP3A inducers or inhibitors (refer to [Appendix 6](#) for a list of these medications) are prohibited during the ramp-up and DLT evaluation period as they may affect the metabolism of sonrotoclax. Moderate CYP3A inhibitors or CYP3A inducers can be used with caution at other times. Strong CYP3A inhibitors or CYP3A inducers should be avoided at all times; however, if no alternative treatment is available, their use may be permitted outside of the ramp-up and DLT evaluation periods after discussion with the medical monitor. Patients taking CYP3A inhibitors or CYP3A inducers should be closely monitored for potential toxicities of sonrotoclax.

Sonrotoclax exhibited IC₅₀ values of 2.3 µM for CYP2C8 in the reversible CYP inhibition study and 3.3 µM for CYP3A4 in the time-dependent inhibition study, which are much higher than the targeted levels expected in humans at therapeutic doses. Therefore, it is unlikely that the concomitant administration of sonrotoclax would interfere with the metabolism of compounds which are CYP2C8 or CYP3A4 substrates.

9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an adverse event or serious adverse event as provided in this protocol.

9.1. Adverse Events

9.1.1. Definitions and Reporting of an Adverse Event

An adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an adverse event include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New condition(s) detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an adverse event or serious adverse event)

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the adverse event or serious adverse event. The investigator will then record all relevant information regarding an adverse event or serious adverse event in the eCRF.

However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In these instances, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.1.2. Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. When applicable, adverse events and serious adverse events should be assessed and graded based upon the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 ([NCI-CTCAE v5.0](#)).

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to adverse event

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific adverse event, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.6.3.

9.1.2.1. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each adverse event or serious adverse event using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the adverse event or serious adverse event to the study drug should be considered and investigated. The investigator should also consult the Investigator’s Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a serious adverse event has occurred, and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every serious adverse event prior to transmission of the serious adverse event report to the sponsor, because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the serious adverse event report/eCRF accordingly.

The causality of each adverse event should be assessed and classified by the investigator as “related” or “not related” based on all information available at the time of reporting. An adverse event is considered related if there is “a reasonable possibility” that the adverse event may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the adverse event to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An adverse event should be considered “related” to study drug if any of the following are met; otherwise, the event should be assessed as “not related”:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the adverse event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the adverse event (eg, the patient's clinical condition or other concomitant adverse events).

9.1.2.2. Following Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All adverse events and serious adverse events documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All adverse events and serious adverse events will be followed until resolution, the condition stabilizes or is considered chronic, the adverse event or serious adverse event is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the adverse event or serious adverse event. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the adverse event or serious adverse event. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the serious adverse event instructions provided to the site within the time frames outlined in Section 9.6.1.

9.1.3. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as adverse events or serious adverse events. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are laboratory test abnormalities that are associated with clinical signs or symptoms, or require active medical intervention, or lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or further diagnostic investigation.

The investigator should closely monitor laboratory abnormalities associated with TLS (Section 7.5.2.4) and take appropriate actions when necessary.

9.2. Definition of a Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: the term “life-threatening” in the definition of “serious” refers to an adverse event in which the patient was at risk of death at the time of the adverse event; it does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

- Results in disability/incapacity.

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Is considered a significant medical adverse event by the investigator or sponsor based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered serious adverse events:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product’s Reference Safety Information) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Investigator’s Brochure.

9.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of study drug, only serious adverse events should be reported.

After initiation of study drug, all adverse events and serious adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until initiation of a new anticancer therapy, whichever occurs first.

Beyond 30 days after the last dose of study drug, only the following should be reported: a) any serious adverse events that the investigator becomes aware of that are believed to be related to the study drug treatment; and b) worsening to Grade 5 of any treatment-emergent adverse event present 30 days after the last dose, provided it occurs prior to the start of new anticancer therapy. Refer to Section 10.2.8.3 for the definition of treatment-emergent adverse event.

9.4.2. Eliciting Adverse Events

The investigator or designee will ask about adverse events by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.5. Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.5.1. Disease Progression

As disease progression is expected in this study population, the term “disease progression” should not be reported as an adverse event term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the adverse event term(s). For instance, in a patient who presents with pleural effusion resulting from disease progression of metastasis to the lungs, the event term should be reported as “pleural effusion” instead of “disease progression.” If a patient experiences fatal multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the serious adverse event with death as the outcome, instead of “fatal disease progression” or “death due to disease progression.” All nonserious adverse events, serious adverse events, and deaths, regardless of relatedness to disease progression, should be recorded and reported.

9.5.2. Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, “death,” “death of unknown cause,” or “death unexplained.”

9.6. Reporting of Serious Adverse Events

9.6.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an adverse event meets the protocol definition of a serious adverse event, the event must be reported promptly (≤ 24 hours after determination) to the sponsor or designee as described in [Table 6](#).

Table 6: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for making initial/follow-up report ^a	Documentation method	Reporting method
All SAEs	≤ 24 hours of first knowledge of the SAE	SAE Form	Electronic submission of SAE Form to safety portal ^b

Abbreviations: SAE, serious adverse event.

^a Report follow-up information that is clinically relevant and pertaining to the SAE, which includes, but is not limited to, the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, and/or relationship to each study drug. Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.

^b SAE reports should be submitted to the sponsor's safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

9.6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that a serious adverse event has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined in [Section 9.6.1](#). The serious adverse event report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding a serious adverse event, he/she is not to wait to receive additional information before notifying the sponsor or designee of the serious adverse event and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality at the time of the initial report as described in [Section 9.1.2.1](#).

The sponsor will provide contact information for serious adverse event report submission.

9.6.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all serious adverse events to the sponsor in accordance with the procedures detailed in [Section 9.6.2](#). The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of serious adverse events to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in Section 9.3), will be submitted to all applicable regulatory authorities and investigators for sonrotoclax studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC, as required by local regulations. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File, as required by local policy and procedures.

9.7. Pregnancy Reporting

If a female patient becomes pregnant while receiving study treatment or ≤ 90 days after the last dose of sonrotoclax, or the female partner of a male patient becomes pregnant while receiving study treatment or ≤ 90 days after the last dose of sonrotoclax, a pregnancy report form is required to be completed and submitted to the sponsor within 24 hours of knowledge to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an adverse event or serious adverse event.

An abortion, whether accidental, therapeutic, or spontaneous should always be reported as a serious adverse event. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as a serious adverse event.

9.8. Poststudy Adverse Event

A poststudy adverse event or serious adverse event is defined as any adverse event that occurs after the adverse event/serious adverse event reporting period, as defined in Section 9.4.1.

Investigators are not obligated to actively seek adverse events or serious adverse events in former patients. However, if the investigator learns of any serious adverse event, including a death, at any time after a patient has been discharged from the study, and he/she considers the serious adverse event related to the study drug(s), the investigator will notify the sponsor.

9.9. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

The sponsor will promptly assess all serious adverse events against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual serious adverse events, the sponsor will assess the expectedness of the serious adverse events using the BGB-11417 Investigator's Brochure.

9.10. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or nonserious) is one of scientific and medical concerns specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor to other parties (eg, regulators) might also be warranted.

AESIs may warrant the collection of additional information across the entire study population to better characterize these events (eg, particular laboratory parameters, vital signs, risk factors, concomitant therapies, and/or concomitant illnesses).

All AESIs are required to be reported to the sponsor immediately (within 24 hours of awareness, similar to serious adverse events (Section 9.6.1; Table 6)). However, no AESI reporting is required during the screening period and > 30 days after the last dose of the study drug.

AESIs for this study are:

Potential Hy's law cases, as defined below in the absence of cholestasis or other causes of hyperbilirubinemia:

- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN, or
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

Clinical TLS based on Howard criteria (Table 5).

Sites must report clinical TLS as an AESI. TLS is a disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells. CTCAE TLS only has $\geq$ Grade 3.

Clinical TLS is defined as laboratory TLS plus ≥ 1 of the following:

- Increased serum creatinine (increase from baseline by 0.3 mg/dL (26.5 μ mol/liter) or > 1.5 x ULN if no baseline) or oliguria
- Cardiac arrhythmia or sudden death
- Any symptomatic hypocalcemia
- Seizure

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

10.1. Study Endpoints

10.1.1. Part 1: Dose Escalation and Safety Expansion

10.1.1.1. Primary Endpoints

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

10.1.1.2. 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}), C_{max} , and 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 (partial response 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. 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.

10.1.1.3. 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

10.1.2. Part 2: Efficacy Expansion

10.1.2.1. Primary Endpoint

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

10.1.2.2. Secondary Endpoints

- ORR determined by the investigator
- DOR determined by the Independent Review Committee and by the investigator, defined as the time from first determination of response until first documentation of progression or death, whichever occurs first
- PFS determined by the Independent Review Committee and by the investigator, defined as the time from start of treatment to the first documentation of disease progression or death, whichever occurs first
- TTR determined by the Independent Review Committee and by the investigator, defined as the time from start of treatment to first documentation of response
- OS, defined as time from the start of treatment to the date of death due to any cause
- Patient-reported outcomes as measured by NFlymSI-18 and EQ-5D-5L
- Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs

10.1.2.3. Exploratory Endpoints

- Derived PK parameters for sonrotoclax, including steady-state C_{trough} and other PK 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 effects burden measured via PRO-CTCAE

10.2. Statistical Analysis

10.2.1. Analysis Sets

10.2.1.1. 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 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

DLT defining events are listed in Section 3.2.2.2. The DLT-evaluable Set will be the primary analysis set used for dose escalation decision and MTD or MAD determination.

