Official Protocol Title:	A Phase 1 clinical study of nemtabrutinib (MK-1026) in Japanese participants with hematological malignancies (BELLWAVE-002)
NCT Number:	NCT05673460
Document Date:	17-Jun-2025

TITLE PAGE

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Protocol Title: A Phase 1 clinical study of nemtabrutinib (MK-1026) in Japanese participants with hematological malignancies (BELLWAVE-002)

Protocol Number: 002-04

Compound Number: MK-1026

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	05673460
EU CT	Not applicable
EudraCT	Not applicable
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WHO	Not applicable
UTN	Not applicable
IND	Not applicable

Approval Date: 17 June 2025

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	17-JUN-2025	To update the follow-up period of Survival Follow-up Contacts.
Amendment 3	26-OCT-2023	To incorporate changes to reflect that concomitant use of CYP3A strong inhibitors could potentially result in a clinically meaningful increase in nemtabrutinib systemic exposure, and to include CYP3A strong inhibitors as exclusionary and prohibited during study participation as a preventative measure.
Amendment 2	20-OCT-2022	To incorporate changes requested by PMDA and correct minor errors.
Amendment 1	18-Aug-2022	To update RP2D, provide rationale for RP2D and reflect RP2D to study design.
Original Protocol	02-MAY-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To update the follow-up period of Survival Follow-up Contacts.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Following text is added to update the follow-up period of Survival Follow-up Contacts: "After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required."	To update the follow-up period of Survival Follow-up Contacts.
Section 1.3.1, Dose Escalation Part	Following text is added to update the follow-up period of Survival Follow-up Contacts: "After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required."	See rationale for section 1.1.

Section Number and Name	Description of Change	Brief Rationale
Section 4.1, Overall Design	Following text is added to update the follow-up period of Survival Follow-up Contacts: "After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required."	See rationale for section 1.1.
Section 8.11.6, Survival Follow-up Contacts	Following text is added to update the follow-up period of Survival Follow-up Contacts: "After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required."	See rationale for section 1.1.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 4.2.1.5, Planned Exploratory Biomarker Research	Updated the language to clarify regarding the biomarker research.	To align with the latest sponsor guidance.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Updated the reporting requirements regarding the potential DILI/DILI events.	To include the requirements to report the all potential DILI event as an ECI and SAE.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Updated the reporting requirements regarding the potential DILI/DILI events.	See rationale for section 8.4.1.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Updated the note about the reporting process.	To meet EU CTR requirements.
Section 8.4.7, Events of Clinical Interest	Updated the reporting requirements regarding the potential DILI/DILI events.	See rationale for section 8.4.1.
Section 10.1.1 Code of Conduct for Clinical Trials	Updated the text throughout the section.	To align with the company latest language.
Section 10.1.3, Data Protection	Added the last sentence to clarify the rule of data protection.	To include the information regarding the data protection.
Section 10.1.5, Compliance with Study Registration and Results Posting Requirements	Added the text regarding a summary of the study results.	To include the information regarding the EMA Clinical Trial Regulation 536/2014.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.7, Data Quality Assurance	Added the text regarding the retention period.	To include the information regarding the EU CTR.
Section 10.3.3, Definition of SAE	Added the reporting requirement regarding all potential DILI event.	See rationale for section 8.4.1.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1 clinical study of nemtabrutinib (MK-1026) in Japanese participants with hematological malignancies (BELLWAVE-002)

Short Title: A Phase 1 clinical study of nemtabrutinib in Japanese participants with hematological malignancies

Acronym: MK-1026-002

Hypotheses, Objectives, and Endpoints:

Hypothesis testing will not be performed in this protocol.

All objectives and endpoints apply to Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of treatment with nemtabrutinib	Dose limiting toxicities (DLTs) Adverse events (AEs) Discontinuing study treatment due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the PK profile of nemtabrutinib	PK parameters including AUC, Cmax, Tmax and Cmin in plasma
To evaluate objective response rate (ORR) and duration of response (DOR) following administration with nemtabrutinib for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) participants per iwCLL criteria 2018, for Waldenström's Macroglobulinemia (WM) /Lymphoplasmacytic lymphoma (LPL) participants per International Workshop on WM (IWWM) 2014 and for mature B-cell neoplasms participants other than CLL/SLL/WM/LPL per Lugano criteria 2014 as assessed by investigator	CLL/SLL participants: - Objective response (OR): complete response (CR), or complete response with incomplete bone marrow recovery (CRi), or nodular partial response (nPR), or partial response (PR) WM/LPL participants: - OR: CR, very good partial response (VGPR), or PR Mature B-cell neoplasms participants other than CLL/SLL/WM/LPL: - OR: CR or PR All participants: - DOR, defined as the time from the first documented evidence of an objective response until disease progression or death due to any cause, whichever occurs first