10.2.1.2. 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.

10.2.1.3. 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 BTK inhibitor therapy and (2) had documented failure to achieve at least partial response 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.

10.2.1.4. 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.

10.2.2. Patient Disposition

The number of patients enrolled, treated, and discontinued from study drug will be counted. The primary reason for study drug discontinuation will be summarized according to the categories recorded in the eCRF. The end-of-study status (alive, death, withdrew consent, or lost to follow-up) will be also summarized.

10.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set using descriptive statistics. Continuous variables include but are not limited to age and weight. Categorical variables include but are not limited to sex, age group (< 65 versus ≥ 65), race, and ECOG performance status.

10.2.4. Disease History

The number (percentage) of patients reporting a history of disease and its characteristic will be summarized descriptively. Disease characteristics include, but are not limited to, time since initial diagnosis of disease to first dose (ie, Ramp-up Week 1 Day 1), relapsed versus refractory disease status, disease stage, MIPI, Ki-67, blastoid histology, bulky disease, and baseline bone marrow involvement.

10.2.5. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug (WHODrug) Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report for this protocol. Prior medications will be defined as medications that started before the first dose of study drug (ie, Ramp-up Week 1 Day 1). 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 patient's last dose of study drug or until initiation of a new anticancer therapy, which occurs first.

10.2.6. Medical History

Medical history will be mapped to a system organ class (SOC) and a PT using the Medical Dictionary for Regulatory Activities (MedDRA[®]) of the version referenced at BeiGene at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded in the eCRF, will be summarized by SOC and PT.

10.2.7. Efficacy Analyses

Response assessments will be performed by the investigator and by the Independent Review Committee per the Lugano classification ([Cheson et al 2014](#)). The disease response assessment by the Independent Review Committee is added for Part 1 in Protocol Amendment 2.0 after Part 1 has started.

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.

Additional details in efficacy analysis will be provided in the SAP.

10.2.7.1. Primary Efficacy Analysis (Part 2)

10.2.7.1.1. Primary Estimand

Primary estimand is defined in Section [2.2](#).

10.2.7.1.2. Primary Analysis for Primary Estimand

The primary endpoint is ORR, defined as the proportion of patients who achieve CR or partial response, as determined by the Independent Review Committee review. In this population, 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 as 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.

The primary efficacy analysis will be conducted at least 6 months after the last patient receives the first dose of study drug (ie, Ramp-up Week 1 Day 1).

10.2.7.1.3. 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.

10.2.7.1.4. Sensitivity Analyses for Primary Endpoint/Estimand

Not planned.

10.2.7.1.5. Supplementary Analysis

Not planned.

10.2.7.2. Secondary and Exploratory Efficacy Analysis (Part 1 and Part 2)

10.2.7.2.1. Duration of Response

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

More details, including the censoring rules, will be provided in the SAP.

10.2.7.2.2. Progression-Free Survival

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.

10.2.7.2.3. Time to Response

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.

10.2.7.2.4. 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.

10.2.7.2.5. Patient-Reported Outcomes

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 least square mean change from baseline at key assessment timepoints (eg, 8 weeks, 16 weeks, and 28 weeks) will be provided.

The EQ-5D-5L scores will be summarized for each assessment timepoint in Part 2. The number (%) of each level of all 5 dimensions at each assessment timepoint will be summarized. The visual analogue scale score at each assessment timepoint and changes from baseline will be summarized descriptively (eg, mean [standard deviation], median, range).

The PGI-S score will be summarized descriptively for Part 2.

More details on the analyses of patient-reported outcome will be provided in the SAP.

10.2.7.3. Sensitivity Analysis

There is no planned sensitivity analysis. Data driven sensitivity analysis may be performed.

10.2.8. Safety Analyses

Safety will be assessed by monitoring and recording all adverse events 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 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.

10.2.8.1. Extent of Exposure

Extent of exposure to sonrotoclax will be summarized descriptively as duration of exposure, cumulative total dose received per patient, actual dose intensity (mg/day), and relative dose intensity (%).

The number (and percentage) of patients with dose reduction, treatment interruptions, and study drug discontinuations will be summarized with the respective reasons. The frequency of dose reductions/interruptions will be summarized descriptively.

Patient data listings will be provided for all dosing records.

10.2.8.2. Dose-Limiting Toxicities

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

10.2.8.3. Adverse Events

The adverse event verbatim descriptions (as recorded by the investigator in the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA lowest level term closest to the verbatim term, PT, and primary SOC.

A treatment-emergent adverse event is defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug (ie, Ramp-up Week 1 Day 1) 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, only the following should be reported: a) any serious adverse events that the investigator becomes aware of that are believed to be related to the study drug treatment; and b) worsening to Grade 5 of any treatment-emergent adverse event present 30 days after the last dose, provided it occurs prior to the start of a new anticancer therapy. Only those adverse events that were treatment-emergent will be included in summary tables. All adverse events, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of treatment-emergent adverse events will be reported as the number (percentage) of patients with treatment-emergent adverse events by SOC and PT. A patient will be counted only once by the highest severity grade according to [NCI-CTCAE v5.0](#) within an SOC and PT, even if the patient experienced more than 1 treatment-emergent adverse event within a specific SOC and PT. The number (percentage) of patients with treatment-emergent adverse events will also be summarized by relationship to the study drug. Treatment-related adverse events will include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

Serious adverse events, deaths, treatment-emergent adverse events with Grade ≥ 3 , treatment-related treatment-emergent adverse events, and treatment-emergent adverse events that led to treatment discontinuation, dose reduction, or treatment interruption will be summarized.

10.2.8.3.1. Tumor Lysis Syndrome Events

The TLS events during the study will be listed by study day.

10.2.8.4. Laboratory Analyses

Clinical laboratory (eg, 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 (eg, 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.

Selected laboratory test results will be assigned toxicity grades using [NCI-CTCAE v5.0](#). Laboratory parameters that are graded using [NCI-CTCAE v5.0](#) will be summarized by CTCAE Grade. In the summary of laboratory parameters grade, parameters with grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

10.2.8.5. Vital Signs

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

10.2.8.6. Patient-Reported Outcomes

The items frequencies in PRO-CTCAE will be summarized for Part 2.

10.2.9. Pharmacokinetic Analyses

PK parameters of sonrotoclax (and its possible major metabolites) will be derived using standard noncompartmental methods. Nominal sampling times will be used for interim PK analysis, while actual sampling times will be used in the final analysis and reporting. Plasma concentration-time data will be summarized by nominal time of collection and displayed in both tabular and graphical form. The PK parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] % associated to the geometric mean).

The PK parameters for a single dose profile (AUC_{last} , AUC , C_{max} , t_{max} , $t_{1/2}$, CL/F , and V_z/F) and after steady state ($AUC_{last,ss}$, $C_{max,ss}$, $t_{max,ss}$), will be calculated, if there are sufficient data. For sparse PK profile, PK parameters such as trough plasma concentration (C_{trough}) at steady state will be summarized.

Additional PK parameters may be calculated if deemed appropriate.

Population PK analyses of PK data from this study, and other studies, may be conducted as appropriate, and the results of such analysis may 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 may be reported separately from the clinical study report.

10.3. Sample Size Consideration

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.

10.3.1. Part 1: Dose Escalation and Safety Expansion

Part 1A will 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 need to be evaluated in Part 1A, per the Safety Monitoring Committee recommendation and sponsor's decision, additional patients (approximately 3 to 6 patients for each additional dose level) may be enrolled.

In Part 1B, up to 2 cohorts will 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.

10.3.2. 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 about >0.90 with approximately 100 patients to demonstrate statistical significance at a 1-sided alpha of 0.025 using binomial exact test.

10.4. Interim Analysis

There is no formal interim analysis planned for this study.

10.5. Final Analysis

A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the SAP.

10.6. Other Statistical Issues

Any other statistical/ analytical issues will be discussed in the SAP.

10.6.1. Multiplicity Adjustment

No formal interim analysis is planned for this study. Adjustment for multiplicity is not planned.

10.6.2. Study Enrollment Interruption Criteria

Study enrollment interruption criteria will be applied during expansion parts (Part 1B and Part 2) of the study to ensure patient safety. If such criteria are triggered, further enrollment will be interrupted, pending an evaluation of toxicity by the Safety Monitoring Committee and sponsor.

10.6.2.1. Treatment-Related Treatment-Emergent Adverse Events Leading to Death

The sponsor will monitor treatment-related treatment-emergent adverse events leading to death in patients during the expansion parts of the study. Upon the first occurrence of a treatment-related treatment-emergent adverse event leading to death, a comprehensive review of the available safety data will be performed and formal study enrollment interruption criteria will be established. The criteria will be elicited using a binomial mortality model and a prior distribution of Beta (0.01, 0.19) for the mortality rate.

Using a 5% mortality threshold for deaths, if the accumulating data suggest that the mortality rate is likely to exceed 0.05 with 90% probability, the sponsor will pause enrollment to review the safety data. This assessment is based on a Bayesian posterior calculation under a binomial mortality model and a prior distribution of Beta (0.01, 0.19).