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	B-cell lymphoma
Population	Participants with mature B-cell neoplasms
Study Type	Interventional
Intervention Model	Single Group This is a multi site dose escalation study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 38 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 6 to 12 participants will be enrolled.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Nemtabrutinib (MK-1026)	Nemtabrutinib (MK-1026)	5 mg or 20 mg	45 mg (DL 1)	Oral	QD	Test Product
Nemtabrutinib (MK-1026)	Nemtabrutinib (MK-1026)	5 mg or 20 mg	65 mg (DL2)	Oral	QD	Test Product

Abbreviations: DL=dose level; QD=once daily.
Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-1026 and ARQ 531.

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final contact. After a screening phase of 28 days, each participant will receive assigned intervention as defined in the protocol. In or after cycle 4, participants receiving 45 mg of nemtabrutinib may be escalated to 65 mg if the tolerability is confirmed at 65 mg of nemtabrutinib and at the discretion of the investigator after discussion with the participant, upon the consultation with sponsor. After the end-of-treatment, each participant will be followed for 30 days for safety. Participants will then enter either efficacy FU (for those who withdraw from treatment without disease progression and have not received new anticancer therapy) or survival FU. After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

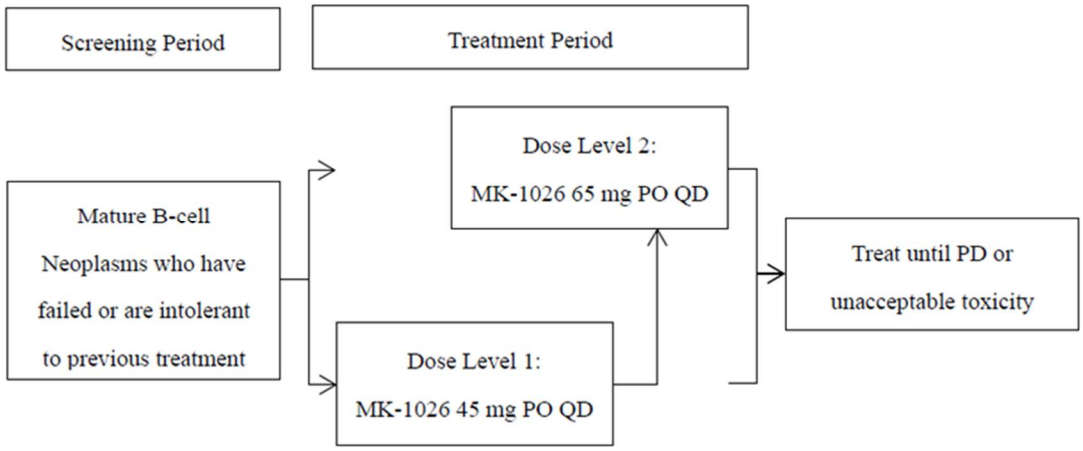
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Abbreviations: PD=progression disease; PO=orally; QD=once daily.

3 to 6 participants per dose level will be enrolled according to a mTPI design. See Sections 4.1 and 4.3.2.

1.3 Schedule of Activities

1.3.1 Dose Escalation Part

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Administrative Procedures														
Informed Consent	X													Informed consent must be obtained prior to any protocol-specific procedures.
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X	X												At Visit 2, site personnel should add the treatment number to the participant identification card.
Demographic and Medical History, including Prognostic profile	X													Refer to Section 8.1.6 for details regarding prognostic profile.
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X			

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Nemtabrutinib Dispensing		X				X	X	X	X					Nemtabrutinib tablets will be administered daily by mouth under fasted condition (either 1 hour prior to, or 2 hours after the meal). Refer to Section 8.1.10.1 for details regarding timing of dose administration.
Nemtabrutinib Return Compliance						X	X	X	X	X				
Efficacy Procedures														
Treatment Response Assessments	X	←											→	Imaging and treatment response assessments are required every 12 weeks (±7 days) and should follow calendar days from C1D1. Imaging frequency can be decreased to every 24 weeks (±7 days) starting the fourth year on study. Refer to Section 8.2 for

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
														details. No further PET scans are required for participants with B-cell malignancies (except CLL/SLL/WM/LPL), which are not FDG-avid at baseline, unless clinically indicated. For FDG-avid participants with B-cell malignancies (except CLL/SLL/WM/LPL) at baseline, PET is required at baseline, Weeks 12 and 24, to confirm CR or as clinically indicated.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes:
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
MRD (CLL/SLL who achieve a CR only)		←							→					MRD (in PB and if available, BM) to be obtained q12W (±7 days) from CR confirmation until progression. The frequency can be decreased to every 24 weeks (±7 days) starting the fourth year on study. Submitting the samples to Central laboratory is required.
Cryoglobulins (WM/LPL participants only)	X	←							→					To be performed at each response assessment visit and if clinically indicated.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes:
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Assessment of B Symptoms	X	←							→					To be performed every 12 weeks (±7 days) and should follow calendar days from C1D1. The frequency can be decreased to every 24 weeks (±7 days) starting the fourth year on study.
Survival Follow-Up		←							→				X	Survival information (vital status) may be requested by the Sponsor at any time during the study. After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Subsequent antineoplastic therapy status										X	X	X	X	Any change in new treatment will be collected. After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required.
Safety Procedures														
Adverse Event monitoring		X	X	X	X	X	X	X	X	X	X			Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention or 30 days after the last dose of study intervention if the participant initiates new anticancer therapy, whichever comes first.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
														When clinic visits are conducted every 3 cycles, the site will contact the participant every cycle to monitor and record AEs.
Physical Examination	X	X	X	X	X	X	X	X	X	X	X			A complete physical examination will be conducted at screening only. For subsequent cycles, a directed physical examination will be performed.
Hight	X													
Weight	X	X	X	X	X	X	X	X	X	X	X			
Vital Sign (pulse, respiratory rate, blood pressure, temperature), SpO_2 measurement	X	X	X	X	X	X	X	X	X	X	X			The measurement of SpO_2 is performed by the investigator or designee by the standard method in each study site.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X				Screening assessment to be performed within 7 days prior to the first dose of study intervention.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Triplicated 12-lead ECG	X	See Table 1								X				Post Cycle 3, ECG assessment only required where clinically indicated.
DLT evaluation		X	X	X	X									
Laboratory Procedures														
Hematology, Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X			Screening assessment to be performed within 7 days prior to the first dose of study intervention.
Tumor Lysis Syndrome (TLS) Monitoring (High Risk Participants only)		See Table 1												See Section 8.1.10.
Urinalysis	X													Screening samples must be taken within 7 days prior to the first dose of study intervention. Postscreening sample only required if clinically indicated.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Pregnancy Test (WOCBP only)	X	X				X	X	X	X	X	X			WOCBP require negative test prior to allocation. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. Pregnancy tests should be performed monthly and/or as per local regulations. Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
β2 Microglobulin	X	X				X	X	X	X					
Serum Immunoglobulin	X	X				X	X	X	X					For IgG, IgA, and IgM
Creatinine clearance	X													
Infection Testing (HCV, HBV, HIV)	X	← Participants with a history of HBV →												Monitoring is required for participants with a history of HBV, if clinically indicated during treatment phase.
Pharmacokinetics/Pharmacodynamics/Biomarkers (Central)														
Blood Samples for PK		See Table 1												
Blood Samples for PD		See Table 1						X*						For C1 to C3: See Table 1 *: Predose Samples will be collected on C4D1, C5D1 and C6D1.