Table 7 provides examples of study enrollment interruption criteria when 10, 20, 30, 40, 50 and 60 patients are treated. When treatment-related treatment-emergent adverse events leading to death are reported, the Bayesian posterior calculation will be implemented to find the study enrollment interruption criteria.

For example, row 3 in Table 7 is interpreted as enrollment will be paused to review the safety data if 20 patients were enrolled and treated with study drug and at least 3 patients experienced treatment-related treatment-emergent adverse events leading to death.

Table 7: Example of Study Enrollment Interruption Criteria for Treatment-Related TEAEs Leading to Death

Number of Patients Treated	Number of Treatment-Related TEAEs Leading to Death
10	≥ 2
20	≥ 3
30	≥ 4
40	≥ 5
50	≥ 5
60	≥ 6

Abbreviations: TEAE, treatment-emergent adverse event.

10.6.2.2. Grade ≥ 4 Treatment-Emergent Adverse Events Related to Sonrotoclax

During the expansion parts of the study (Part 1B and Part 2), a Bayesian method will be used to estimate study enrollment interruption criteria for Grade ≥ 4 treatment-emergent adverse events related to sonrotoclax at any timepoint. A prior distribution of Beta (0.1, 0.9) for Grade ≥ 4 treatment-emergent adverse event rate will be used. After ≥ 10 patients each have received treatment for ≥ 8 weeks, or have had ≥ 1 sonrotoclax-related Grade ≥ 4 treatment-emergent adverse event, or have treatment discontinuation, the following criteria based on the posterior distributions of Grade ≥ 4 treatment-emergent adverse event rate will be implemented:

Probability (Rate of Grade ≥ 4 treatment-emergent adverse events related to the study treatment at any timepoint > 0.12) > 0.9 .

In practice, this means that enrollment will be paused to review the safety data after 10 patients if ≥ 3 out of these 10 patients have Grade ≥ 4 treatment-emergent adverse events related to sonrotoclax. Table 8 provides examples of study enrollment interruption criteria when 10, 20, 30, 40, 50, and 60 patients are enrolled and treated. The Bayesian posterior calculation will be implemented to find the study enrollment interruption criteria in each Safety Monitoring Committee meeting.

Table 8: Example of Study Enrollment Interruption Criteria for Grade ≥ 4 Treatment-Emergent Adverse Events Assessed as Related to Sonrotoclax

Number of Patients Treated	Number of Patients Experiencing Grade ≥ 4 TEAEs Related to Sonrotoclax
10	≥ 3
20	≥ 5
30	≥ 7
40	≥ 8
50	≥ 10
60	≥ 11

Abbreviation: TEAE, treatment-emergent adverse event.

11. STUDY COMMITTEES AND COMMUNICATION

11.1. Safety Monitoring Committee

A Safety Monitoring Committee will be utilized to advise on interpretation of key safety data during the study and advise on dosing, ramp-up, and monitoring decisions to ensure study treatment is tolerable and patients are adequately monitored. The details of Safety Monitoring Committee membership, responsibilities, and meeting schedule are outlined in a separate Safety Monitoring Committee charter.

11.1.1. Safety Monitoring Committee Membership

The Safety Monitoring Committee will consist of key study team members, BeiGene representatives, and ≥ 1 investigator from the study. Study principal investigators relevant to the patients being discussed may also be requested to participate in Safety Monitoring Committee meetings on an ad hoc basis.

11.1.2. Safety Monitoring Committee Responsibilities

The Safety Monitoring Committee will review data from dose escalation and safety expansion (Part 1), as well safety data from efficacy expansion (Part 2). Key responsibilities during dose finding are listed in Section 3.2. Further details are provided in the Safety Monitoring Committee charter.

11.2. Study Steering Committee

A Study Steering Committee will advise the sponsor regarding the design of the study, the need for protocol modification during the conduct of the study, the resolution of significant issues during the conduct of the study, and data analysis and interpretation. The Study Steering Committee will also collaborate with the sponsor to prepare the primary publications of study data. The details of Study Steering Committee membership, responsibilities, and meeting schedule are outlined in a separate Study Steering Committee charter.

11.3. Independent Review Committee

The sponsor will contract with an Independent Review Committee facility to provide an independent and blinded review of imaging and clinical data necessary to assess tumor response in Study BGB-11417-201. This will be conducted by qualified, board-certified radiologists and hematologists assigned to Study BGB-11417-201. An Independent Review Committee Charter will describe the independent review and define the processes, roles, and responsibilities of the sponsor, the sites, the Independent Review Committee facility, and the reviewers.

11.4. Provision of Study Results and Information to Investigators

When the Clinical Study Report is completed, the sponsor will provide the major findings of the study to the investigator.

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Investigator Responsibilities

12.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki," International Council on Harmonisation E6(R2) guideline for Good Clinical Practice, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to. Additionally, the investigator will ensure any applicable country-specific "Good Clinical Practice" requirements are adhered to.

12.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's ICF, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IEC/IRB approval of the amended form before new patients can consent to take part in the study using this version of the form. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

12.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent.

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

12.2.4. Investigator Reporting Requirements

As indicated in Section 9.6.3, the investigator (or sponsor, where applicable) is responsible for reporting serious adverse events to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

12.2.5. Patient and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to the sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- *full* dates of birth;
- contact information (such as phone numbers, home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province or local equivalent (such as city, county, zip code or other equivalent geographic identifiers); or
- information about marital status, family or household members, employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms (except in China) or on product dispensing logs provided to the sponsor, etc).

The investigator and site must use only the specific forms and clinical trial systems, eg, the electronic data capture (EDC) system and any secure file transfer platforms (SFTPs) designated by sponsor for sharing and transfer of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study (including information that was used to determine patient eligibility, such as local pathology reports confirming diagnosis) must be available for inspection upon request by representatives of the US FDA, the China National Medical Products Administration (China NMPA), the European Medicines Agency (EMA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

12.2.6. Data Collection

Data required by the protocol will be entered into the eCRFs in an EDC system that is compliant with all regulatory requirements. All study-related data collected or received by the investigator

or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by sponsor.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified in the Statement of Investigator Form must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

12.2.7. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies and completeness.

During the course of the study, a study monitor (or clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

Adverse events will be coded using MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

12.2.8. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements. During the

course of the study or at the end of the study, following drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, study drug supplies returned by patients, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused and returned study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12.2.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

12.2.10. Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the IRB/IEC-approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures and shall report all protocol deviations to the sponsor.

12.2.11. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient's last visit).

12.3. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the study.

12.4. Study Report and Publications

A Clinical Study Report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council on Harmonisation Guideline for Structure and Content of Clinical Study Reports ([International Council on Harmonisation E3](#)). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. Because this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria ([International Committee of Medical Journal Editors 2021](#)).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for ≥ 2 years.

No such communication, presentation, or publication will include BeiGene's confidential information.

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation, in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

12.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor

- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Shipment of PK samples to assay laboratories
- Shipment of biological samples (eg, archival tumor tissue)

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

12.6. Records Retention and Study Files

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, and screening and enrollment log.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in

a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the Contract Research Organization managing the biological samples, for the shorter of a period of up to 10 years or as allowed by the IRB/IEC.

12.7. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel

- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 12.4.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.8. Joint Investigator/Sponsor Responsibilities

12.8.1. Access to Information for Monitoring

In accordance with International Council on Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.8.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening ^a	Dose ramp-up	Treatment with target dose level ^b										Safety Follow-up ^c	Long-term Follow-up ^d	Survival Follow-up ^e
Days	-28 to -1	All ramp-up visits (see Appendix 4 for schedule)	W1 D1	W1 D2	W2 D1 ^f	W3 D1 ^f	W4 D1	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1 Q12W until last dose	30 d after last dose	Q12W or Q24W or yearly ^g	Every 6 mos
Window (days) ^h			± 1	± 0	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Informed consent ⁱ	X														
Review inclusion/exclusion criteria	X														
Demographic data	X														
General medical history & baseline conditions	X														
Vital signs	X	See Appendix 2 and Appendix 3	X	X	X	X	X	X	X	X	X	X	X		
Weight (& Height at screening)	X	X ^j	X				X	X	X	X	X	X	X	X	
Physical examination ^k	X	X ^l	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X ^l	X	X	X	X	X	X	X	X	X	X	X	X	
Echocardiogram or MUGA or GHPS scan ^m	X														
12-lead ECG ⁿ	X												X		

	Screening ^a	Dose ramp-up	Treatment with target dose level ^b										Safety Follow-up ^c	Long-term Follow-up ^d	Survival Follow-up ^e
Days	-28 to -1	All ramp-up visits (see Appendix 4 for schedule)	W1 D1	W1 D2	W2 D1 ^f	W3 D1 ^f	W4 D1	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1 Q12W until last dose	30 d after last dose	Q12W or Q24W or yearly ^g	Every 6 mos
Window (days) ^h			± 1	± 0	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Review of patient diary ^o		X	X		X	X	X	X	X	X	X	X			
Review of concomitant medications ^p	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs (including serious) ^q	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensation ^r		X	X				X	X	X	X	X	X			
PET-CT and CT scans ^{s,t}	X						X		X ^u						
CT scan ^s												X ^v		X	
B symptoms ^w	X	X ^l	X				X	X	X	X	X	X	X	X	
Targeted physical examination ^x	X	X												X	
Bone marrow examination ^y	X	X												X	
Endoscopy ^z	X	X												X	
Disease evaluation ^{aa}	X	X												X	
PRO questionnaires ^{bb}		X												X	