Study Period	Screening Phase	Treatment Phase								End of Treatment (EOT)	Post-Treatment			Notes: Each cycle consists of 4 weeks (28 calendar days). If dosing is interrupted or delayed see Section 6.1.1 for details.
Treatment Cycle/Day		C1				C2	C3	C4~ C27	C28+		Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
		1	8	15	22	1	1	1	1					
Visit Number/Frequency	1	2	3	4	5	6	7	Every cycle	Every 3 cycles	At treatment discontinuation	30 days after post discontinuation	Every 12 weeks	Every 12 weeks	
Window (days)	-28 to -1	0	0	0	0	±3	±3	±3	±3		+7	±7	±14	
Blood for BTK C481 mutation analysis (CLL/SLL participants only)		X												Predose sample required.
Blood for Genetic Analysis		X												Predose sample required. See Section 8.8

Abbreviations: BM=bone marrow; BTK=Bruton's tyrosine kinase; CLL=chronic lymphocytic leukemia; CR=complete response; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EOT=end of treatment; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ID=identification; Ig=immunoglobulin; LPL=lymphoplasmacytic lymphoma; MRD=minimal residual disease; PB=peripheral blood; PD=pharmacodynamics; PK=pharmacokinetics; q12w=every 12 weeks; SLL=small lymphocytic lymphoma; WM=waldenström's macroglobulinemia; WOCBP=women of childbearing potential.

Table 1 Collection schedule of PK, PD samples, ECG (Triplicate) assessments and TLS Monitoring (Cycles 1 to 3)

Study Period	Treatment phase																		Notes: Each cycle consists of 4 weeks (28 calendar days)
Treatment Cycle/Day	C1D1							C1 D2	C2D1							C2 D2	C3D1		
Visit Number	2								6								7		
Time frame (hours)	Pre dose	Post dose							Pre dose	Post Dose							Pre dose	Post dose	
		1	2	4	6	8	10	24		1	2	4	6	8	10	24		2	4
Blood Samples for PK	X[*1]	X	X	X	X	X	X	X[*2]	X[*2]	X	X	X	X	X	X	X[*2]	X[*2]	X	X
Blood Samples for PD	X[*1]		X	X				X[*2]	X[*2]								X[*2]		
Triplicated 12-lead ECG	X		X					X	X		X					X	X		X

*1: Prior to first dose
*2: Within 120 minutes prior to next dose
Other timepoints: ±10 minutes

All Predose triplicate ECGs will be collected within 30 minutes prior to predose PK sample collection. All postdose triplicate ECGs will be collected within 10 minutes prior to postdose PK sample collection.
Participant should refrain from the food from ECG assessment at pre-dose on Day 1 of each Cycle until the completion of ECG assessment at 2 hour (C1D1 and C2D1) or 4 hour (C3D1) post-dose.

Study Period	Treatment phase																		Notes: Each cycle consists of 4 weeks (28 calendar days)
Treatment Cycle/Day	C1D1							C1 D2	C2D1							C2 D2	C3D1		
Visit Number	2								6								7		
Time frame (hours)	Pre dose	Post dose							Pre dose	Post Dose							Pre dose	Post dose	
		1	2	4	6	8	10	24		1	2	4	6	8	10	24		2	4
TLS Monitoring (High Risk Participants only)	X					X		X												For high-risk participants, hematology and serum chemistry samples will be taken predose on C1D1 and at 8 and 24 hours C1D2 postdosing. Post Cycle 1 monitoring only required where clinically indicated.
Abbreviations: ECG=electrocardiogram; PD=pharmacodynamics; PK=pharmacokinetics; TLS=tumor lysis syndrome.																			

2 INTRODUCTION

Nemtabrutinib (MK-1026; formerly ARQ 531) is an orally available reversible non-covalent ATP competitive inhibitor of BTK.

Nemtabrutinib is a small molecule which is an inhibitor of BTK and multiple clinical trials are ongoing for participants with Mature B-cell neoplasms. This is a Phase 1, open-label, multisite, dose escalation study to evaluate the safety and the tolerability of nemtabrutinib in Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment.

2.1 Study Rationale

BTK is a key regulator of the B-cell receptor signaling pathway that mediates signaling from the cell surface to the cytoplasm and into the nucleus. BTK is expressed in the cells of all hematopoietic lineages except for T and plasma cells, and regulates all aspects of B-cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration. It is known that activation of the B-cell BTK signaling pathway regulates B-cell survival and mediates B-cell growth and adhesion. The rationale for use of BTKi is provided because BTKi may plays the role of suppressing the growth of B-cell malignancy.

The purpose of this study is to evaluate the safety and tolerability, as well as PK and preliminary efficacy, of nemtabrutinib, an orally available reversible non-covalent ATP competitive inhibitor of BTK, in Japanese participants with Mature B-cell neoplasms.