	Screening ^a	Dose ramp-up	Treatment with target dose level ^b										Safety Follow-up ^c	Long-term Follow-up ^d	Survival Follow-up ^e
Days	-28 to -1	All ramp-up visits (see Appendix 4 for schedule)	W1 D1	W1 D2	W2 D1 ^f	W3 D1 ^f	W4 D1	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1 Q12W until last dose	30 d after last dose	Q12W or Q24W or yearly ^g	Every 6 mos
Window (days) ^h			± 1	± 0	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7
LOCAL LABORATORY STUDIES															
Hematology ^{cc}	X	See Appendix 2 and Appendix 3	X	X	X	X	X	X	X	X	X	X	X		
Clinical chemistry ^{dd}	X	X ^l	X	X	X	X	X	X	X	X	X	X	X		
Coagulation	X														
Serum immunoglobulins ^{ee}	X		X						X ^{ee}			X ^{ee}	X		
TLS prophylaxis ^{ff}	X	X	X												
TLS laboratory assessments ^{gg}	X	See Appendix 2 and Appendix 3	X												
Urinalysis ^{hh}	X														
β2-microglobulin ⁱⁱ	X														
Pregnancy test ^{jj}	X	X ^j	X				X	X	X	X	X	X	X	X	
HBV and HCV (DNA/RNA if needed) ^{kk}	X	(X)	(X)				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
HIV test ^{ll}	X														
CENTRAL LABORATORY STUDIES															
PK blood sampling		See Appendix 2 and Appendix 3													
Biomarker blood sampling ^{mm}		To be collected at RW1D1 predose, time of first response, and disease progression													

	Screening ^a	Dose ramp-up	Treatment with target dose level ^b										Safety Follow-up ^c	Long-term Follow-up ^d	Survival Follow-up ^e
Days	-28 to -1	All ramp-up visits (see Appendix 4 for schedule)	W1 D1	W1 D2	W2 D1 ^f	W3 D1 ^f	W4 D1	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1 Q12W until last dose	30 d after last dose	Q12W or Q24W or yearly ^g	Every 6 mos
Window (days) ^h			± 1	± 0	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Tumor tissue ⁿⁿ	X	At time of disease progression (optional)													

Abbreviations: β2, Beta 2; AE, adverse event; BIW, twice a week; CBC, complete blood count; CR, complete remission; CT, computed tomography; ctDNA, circulating tumor deoxyribonucleic acid; D, day; DLT, dose-limiting toxicity; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EDC, electronic data capture; EQ-5D-5L, European Quality of Life 5 Dimension 5 Level Questionnaire; FDG, [¹⁸F]fluorodeoxyglucose; FFPE, formalin-fixed, paraffin-embedded; GHPS, gated heart pool scan; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgA, immunoglobulins A; IgG, immunoglobulins G; IgM, immunoglobulins M; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; mos, months; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NfLymSI-18, National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18; PCR, polymerase chain reaction; PET, positron emission tomography; PGI-S, Patient Global Impression of Symptom Severity; PK, pharmacokinetic; PRO, patient-reported outcome; Q4W, once every 4 weeks; Q12W, once every 12 weeks; RWXDX, Ramp-up Week X Day X; RNA, ribonucleic acid; SAE, serious adverse event; TLS, tumor lysis syndrome; ULN, upper limit of normal; W, week; WBC, white blood cell.

^a Screening assessments will be completed within 28 days prior to the first dose of the study drug (ie, Ramp-up Week 1 Day 1).

^b The duration of treatment will be until any of the events listed in Section 5.4.1 occurs. The DLT window, when applicable, will be from the first dose (ie, Ramp-up Week 1 Day 1) until completion of ramp-up and 21 days after the first target dose.

^c The Safety Follow-up Visit will occur 30 days after the last dose of study drug (± 7 days) or before the initiation of a new anticancer therapy, whichever occurs first.

^d Patients who discontinue study drug due to reasons other than disease progression or death will remain on the study and continue to undergo Long-Term Follow-up tumor assessments according to Section 6.8 until the patient exhibits the first disease progression, starts a new anticancer therapy, withdraws consent, is lost to follow-up, dies, or the study is terminated by the sponsor, whichever occurs first (see Section 5.5.2). If a patient had already transitioned to tumor assessments interval of every 24 weeks or yearly when the treatment was discontinued, the response assessment may continue to follow the same visit frequency in Long-term Follow-Up until the documented disease progression.

^e Patients who discontinue study drug and have disease progression or initiation of a new anticancer therapy, will enter into survival follow-up. During survival follow-up, patients will not return to the clinic but will be contacted every 6 months by telephone to assess survival status and subsequent therapies for MCL until withdrawal of consent, death, the patient is lost to follow-up, or the end of study, whichever occurs first (see Section 5.5.3).

^f For patients in Part 2 after Protocol Amendment 2.0 is implemented, the Week 2 Day 1 and Week 3 Day 1 visits will not be performed.

^g Response assessment visits should be performed at the frequency specified in Section 6.8. Thus, if a patient has already transitioned to response assessments every 24 weeks or yearly, they may continue to follow the same visit frequency in Long-term Follow-Up.

^h Windows: days allowed for reschedule of an entire visit due to logistic reasons (eg, public holidays). In all cases, including on Week 1 Day 1, elements relating to medical assessment may be performed 24 hours prior to the scheduled day. These are B symptoms, physical examination, ECOG, concomitant medications, AEs, hematology, clinical chemistry, coagulation, pregnancy test, and urinalysis.

ⁱ Informed consent may be obtained up to 14 days before the 28-day screening period; the screening window will start with the first protocol-required screening procedure.

^j Only required on Ramp-up Week 1 Day 1 and Ramp-up Week 5 Day 1.

^k Physical examination includes an assessment of body systems according to the standard of care at the study site and as clinically indicated by symptoms.

^l Only required on Day 1 of each ramp-up week, or the first study visit of the ramp-up week.

- ^m An echocardiogram or MUGA or GHPS scan will be performed at screening and may be performed during other visits as medically indicated.
- ⁿ Perform 12-lead ECG in triplicate at screening (locally) and at the Safety Follow-up Visit (locally). During the treatment period, may be performed as clinically indicated. The same machine should be used for each patient whenever possible.
- ^o A diary will be provided to the patients. Patients must be instructed to record the date and time they take the study drug each day. Patients should clearly record any missed doses as well. Patients will be instructed to bring the diary with them to each clinic visit. The diary must be reviewed with the patient to ensure correct recording of doses in the EDC. During the ramp-up period, it's applicable if the patient has dosed outside of clinic since the last study visit.
- ^p During the survival follow-up phase, only information on new anticancer therapy will be collected.
- ^q All AEs (including serious) must be captured from the first dose (ie, Ramp-up Week 1 Day 1) until 30 days after the last dose of study drug. Beyond 30 days after the last dose of study drug, only the following should be reported: a) any SAEs that the investigator becomes aware of that are believed to be related to the study drug treatment; and b) worsening to Grade 5 of any treatment-emergent adverse event present 30 days after the last dose, provided it occurs prior to the initiation of a new anticancer therapy. Nonserious events during screening may be recorded as medical history. Any SAEs occurring during the screening period but prior to the first dose of study drug (ie, Ramp-up Week 1 Day 1) must also be recorded (see Section 9.4.1).
- ^r Study drug should be dispensed to patients to ensure that enough drug is available to get to their next study visit. After Week 24, drug can be dispensed every 12 weeks to align with study visits. Enough medication should be dispensed to allow for visits to occur at the end of the visit window. During ramp-up, increasing the dose on days without study visits is allowed only in specific circumstances: please refer to the guidance given in [Appendix 4](#). Ensure the patient has appropriate drug supply to dose as needed in between study visits as applicable. For detailed information, please refer to pharmacy manual.
- ^s All patients will undergo PET or combined PET-CT scans at screening. For patients with FDG-avid diseases, PET-CT scans should be repeated at 8 weeks (study day 56 $\pm$ 7 days) and 16 weeks (study day 112 $\pm$ 7 days) after the first dose (ie, Ramp-up Week 1 Day 1). Patients who had non-FDG-avid disease at screening confirmed by the IRC will be followed by CT-based assessments alone. CT scan with contrast of chest, abdomen, and pelvis, and neck if clinically indicated, will be performed at screening; at 8 weeks (study day 56 $\pm$ 7 days) and 16 weeks (study day 112 $\pm$ 7 days) after the first dose; then every 12 weeks up to one year; then every 24 weeks for 2 years, and yearly thereafter until disease progression, initiation of a new anticancer therapy, withdrawal of consent, death, lost to follow-up, or study termination by the sponsor, whichever occurs first. For patients with a contraindication to receiving intravenous contrast for CT scan (eg, contrast allergy or other medical contraindication, such as renal insufficiency), an MRI scan may be used in place of a CT scan. For patients being assessed via MRI scans, a non-contrast chest CT scan is acceptable and preferred in place of a chest MRI scan to evaluate the lung parenchyma. The same imaging technique (ie, CT or MRI scan) should be used consistently throughout a patient's time on the study. The response-relevant imaging may be performed within the $\pm$ 7-day window of the scheduled date.
- ^t CT scans are required if the CT component of the PET-CT scan does not meet the criteria for diagnostic quality.
- ^u Beyond this response assessment timepoint, PET scans are only required for confirmation of complete and partial response determined by CT scan or if clinically indicated (including confirmation of disease progression in case of the absence of any clinical symptoms or ambiguous CT-based assessment).
- ^v CT scans are only to be performed at 28 weeks, 40 weeks, 52 weeks, then every 24 weeks for 2 years, and yearly thereafter until disease progression or initiation of new anticancer therapy, whichever occurs first.
- ^w Disease-related constitutional symptoms (B symptoms) are listed in Section 6.8.6 and may be assessed within a $\pm$ 7-day window of the scheduled date.
- ^x Targeted physical examination for response assessment includes assessment of enlargement of the liver, spleen, and lymph nodes; is performed at each response assessment visit; and may be performed within a $\pm$ 7-day window of the scheduled date.
- ^y Bone marrow biopsy and aspirate is required during screening to assess bone marrow involvement of lymphoma. If a patient has had bone marrow examination performed after the discontinuation of last line anti-MCL therapy and within 42 days prior to the first dose of study drug (ie, Ramp-up Week 1 Day 1) or if the patient had cytological and phenotypical evidence of circulating lymphoma cells at screening, a bone marrow biopsy/aspirate during screening is not required. Repeat bone marrow biopsy and aspirate are required if imaging results demonstrate a CR in patients with bone marrow involvement of lymphoma at baseline. Bone marrow examination for response assessment may be performed within the $\pm$ 7-day window of the scheduled date.
- ^z Endoscopy may be performed at screening for patients with gastrointestinal involvement of their MCL. Patients who had an endoscopy performed during the screening period that confirmed gastrointestinal involvement of MCL will require an endoscopy to confirm CR, which may be performed within a $\pm$ 7-day window of the scheduled date.
- ^{aa} Assessments of MCL status during the study will include disease-related symptoms; targeted physical examination of lymph nodes, liver, spleen, and skin; bone marrow examination (only in case of CR and with bone marrow involvement at baseline); PET-CT and CT scan with contrast of chest, abdomen, pelvis, and neck if clinically indicated; and endoscopy if clinically indicated. Response assessment should be done at 8 weeks and 16 weeks after the first dose (ie, Ramp-up Week 1 Day 1); then every 12 weeks up to one year; then every 24 weeks for 2 years, and yearly thereafter until disease progression, start of a new anticancer therapy, withdrawal of consent, death, lost to follow-up, or

study termination by the sponsor, whichever comes first. The response assessments may be performed within a ± 7 -day window of the scheduled date. For patients who permanently discontinue study treatment before disease progression or start of a new anticancer therapy, tumor assessments (including imaging) will continue until disease progression determined by the investigator (Part 1) or confirmed by the Independent Review Committee (Part 2), or the start of a new anticancer therapy.

^{bb} In Parts 1 and 2, patients should complete NFlymSI-18 on Ramp-up Week 1 Day 1 (prior to the first dose, serving as baseline), at 8 weeks and 16 weeks after the first dose, then every 12 weeks up to one year, then every 24 weeks for 2 years, and yearly thereafter. In Part 2, patients should complete EQ-5D-5L on Ramp-up Week 1 Day 1 (prior to the first dose, serving as baseline), at 8 weeks and 16 weeks after the first dose, then every 12 weeks up to one year, then every 24 weeks for 2 years, and yearly thereafter. In Part 2, PGI-S assessment will also be performed on Ramp-up Week 1 Day 1 (prior to the first dose, serving as baseline), and at 28 weeks the first dose. Patients should complete the questionnaires before the first dose of study drug and before performing any other procedures at the indicated visits. The last NFlymSI-18 and EQ-5D-5L questionnaires are to be completed at the last response evaluation visit when disease progression is determined. If a patient discontinues treatment for reasons other than disease progression and enters the long-term follow-up period, those PRO assessments will continue to be assessed until disease progression, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first. In addition, in Part 2, PRO-CTCAE will be collected at W8D1, W20D1, W36D1, and W48D1, and every 24 weeks for the next 2 years and yearly thereafter. PRO-CTCAE assessments will continue until the Safety Follow-up Visit. The PRO (including PRO-CTCAE) assessments may be performed within a ± 7 -day window of the scheduled date.

^{cc} Hematology - CBC with differential is required to be performed as indicated. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, WBC count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils.

^{dd} Clinical chemistry includes sodium, potassium, chloride, bicarbonate or carbon dioxide, glucose, blood urea nitrogen (or urea), creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, LDH, alkaline phosphatase, and uric acid. An increase of serum aminotransferase to $> 3 \times$ ULN should be followed by repeat testing within 48 to 72 hours of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Clinical chemistry for screening includes lipase.

^{ee} Quantitative serum immunoglobulins (IgG, IgM, IgA) will be measured at screening, W1D1, then every 12 weeks during the treatment phase, and at the Safety Follow-up Visit. Quantitative assessment of serum immunoglobulins may be performed within the ± 7 -day window of the scheduled date.

^{ff} All patients must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 7.5.2.

^{gg} Mandatory TLS laboratory assessments are potassium, phosphorus, uric acid, calcium, and serum creatinine. These assessments must be run immediately at the timepoints indicated. More TLS laboratory assessments could be added on a scheduled visit day or on an unscheduled visit day per the investigator's decision if clinically indicated (see recommendation in [Appendix 9](#)). Predose laboratory values are not required to be reviewed before the dosing if laboratory values from the previous laboratory assessments were within normal limits. Patients should not leave the clinic until the 4- to 6-hour post-dose TLS laboratory tests results have been reviewed. If a case meets clinical TLS criteria, it must be reported within 24 hours (Section 9.10). Note that predose clinical chemistry assessment may also be required on study visit days. In such cases, a single clinical chemistry assessment may suffice for both clinical chemistry and TLS laboratory assessments provided it includes the required TLS laboratory parameters. Refer to Section 6.12.2.1 for details.

^{hh} Urinalysis will include pH, glucose, proteins, ketones, and specific gravity.

ⁱⁱ A $\beta 2$ -microglobulin assessment made after discontinuation of last line anti-MCL therapy and ≤ 42 days before the first dose of study drug (ie, Ramp-up Week 1 Day 1) may be used for screening.

^{jj} All women of childbearing potential (including those who have had a tubal ligation, see [Appendix 14](#)) will have a serum pregnancy test ≤ 7 days before the first dose of sonotoclast (ie, Ramp-up Week 1 Day 1) as part of the screening process. Either serum or urine pregnancy tests will be performed at baseline, RW5D1 (if 320 mg), W1D1, W4D1, and then every 4 weeks during the treatment period at specified visits. For patients at the 320 mg dose level under the daily dose ramp-up schedule and for patients in the BIW dose ramp-up schedule, pregnancy tests for RW5D1 and W1D1 can be combined. This will require additional visits after Week 24. If there are more than 4 ramp-up weeks for a patient, additional testing will be required to ensure a minimum of 1 pregnancy test every 4 weeks. Either serum or urine pregnancy tests will continue to be performed every 4 weeks until ≥ 90 days after the last dose of study drug and may be performed within the ± 7 -day window of the scheduled date. This will require additional visits after the Safety Follow-up Visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

^{kk} If HBV or HCV serology is abnormal at screening (see Section 6.12.6 for details), then monitor HBV DNA or HCV RNA by PCR every 4 weeks from the first dose of study drug (eg, Ramp-up Week 1 Day 1) until Safety Follow-up or every 12 weeks from the first dose of study drug if prophylactic antivirals are being administered. Inform the medical monitor of any suspected HBV or HCV reactivation. When study visits become less frequent (eg, after Week 24), keep viral monitoring (if applicable) at the same

frequency as before (eg, every 4 weeks). If there are more than 4 ramp-up weeks for a patient, testing will be required to ensure 1 assessment per month minimum. Afterwards, monitoring should continue every 12 weeks for 12 months. HBV DNA or HCV RNA assessment by PCR may be performed within the $\pm$ 7-day window of the scheduled date.

^{ll} HIV testing will be performed during screening unless previous HIV test results from $\leq$ 4 weeks prior to screening are available.

^{mmm} Central laboratory blood samples will be collected at RW1D1 predose, time of the first response (immediately or at the next scheduled site visit), and at disease progression (immediately or at the next scheduled site visit). Blood-based biomarker analysis (such as DNA/ctDNA sequencing, ctDNA amount) will be performed to explore the association with response, resistance, and prognosis to sonrotoclax.

ⁿⁿ Patients are required to provide archival tumor tissues (FFPE blocks or approximately 17 unstained slides) before the first dose of study drug (ie, Ramp-up Week 1 Day 1) for confirmation of diagnosis or biomarker analysis. If archival tissue is not available, patients must undergo another tumor biopsy to obtain fresh samples prior to enrollment. Optional biopsy samples will also be taken from patients at disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism (additional written informed consent is required prior to fresh tumor biopsy). If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the screening biopsy.