2.2 Background

Refer to the IB for detailed background information on nemtabrutinib.

2.2.1 Pharmaceutical and Therapeutic Background

Nemtabrutinib is a reversible non-covalent ATP competitive inhibitor of BTK that does not require the C481 residue of BTK for binding and inhibition of kinase activity. Although a number of BTK inhibitors eg, ibrutinib are currently approved in Japan for the treatment of B-cell malignancies, resistance to these therapies is known to develop [Zhang, S. Q., et al 2015]. One mechanism of resistance is the development of a mutations at the C481 residue of BTK gene. Since nemtabrutinib does not require this residue for binding and inhibition of activity, it can target both the wild-type and C481 mutant forms of BTK gene and therefore offers a potential new treatment for BTK inhibitor-resistant B-cell malignancies in patients who harbor the BTK-C481 mutation.

To date, nemtabrutinib has demonstrated a manageable safety profile, long PK half-life, and preliminary antitumor activity in BTK-C481 mutant B-cell malignancies patients. A comprehensive review of nonclinical and clinical data is included in the IB.

Mature B-cell neoplasms have been classified according to the morphology and nature of cancer cells, including chronic lymphocytic leukemia (CLL)/small cell lymphoma (SLL), Richter's syndrome, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL),

mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL) and waldenström macroglobulinemia (WM)/ lymphoplasmacytic lymphoma (LPL).

CLL and SLL are different manifestations of the same malignant cells and are managed in the same way. The major difference is a significant number of the abnormal lymphocytes are also found in the bone marrow and peripheral blood in CLL, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes and bone marrow [Zelenetz, A. D., et al 2015]. The term of CLL and SLL are used interchangeably and often refer to the same patient population. Although CLL is the most common type of leukemia in western countries [Wierda, W. G., et al 2019] [Butler, T. and Gribben, J. G. 2010], this is a rare disease in Japan. CLL is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen. Many of them show a slow progression, but some get worsened rapidly and have a poor prognosis. Especially, deletions of the short arm of chromosome 17 (17p) are found in 5% to 8% of treatment-naïve patients. These deletions almost always include the prominent tumor suppressor gene TP53, and these patients show marked resistance to chemotherapies [Hallek, M. 2019]. In Japan, BTK inhibitors and rituximab-combination chemotherapy are used as standard of care, but the prognosis is poor for refractory patients, and development of new drugs is required.

Richter's transformation is a life-threatening complication of CLL and transformation to rapidly progressing tumors, which is present in the preceding CLL clone and with newly acquired gene abnormalities. The development of Richter's transformation is characterized by the onset of B symptoms, rapid growth of lymphadenopathy, extranodal disease, significant elevations of LDH, and associated multiorgan dysfunction from invasive or obstructive processes [Allan, J. N. 2019]. Most cases represent transformation to DLBCL and are known as chemo-refractory. Because treatment option follows the transformed tissue diagnosis, chemotherapy is also often administrated according to DLBCL. Current chemotherapy approaches have done little to impact upon outcomes and a standard of care is not established.

MCL is a distinct subtype of NHL, accounting for 10% of lymphoma cases, and showing that the cell surface characteristics is similar to B-cells constituting the mantle layer of lymph node follicles. Patients usually present with extensive disease, including widespread lymphadenopathy and bone marrow involvement. MCL is not curable, and relapse is common. A standard of care for first line treatment is not established, and there is an unmet medical need for effective therapies in Japan.

MZLs are derived from B-cells, which consist of a diverse subtype. MZL originates from memory B lymphocytes harbored in the marginal zone of secondary lymphoid follicles present in the spleen, mucosa-associated lymphoid tissues, and rarely lymph nodes. They are classified into extra nodal marginal zone lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma according to the site of occurrence. Although there are many subtypes and no standard treatment has been established, nodal marginal zone lymphoma, for example, is often treated with chemotherapy according to FL. The development of MZL is associated with chronic BCR activation in most cases, which has implications of efficacy for BTK inhibition [Denlinger, N. M., et al 2018].

FL is the second most common NHL, comprising 17% to 22% of cases. Data suggests that the tumor microenvironment may contribute to the development and progression of FL, and the interaction of FL cells with immune cells in the tumor may influence the clinical course and response to therapy [Gopal, A. K., et al 2018]. Most patients are initially treated with chemoimmunotherapy or rituximab; however, despite good initial responses, FL is incurable because most patients experience relapses many times. A standard of care for relapse FL is not established in Japan, and new treatment option is desired.