APPENDIX 2. SCHEDULE OF PK AND TLS MONITORING – PART 1

Part 1: Dose Escalation and Safety Expansion

Day	Ramp-up Week 1 Day 1, Week 1 Day 1, and Week 4 Day 1 (see Appendix 4 for schedule)					
Hours ^a	Predose	0	2	4	6	8
Window (minutes)	≤ 60	NA	± 10	± 10	± 30	± 30
Vital signs	X ^b		X ^c	X ^c	X ^c	X ^c
TLS laboratory assessments (send immediately) ^d	X ^e			X ^e		X ^e
Hematology ^f	X ^b			X ^f		
PK blood sampling ^g	X		X	X	X	X
Study drug administration		X				

Day	All other Ramp-Up Visits ^g (see Appendix 4 for schedule)		
Hours	Predose	0	4
Window (minutes)	≤ 60	NA	± 10
Vital signs	X		X
TLS laboratory assessments (send immediately) ^h	X		X ^e
Hematology	X		X
Study drug administration		X	

Abbreviations: AE, adverse event; eCRF, electronic case report form; NA, not applicable; PK, pharmacokinetic; TLS, tumor lysis syndrome.

Note: Actual drug dosing and PK sampling times must be documented by the sites and will be captured in the database.

General note: It is important that PK sampling occurs as close as possible to the scheduled time. To achieve this, some of the other assessments scheduled at the same time need to be initiated before or after the timepoint to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated timepoint. Thus, the sequence at a particular timepoint is: 1) vital sign measurements; 2) PK blood samples; and 3) any other scheduled or unscheduled measurements at that timepoint.

^a Sampling window: All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained outside of the sampling window will not be captured as a protocol deviation if the exact time of the sample collection is noted in the source document and eCRF. Hour 0 indicates the time of dosing.

^b At Week 4 Day 1, measurement of vital signs and collection of hematology sample may be performed anytime with respect to dose.

- ^c Not required for Week 4 Day 1.
- ^d Mandatory TLS laboratory assessments are potassium, phosphorus, uric acid, calcium, and serum creatinine. More TLS laboratory assessments could be added per the investigator's decision if clinically indicated.
- ^e TLS monitoring is not required at W4D1. These assessments must be run immediately at the timepoints indicated. Predose laboratory values are not required to be reviewed before the first dose (ie, Ramp-up Week 1 Day 1) if laboratory values from the previous laboratory assessments were within normal limits. Patients should not leave clinic until 4-hour TLS laboratory test results have been reviewed. Note that predose TLS laboratory assessments also be required on study W1D2. In such cases, a single clinical chemistry assessment may suffice for both clinical chemistry and TLS laboratory assessments as long as it includes the required TLS laboratories.
- ^f Hematology samples will be used for TLS monitoring, and not required on W4D1.
- ^g The timepoint of predose on W1D1 and W4D1 is approximately 24 hours after the previous day's dose. PK samples at this timepoint must be collected before dosing for this day. The time of dose administration before PK sampling and the timepoints for PK sampling must be recorded in eCRFs. Should a TLS or other AEs be suspected or observed on other daily ramp-up days, additional blood samples may be taken (as close to 4-hour postdose if possible) for PK analyses. The time of dose administration before PK sampling and the timepoints for PK sampling must be recorded in eCRFs.
- ^h More TLS laboratory assessments could be added on scheduled visit day, or on unscheduled visit, per the investigator's decision if clinically indicated.

APPENDIX 3. SCHEDULE OF PK AND TLS MONITORING – PART 2

Part 2: Efficacy Expansion

Day	Ramp-up Week 1 Day 1	All other ramp-up visits	Week 1 Day 1	Week 1 Day 2	Week 4 Day 1	Week 8 Day 1
TLS laboratory assessments (send immediately) ^{a,b}	X	X	X	X		
Hematology ^a	X	X	X	X	See Appendix 1	See Appendix 1
Vital signs ^a	X	X	X	X	See Appendix 1	See Appendix 1
Study drug administration ^c	X	X	X	X	X	X
PK blood sampling ^d			X		X	X

Abbreviations: AE, adverse event; eCRF, electronic case report form; PK, pharmacokinetic; TLS, tumor lysis syndrome.

Note: Actual drug dosing and PK sampling times must be documented by the sites and will be captured in the database.

General note: It is important that PK sampling occurs as close as possible to the scheduled time. To achieve this, some of the other assessments scheduled at the same time need to be initiated before or after the timepoint to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated timepoint. Thus, the sequence at a particular timepoint is: 1) vital sign measurements; 2) PK blood samples; and 3) any other scheduled or unscheduled measurements at that timepoint.

^a Assessments are to be performed ≤ 60 minutes predose and 4 to 6 hours postdose except at Week 1 Day 2, when only the predose timepoint is required. Predose laboratory values are not required to be reviewed before the dosing if laboratory values from the previous laboratory assessments were within normal limits.

^b Mandatory TLS laboratory assessments are potassium, phosphorus, uric acid, calcium, and serum creatinine. These assessments must be run immediately at the timepoints indicated. More TLS laboratory assessments could be added on a scheduled visit day or on an unscheduled visit day per the investigator's decision if clinically indicated (see recommendations in [Appendix 9](#)). Patients should not leave the clinic until the 4- to 6-hour post-dose TLS laboratory tests results have been reviewed. If a case meets clinical TLS criteria, it must be reported within 24 hours (Section [9.10](#)). Note that predose clinical chemistry assessment may also be required on study visit days. In such cases, a single clinical chemistry assessment may suffice for both clinical chemistry and TLS laboratory assessments provided it includes the required TLS laboratory parameters. Refer to Section [6.12.2.1](#) for details.

^c Sonrotoclax doses will be achieved by orally administering 1-mg, 5-mg, 20-mg, or 80-mg film-coated tablets. Each dose will be administered with food once a day. Sonrotoclax film-coated tablets should not be broken or chewed at any time.

^d PK samples are to be taken ≤ 60 minutes predose and 4 to 6 hours postdose on Week 1 Day 1, Week 4 Day 1, and Week 8 Day 1. Should a TLS AE or other AEs be suspected or observed on other ramp-up days, an additional blood sample may be taken (as close to 4 to 6 hours postdose, if possible) for PK analyses. The time of dose administration before PK sampling and the timepoints for PK sampling must be recorded in the eCRFs. All efforts will be made to obtain the PK samples at the designated time window relative to dosing. However, samples obtained outside of the sampling window will not be captured as a protocol deviation if the exact time of the sample collection is noted in the source document and eCRF. Hour 0 indicates the time of dosing.

APPENDIX 4. DAILY AND TWICE-A-WEEK RAMP-UP SCHEDULES VISIT GUIDANCE

Daily Ramp-up Schedule

The daily ramp-up schedule is shown below. Dosing is the same for all patients, but the study visits will vary depending on the patient (see “Study Visit Schedule” below).

Patients should follow the dosing schedule until they reach their target dose, at which point they take that same dose daily. For example, a patient with a target dose of 160 mg should ramp up until Ramp-up Week 4 Day 5 and then take 160 mg daily from that day on. That final ramp-up day where the target dose is reached will be considered Week 1 Day 1 for study scheduling purposes (see Schedule of Assessments [[Appendix 1](#)]).

Daily Ramp-up Schedule: Dosing and Visit Schedule

Week	Ramp-up Week 1							Ramp-up Week 2						
Days	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7
Daily Dose (mg)	1	2	3	4	5	5	5	6	8	10	13	15	15	15
Study Visit	X	-	X	-	X	-	-	X	-	-	X	-	-	-
Week	Ramp-up Week 3							Ramp-up Week 4						
Days	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7
Daily Dose (mg)	20	25	30	40	50	50	50	60	80	100	120	160 ^a	160	160
Study Visit	X	-	-	X	-	-	-	X	-	-	X	(X ^a)	-	-
Week	Ramp-up Week 5													
Days	D1	D2	D3	D4	N/A	N/A	N/A							
Daily Dose (mg)	200	240	280	320 ^a										
Study Visit	X	-	-	X										

Abbreviations: D, Day; N/A, not applicable.

^a The day the patient ramps up to the target dose should be considered Week 1 Day 1 for study purposes and follow the Schedule of Assessments in [Appendix 1](#).

For ease of planning, it is suggested to start the Ramp-up Week 1 Day 1 on a Monday to avoid daily ramp-up increases on the weekends when there are no planned study visits. Thus, the same dose is given for 3 days each ramp-up week (Day 5 to Day 7). These weekend days may be used to increase the dose (eg, in the event of a missed dose) provided certain conditions are met (see “Study Visit Schedule” below).

If Ramp-up Week 1 Day 1 cannot occur on a Monday, adjustments may be needed as weekends will land at different dose levels than in the planned dosing schedule listed above. Doses should not be escalated without close monitoring during the weekend. It is advised to confirm the planned dosing schedule with the study team in such instances.

Study Visit Schedule

Hospitalization is not mandatory but recommended for high-risk patients from Ramp-up Week 1 Day 1 up to Ramp-up Week 1 Day 5. Patients could be discharged from the hospital on Ramp-up

Week 1 Day 5, after the review of the 4-hour postdose tumor lysis syndrome (TLS) laboratory assessments. If hospitalization is not suitable, the patients still need to schedule site visits at least on Ramp-up Week 1 Day 1, Ramp up Week 1 Day 3, and Ramp up Week 1 Day 5, and follow the TLS monitoring guidance in [Appendix 2](#) and [Appendix 3](#).

Hospitalization should be considered if the patient is exhibiting signs or symptoms that may be related to TLS (eg, TLS-related laboratory abnormalities), or the patient has high tumor burden or renal dysfunction factors that lead to a high risk of TLS. Hospitalization may be used where needed per the investigator's discretion (see Section [7.5.2.3](#)). Elective hospitalization is not a serious adverse event.

Starting from Ramp-up Week 2 Day 1, study visits will occur ≥ 2 days per week, Monday and Thursday (Ramp up Week X Day 1 and Ramp up Week X Day 4), of each ramp-up week.

During daily ramp-up, the patient will still increase dose on the days in between study visits (Ramp-up Week X Day 2, Ramp-up Week X Day 3, and Ramp-up Week X Day 5). Dosing should be kept at the current dose level whenever there is more than 2 days between study visits.

The dose is kept at the same level for 3 consecutive days each week (Ramp-up Week X Day 5, Ramp-up Week X Day 6, and Ramp-up Week X Day 7) to account for there being no study visits on weekends. Where needed, the patient may ramp up on the weekend days. This weekend ramp-up is useful to get the patient back on schedule, if needed, but is not expected per the standard ramp-up schedule expectations. Assuming the patient is completing the Ramp-up Week X Day 4 study visit, the patient is free to escalate on Day 6 of the same week without requiring any additional unscheduled visits, but it is recommended to follow the expected schedule where possible.

See the example scenario below ([Example of a Missed Study Visit](#)) for general guidance on the situation where a planned study visit during daily ramp-up needs to be missed. Consider consulting the study team about any adjustments to the planned dosing schedule due to missed study visits.

Note that the day the patient reaches their target dose should be considered Week 1 Day 1 and always requires a study visit. Once the patient reaches Week 1 Day 1, follow the Schedule of Assessments for visits at target dose ([Appendix 1](#)) for required study visits.

Example of a Missed Study Visit

Assume that a patient starting on Monday needs to miss the scheduled Ramp-up Week 3 Day 4 (Thursday) study visit (scheduled for 40 mg). Since it has now been more than 2 days since the last study visit, the patient should not increase the dose to 40 mg on this day and should dose at 30 mg. The patient now has 2 options:

- Complete an unscheduled study visit on Ramp-up Week 3 Day 5 (Friday) to increase to 40 mg dose. Dose on Ramp-up Week 3 Day 6 (Saturday) at 50 mg. The patient will now be back on the standard schedule as of Ramp-up Week 3 Day 7 (Sunday).
- Dose at 30 mg on Ramp-up Week 3 Day 5 (Friday). The patient now has 2 options:
 - Complete an unscheduled visit on Ramp-up Week 3 Day 6 (Saturday) at 40 mg. Dose at 50 mg on Ramp-up Week 3 Day 7 (Sunday). The patient is now back on the expected schedule as of Ramp-up Week 4 Day 1 (Monday).

- Dose on Ramp-up Week 3 Day 6 (Saturday) at 30 mg. Dose at 30 mg on Ramp-up Week 3 Day 7 (Sunday). Complete the scheduled study visit on Ramp-up Week 4 Day 1 (Monday) dosing at 40 mg. The patient is now 2 days behind the expected schedule, and the ramp-up will take ≥ 2 more days to reach the target dose. Dose increases on Day 5 and Day 6 in future ramp-up weeks can be used to get the patient back on schedule without needing any unscheduled visits.

Twice-a-week Ramp-up Schedule

The twice-a-week (BIW) ramp-up schedule, to be utilized after implementation of Protocol Amendment 2.0, is shown below. In case of a dosing start day other than a Monday or in case of a missed visit, dosing may be adjusted as recommended below, and the study visits may slightly vary accordingly (see “Study Visit Schedule” below).

Patients should follow the dosing schedule until they reach the target dose (recommended phase 2 dose [RP2D]), at which point they take that same dose daily. For example, in case the RP2D is communicated to be 320 mg, a patient should ramp up until Ramp-up Week 5 Day 1 and then take 320 mg daily from that day on. That final day of ramp-up where the target dose is reached will be considered Week 1 Day 1 for study scheduling purposes (see Schedule of Assessments [[Appendix 1](#)]).

BIW Ramp-up Schedule: Dosing and Visit Schedule

Week	Ramp-up Week 1							Ramp-up Week 2						
Days	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7
Daily Dose (mg)	1	1	1	2	2	2	2	5	5	5	10	10	10	10
Study Visit	X	-	-	X		-	-	X	-	-	X	-	-	-
Week	Ramp-up Week 3							Ramp-up Week 4						
Days	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7
Daily Dose (mg)	20	20	20	40	40	40	40	80	80	80	160 ^b	160	160	160
Study Visit	X	-	-	X ^a	-	-	-	X	-	-	X ^a	-	-	-
Week	Ramp-up Week 5													
Days	D1	N/A	N/A	N/A	N/A	N/A	N/A							
Daily Dose (mg)	320 ^b													
Study Visit	X													

Abbreviations: BIW, twice a week; D, Day; N/A, not applicable.

^a The Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits may be removed in the future, as recommended by the Safety Monitoring Committee and based on the review of safety data of the first approximately 15 patients dosed with the BIW ramp-up schedule.

^b The day the patient ramps up to the target dose should be considered Week 1 Day 1 for study purposes and follow the Schedule of Assessments in [Appendix 1](#).

Study Visit Schedule

Hospitalization is not mandatory but recommended for high-risk patients from Ramp-up Week 1 Day 1 up to Ramp-up Week 1 Day 5. Patients could be discharged from the hospital on Ramp-up Week 1 Day 4, after the review of the 4-hour postdose TLS laboratory assessments. If

hospitalization is not suitable, the patients still need to schedule site visits at least on Ramp-up Week 1 Day 1 and Ramp-up Week 1 Day 4, and follow the TLS monitoring guidance in [Appendix 2](#) and [Appendix 3](#).

Hospitalization should be considered if the patient is exhibiting signs or symptoms that may be related to TLS (eg, TLS-related laboratory abnormalities), or the patient has high tumor burden or renal dysfunction factors that lead to high risk of TLS. Hospitalization may be used where needed per the investigator's discretion (see Section [7.5.2.3](#)). Elective hospitalization is not a serious adverse event.

Starting from Ramp-up Week 1 Day 1, study visits will occur ≥ 2 days per week, Monday and Thursday (Ramp-up Week X Day 1 and Ramp-up Week X Day 4), of each ramp-up week.

The Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits may be removed in the future, as recommended by the Safety Monitoring Committee and based on the review of safety data of the first approximately 15 patients dosed with the BIW ramp-up schedule. The Safety Monitoring Committee will review that the following observations are met:

- No more than one patient with a laboratory TLS treatment-emergent adverse event
- No clinical TLS treatment-emergent adverse event
- No serious TLS treatment-emergent adverse event

In the event the Safety Monitoring Committee recommends that the Ramp-up Week 3 Day 4 and Ramp-up Week 4 Day 4 monitoring visits can be omitted, patients subsequently reaching these weeks in their ramp-up schedule will attend monitoring visits according to the reduced schedule as outlined above (see [BIW Ramp-up Schedule: Dosing and Visit Schedule](#)), unless the investigator evaluates a persistent TLS risk.

With the BIW ramp-up schedule, the dose is doubled on the 1st and 4th day of each ramp-up week, from Ramp-up Week 1 Day 1 to Ramp-up Week 5 Day 1 (ie, the last day on which doubling of dose is allowed to reach the target dose) inclusive ([Figure 4](#)). This schedule assumes that the patient started on a Monday and accounts for there being no study visits on weekends. If a weekend ramp-up (or escalation) is needed to get the patient back on schedule for the following week, (eg, if a patient started on a day other than a Monday or resumed after a dose hold), a dose ramp-up must always be accompanied by a visit to allow for safety monitoring due to doubling of doses in the BIW schedule, and the same assessments as for a Ramp-up Week X Day 4 visit will be required on a weekend day in which a dose ramp-up has occurred, unless the Safety Monitoring Committee recommends a reduction of the monitoring visits.

Note that the day the patient reaches their target dose should be considered Week 1 Day 1 and always requires a study visit. Once the patient reaches Week 1 Day 1, follow the Schedule of Assessments for visits at target dose ([Appendix 1](#)) for required study visits.

Example of a Missed Study Visit

Assume that a patient starting on Monday needs to miss the scheduled Ramp-up Week 3 Day 4 (Thursday) study visit (scheduled for 40 mg). The patient should not increase the dose to 40 mg on this day and should dose at 20 mg on Ramp-up Week 3 Day 4. The patient should then complete an unscheduled study visit on Ramp-up Week 3 Day 5 (Friday) to increase to 40 mg dose and to complete the assessments that were to be done on Ramp-up Week 3 Day 4. The

patient will now be back on the standard schedule as of Ramp-up Week 3 Day 6 (Saturday) continuing on 40 mg dose until Ramp-up Week 3 Day 7 (Sunday) included.