WM/LPL is a rare subtype of B-cell lymphoma that is characterized by elevated serum levels of IgM and infiltration of the bone marrow and other organs by IgM-producing clonal lymphoplasmacytic cells. Rituximab monotherapy and rituximab in combination with alkylating agents, proteasome inhibitors, nucleoside analogs, and more recently ibrutinib are frequently used in these patients [Dimopoulos, M. A., et al 2018]. In WM/LPL, it is suggested that tumor-cell survival is influenced through BTK-triggered activation of NF-κB, and BTK inhibitor is considered as a new treatment option.

DLBCL is the most frequent disease type, accounting for more than 30% of all NHLs in Japan. DLBCL is a heterogeneous group of disorders that present with a variety of pathophysiologisies. In addition to its initial presentation as a DLBCL, there are also cases of histological transformation from other low-grade B-cell lymphomas. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) is recommended as the standard therapy treatment for newly diagnosed DLBCL. On the other hand, since there is no evidence other than high-dose chemotherapy (HDC/AHSCT) combination with autologous hematopoietic stem-cell transplantation for refractory or recurrence DLBCL, the superiority or inferiority of each salvage chemotherapy is not clear, and DHAP therapy and (R-) ESHAP therapy are chosen. Allogeneic hematopoietic stem-cell transplantation, Anti-CD19 CAR T-cell therapy, Loncastuximab Tesirine-lpyl and Selinexor are the possible treatment options for patients with recurrent/relapse DLBCL after HDC/AHSCT, but there are few evidence of its effectivity.

Thus, there is still a high unmet medical need for treatment of recurrence or refractory B-cell neoplasms though there are treatments depending on the morphology and nature of the different cancer cells.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Pharmacology

Studies to date have not revealed any safety pharmacology issues with nemtabrutinib treatment in vitro or in vivo. Refer to the IB for additional information.

2.2.2.2 Preclinical Studies

A comprehensive review of nonclinical data is included in the IB.

Nonclinical Pharmacology Studies

The pharmacological activity of nemtabrutinib has been studied in both in vitro and in vivo models. Nemtabrutinib is a potent inhibitor of BTK and does not require C481 residue for binding to BTK. Nemtabrutinib has displayed distinct kinase selectivity profile, showing specificity for additional kinases that are oncogenic drivers in B-cell malignancies. In-vitro treatment of patient derived CLL cells with nemtabrutinib decreased BTK-mediated functions including BCR signaling, viability, migration, CD40 and CD86 expression, and NF-κB gene transcription. In vivo, nemtabrutinib was found to increase survival over ibrutinib in a murine Eμ-TCL1 engraftment model of CLL and a murine Eμ-MYC/TCL1 engraftment model resembling Richter's transformation. Additionally, nemtabrutinib inhibited CLL cell survival and suppressed BCR-mediated activation of C481S BTK and PLCγ2 mutations which facilitate clinical resistance to ibrutinib. In DLBCL tumor models, nemtabrutinib suppressed BCR signaling, downregulated the expression of c-MYC, BCL-6, antiapoptotic MCL-1 proteins and showed potent antitumor activity in the mouse xenograft tumor models of ABC and GCB DLBCL subtypes.

Nonclinical Pharmacokinetic Characteristics and Metabolism of nemtabrutinib

Overall, nemtabrutinib showed [redacted] Nemtabrutinib showed low clearance across species, [redacted] volume of distribution. The half-life following IV administration varied across species with values of [redacted] in rats, dogs, and monkeys, respectively. Nemtabrutinib was highly bound to [redacted]

[redacted]

CCI

[redacted]

Nonclinical Toxicology and Safety Pharmacology

CCI

[redacted]

2.2.2.3 Ongoing Clinical Studies

The nemtabrutinib 2 clinical program includes two ongoing studies exploring the use of nemtabrutinib in various hematological malignancies:

MK-1026-001 (BELLWAVE-001)

This is an ongoing open-label, single arm, Phase 1/2 dose escalation study of nemtabrutinib in selected participants with relapsed or refractory hematologic malignancies. The study consists of 2 parts: Part 1 dose escalation (exploring 5 to 75 mg daily dosing) and Part 2 cohort expansion. The results demonstrate that nemtabrutinib has a manageable safety profile and preliminary antitumor activity in CLL/SLL participants with and without BTK-C481 mutations and NHL participants. The study will assess ECG at PK timepoints to determine whether further information is needed to monitor ECGs at more frequent intervals, and the effect of food on the rate and extent of nemtabrutinib absorption. The results of these

evaluations are not yet available but may result in amendments to the MK-1026-002 (BELLWAVE-002) assessments and administration instructions.

As of the data cutoff of 08-APR-2022, 138 participants with B-cell malignancies have been enrolled and 136 treated (median age was 66.0 years) in the study. Participants were heavily pretreated (including prior BTK and BCL2 inhibitors). A total of 107 (78.7%) treated participants discontinued the study treatment; primarily due to clinical disease progression (23.5%) or radiological disease progression (19.1%). Of the 136 treated participants, 112 participants (82.4%) received 65 mg nemtabrutinib and 57 were CLL/SLL participants. The CLL/SLL population was heavily pretreated; median number of prior lines of therapy was 4. In the CLL/SLL population, 94.7% has received prior BTKi therapy and 42.1% has received both prior BTKi and BCL2i therapy.

A total of 6 participants treated at 65 mg QD reported 8 DLTs, 7 were considered related to nemtabrutinib and 1 not related per investigator. Of these 6 participants, 1 participant experienced neutropenia (Grade 4), 1 participant experienced neutropenia twice (Grade 2 and Grade 3), 1 participant experienced thrombocytopenia (Grade 4), 1 participant experienced erythematous rash (Grade 3), 1 participant experienced pruritus (Grade 3) and maculopapular rash (Grade 3), and 1 participant experienced supraventricular tachycardia (Grade 3).

The most common (≥10%) treatment-related AEs observed across all doses included dysgeusia (18.4%), neutrophil count decreased (17.6%), nausea and fatigue (both at 12.5% each), and platelet count decreased (10.3%). SAEs were reported in 47.1% participants, of which, 8.1% were assessed by the investigator as treatment related. SAEs that were assessed by the investigator as related to nemtabrutinib included 2 cases of rash maculo-papular and singular events of febrile neutropenia, bradycardia, supraventricular tachycardia, diarrhea, cellulitis, blood creatinine increased, lipase increased, neutrophil count decreased, drug reaction with eosinophilia and systemic symptoms and rash erythematous. A total of 28 (20.6%) participants discontinued study treatment due to an AE; 16 (11.8%) were considered to be related to study treatment. There were 7 reported deaths; none were assessed as related to nemtabrutinib or met the definition of DLT. Of the 7 deaths, 3 were due to acute respiratory failure and 1 each from respiratory failure, dyspnea, fall and sepsis.

The median follow-up for the 57 CLL/SLL treated with 65 mg nemtabrutinib was 8.1 months (range 0.1 to 38.8 months). The efficacy results showed ORR of 56.1% (95% CI: 42.4, 69.3). The ORR excluding PRL was 29.8%. In addition, participants responded to nemtabrutinib treatment regardless of whether the BTK-C481 mutation was present or not; expansion phase Cohort A (25 CLL/SLL with the present of BTK-C481 mutation) ORR of 60.0% and Cohort B (10 CLL/SLL with the absence of BTK-C481 mutation) ORR of 40.0%, respectively. Of the CLL/SLL participants, 2 (3.5%) had a complete remission (1 participant in the dose escalation phase and 1 participant in Cohort B in the expansion phase). The number of participants achieving a PR was 15 (26.3%) or SD was 16 (28.1%).

Overall, preliminary data demonstrated that nemtabrutinib has a manageable safety profile, favorable PK profile and has demonstrated preliminary signs of antitumor activity in CLL/SLL including both ibrutinib-resistant BTK-C481S mutant CLL and B-cell NHL participants.

MK-1026-003 (BELLWAVE-003)

This is a Phase 2 open-label, dose escalation and confirmation followed by a single group parallel study to evaluate the safety and efficacy of nemtabrutinib in participants with hematologic malignancies, including CLL/SLL, Richter's transformation, MZL, MCL, FL, and WM. The study is divided into 2 parts; dose escalation and confirmation (Part 1) and cohort expansion (Part 2). Part 1 consisted of dose escalation (starting with 80 mg QD dose level) and confirmation of the dose of nemtabrutinib in CLL/SLL participants to establish the RP2D of nemtabrutinib, which was assessed as a primary objective. Following determination of a RP2D, this study will proceed with Part 2 in 8 expansion cohorts in participants with various hematological malignancies.