It is not advised to further delay the increase to 40 mg for scheduling reasons beyond Ramp-up Week 3 Day 5, in order to keep a well-balanced number of days with a stable dose in the BIW ramp-up.

Approved Date 13.06.2024

APPENDIX 5. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX 6. CYP3A INHIBITORS AND INDUCERS

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor.

Strong CYP3A Inhibitors	
Antibiotics:	clarithromycin, telithromycin, troleandomycin
Antifungals:	itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals:	boceprevir, telaprevir
Other:	cobicistat, conivaptan, elvitegravir, idelalisib, mibefradil, nefazodone
Protease inhibitors:	indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors	
Antibiotics:	ciprofloxacin, erythromycin
Antifungals:	fluconazole, clotrimazole
Protease inhibitors:	amprenavir, atazanavir, darunavir/ritonavir combination, fosamprenavir
Calcium channel blockers: diltiazem, verapamil	
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib	
Food products:	grapefruit (<i>Citrus paradisi</i>), Seville oranges, starfruit (<i>Averrhoa carambola</i>)
Herbal medications:	Schisandra sphenanthera
Others:	amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers	
Avasimibe, bosentan, carbamazepine, efavirenz, enzalutamide, etravirine, mitotane, modafinil, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (<i>Hypericum perforatum</i>)	

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>

Abbreviation: CYP3A, cytochrome P450 family 3 subfamily A.

Note: For a more complete list, please refer to the Flockhart Table:

<https://drug-interactions.medicine.iu.edu/MainTable.aspx>

APPENDIX 7. ECOG PERFORMANCE STATUS

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

As published by ([Oken et al 1982](#)). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 8. LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

Response and Site	PET-CT-Based Response (Patients with PET-Avid Disease at Screening)	CT-Based Response (Patients Without PET-Avid Disease at Screening)
Complete Lymph nodes and extra-lymphatic sites	Complete metabolic response Score 1, 2, 3* with or without a residual mass on 5-point scale [□] It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Complete radiologic response (all of the following): Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion No extra-lymphatic sites of disease
Non-measured 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, immunohistochemistry negative

Response and Site	PET-CT-Based Response (Patients with PET-Avid Disease at Screening)	CT-Based Response (Patients Without PET-Avid Disease at Screening)
Partial Lymph nodes and extra-lymphatic sites	Partial metabolic response Score 4 or 5 [□] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	Partial remission (all of the following): ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extra-nodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	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 MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response Score 4 or 5 [□] with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extra- nodal sites; no criteria for progressive disease are met
Target nodes/nodal masses, extra-nodal lesions		
Non-measured lesions	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 and Site	PET-CT-Based Response (Patients with PET-Avid Disease at Screening)	CT-Based Response (Patients Without PET-Avid Disease at Screening)
Progressive disease Individual target nodes/nodal masses Extra-nodal lesions	Progressive metabolic disease Score 4 or 5 [□] 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	Progressive disease requires ≥ 1 of the following cross products of the longest transverse diameter of a lesion and perpendicular diameter progression: An individual node/lesion must be abnormal with: Longest transverse diameter of a lesion > 1.5 cm and Increase by $\geq 50\%$ from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion 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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by ≥ 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing non-measured 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

Abbreviations: CT, computed tomography; FDG, [¹⁸F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

Modified from [Cheson et al 2014](#).

*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to

consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

□PET 5-point scale (Deauville Criteria):

- 1: no uptake above background
- 2. uptake $\leq$ mediastinum
- 3. uptake $>$ mediastinum but $\leq$ 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

Note: 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 9. RECOMMENDATIONS FOR MANAGEMENT OF TLS-RELATED LABORATORY ABNORMALITIES

Abnormality	Management Recommendations
Hyperkalemia	
Potassium ≥ 0.5 mmol/L increase from prior value <i>(even if potassium within normal limits)</i>	Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately. If further ≥ 0.2 mmol/L increase in potassium, but still $<$ upper limit of normal (ULN), manage per potassium $\geq$ ULN. Otherwise recheck in 1 hour. Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium $<$ ULN, and no other evidence of tumor lysis. At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium $\geq$ ULN	Perform ECG immediately and commence telemetry. Nephrology notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg intravenous $\times 1$. Administer calcium gluconate 100 to 200 mg/kg intravenous slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately. If potassium $<$ ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 5.0 mmol/L <i>(if first dose of sonrotoclax)</i>	Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately. Manage per potassium $\geq$ ULN.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	Perform ECG immediately and commence telemetry. Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg intravenous $\times 1$. Administer insulin 0.1 U/kg intravenous + D25 2 mL/kg IV. Administer sodium bicarbonate 1 to 2 mEq/kg intravenous push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 to 200 mg/kg intravenous slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same intravenous line as sodium bicarbonate. Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour sent immediately.

Abnormality	Management Recommendations
Potassium ≥ 5.0 mmol/L (if first dose of sonrotoclax)	Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μ mol/L)	Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately.
Uric acid ≥ 10 mg/dL (595 μ mol/L) OR Uric acid ≥ 8.0 mg/dL (476 μ mol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Consult nephrology. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour sent immediately. If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) OR Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	Administer calcium gluconate 50 to 100 mg/kg intravenous slowly with ECG monitoring. Telemetry. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hyperphosphatemia	
Phosphorus ≥ 4.5 mg/dL with ≥ 0.5 mg/dL increase (if first dose of sonrotoclax)	Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately.
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Nephrology notification (dialysis required for phosphorus > 10 mg/dL) Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour sent immediately. If phosphorus < 5.0 mg/dL 1-hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Creatinine	
Increase $\geq 25\%$ from baseline	Start or increase rate of intravenous fluids. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours sent immediately.

Note: Sites should follow institutional guidelines when available.

APPENDIX 10. DEFINITIONS OF TREATMENT INTOLERANCE

The definitions of treatment intolerance are listed below for the investigators' reference.

Treatment intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued despite dose justification and optimal supportive care because of one of the following:

- $\geq$ one Grade 3 or $\geq$ two Grade 2 nonhematologic toxicities or
- $\geq$ one Grade 3 neutropenia with infection or fever or
- $\geq$ one Grade 4 hematologic toxicity

The above leads to treatment discontinuation for $\geq$ 14 days.

APPENDIX 11. NATIONAL COMPREHENSIVE CANCER NETWORK- FUNCTIONAL ASSESSMENT OF CANCER THERAPY LYMPHOMA SYMPTOM INDEX-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
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APPENDIX 12. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

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

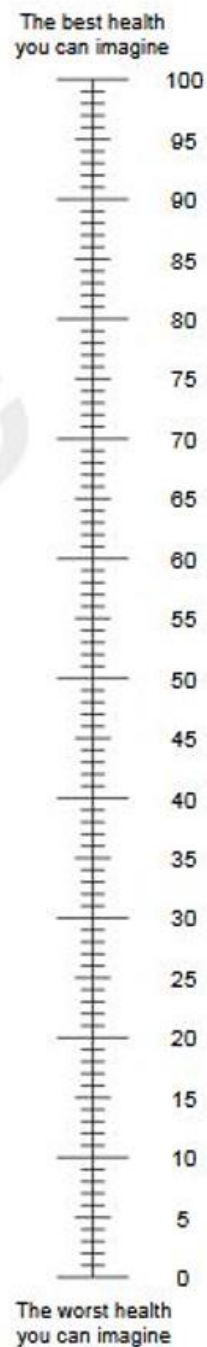
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

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 13. PATIENT GLOBAL IMPRESSION SYMPTOM OF SEVERITY FOR 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 14. NCI PRO-CTCAE™ ITEMS - ENGLISH

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?				
☐ None	☐ 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

53: PRO-CTCAE™ Symptom Term: Fatigue

b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?

☐ 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 NCI at the National Institutes of Health in Bethesda, Maryland, USA. The use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

Version date: 26 April 2020

APPENDIX 15. GUIDELINES AND DEFINITIONS OF “WOMEN OF CHILDBEARING POTENTIAL,” “NO CHILDBEARING POTENTIAL”

Contraception Guidelines

The Clinical Trials Facilitation Group’s recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control ([Clinical Trials Facilitation Group 2014](#)). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
 - Oral, intravaginal, or transdermal
 - Progestogen-only hormonal contraception associated with the inhibition of ovulation:
 - Oral, injectable, or implantable

Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a barrier method of contraception (eg, condoms with or without spermicide) as well.
 - Intrauterine device
 - Intrauterine hormone-releasing system
 - Bilateral tubal occlusion
 - Vasectomized male partner
- Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success. See also the definition of sterile male below.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
- Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient’s usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception. If used, this method must be combined with another acceptable method listed above.

Patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well.

Definition of “Sterile Man”

For the purposes of this study, a sterile man is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility. Men with known “low sperm counts” (consistent with “sub-fertility”) are not to be considered sterile for purposes of this study.

Definitions of “Women of Childbearing Potential,” “Women of No Childbearing Potential”

As defined in this protocol, “women of childbearing potential” are female patients who are physiologically capable of becoming pregnant.

Conversely, “women of no childbearing potential” are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
 - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
 - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 mIU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If a follicle-stimulating hormone measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from [Clinical Trials Facilitation Group 2014](#).

Signature Page

Approval with eSignature	 Clinical Development 13-Jun-2024 05:53:47 GMT+0000
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