As of the database cutoff date of 24-MAY-2022, a total of 38 participants had been treated with at least 1 dose of nemtabrutinib 80 mg QD in the study (23 participants with CLL/SLL, 15 participants with NHL as per data cutoff). The median follow up duration was 2.1 months (range 0.2 to 12.9 months) for the entire population and 4.4 months (range 1.0 to 12.9 months) for the CLL/SLL population. The median age for participants enrolled was 69.0 years. Ten participants have discontinued treatment: 3 due to progressive disease and 6 due to individual AEs of haematoma, COVID-19, septic shock, drug eruption, hepatic function abnormal, subcapsular splenic haematoma, thrombocytopenia and cardiac failure. The majority (78.3% [18 out of 23]) of the participants with CLL/SLL have received at least 3 prior lines of therapy, and 69.6% (16 out of 23) participants have received both BTKi and BCL-2i therapies prior to entering this study.

Out of 24 DLT-evaluable participants, 5 participants reported DLTs including cardiac failure (Grade 3 in 1 participant), hepatic function abnormal (Grade 3 in 1 participant), drug eruption (Grade 3 in 2 participants), and hematoma (Grade 3 in 1 participant) and intracranial hemorrhage (Grade 5 in 1 participant). All DLTs occurred within the 8-week DLT observation period, except 1 occurrence of Grade 3 hematoma (occurring on Study Day 59) and Grade 5 intracranial hemorrhage (occurring on Study Day 61). Both cases of drug eruptions and the first occurrence of hematoma resolved after 6 days to 2 weeks. The other DLTs (second occurrence of hematoma, hepatic function abnormal, and cardiac failure) had not resolved at the time of the data extraction. Although the current DLT rate is 20.8% (5 out of 24 participants), this is below the target DLT rate of 30%, new DLTs occurred at the 80 mg dose level that were not observed at the 65 mg dose level, except for drug eruption. Additionally, 1 participant experienced Grade 3 urinary tract infection that was deemed a DLT; however, due to data entry error, this DLT was not included in this data extraction. This event occurred on study day 23 and resolved after 1 week. The corrected DLT rate including this additional DLT participant was 25% (6 out of 24 DLT-evaluable participants).

The most common AEs (>10%) were constipation (26.3%); peripheral edema (21.1%); dysgeusia (18.4%); anemia and fatigue (15.8% each); pyrexia (13.2%); and ALT increased, AST increased, COVID-19, cough, and upper respiratory tract infection (10.5% each). Of the 38 participants, 24 (63.2%) had at least 1 Grade 3 to 5 TEAE, of which 15 (39.5%) were assessed by the investigator as related. Grade 3 to 5 TEAEs occurring in 5% participants included anemia (13.2%); COVID-19, sepsis, and thrombocytopenia (7.9% each); and drug eruption, febrile neutropenia, GGT increased, hematoma, hepatic function abnormal,

neutrophil count decreased, and urinary tract infection (5.3% each). SAEs occurred in 16 (42.1%) of participants as of the data extraction, of which 6 (15.8%) were assessed by the investigator as treatment related. SAEs that occurred in ≥5% of participants were COVID-19 and sepsis (7.9% each); and pneumonia, drug eruption, and hematoma (5.3% each). A total of 6 (15.8%) deaths were reported at the time of the data extraction. Four (4) participants (10.5%) experienced AEs with a fatal outcome, sepsis, septic shock, tumor lysis syndrome, and intracranial hemorrhage. Only intracranial hemorrhage was considered related to study treatment per investigator's assessment. An additional 2 participants died of disease progression after stopping study treatment at 33 days and 39 days.

A total of 23 participants with CLL/SLL participants were evaluable for efficacy. The efficacy results showed ORR of 39.1% (95% CI: 19.7, 61.5) (9 participants out of 23). The ORR excluding PRL was 26.1% (6 participants out of 23). A total of 6 participants achieved a partial response (26.1%), 3 participants achieved PRL (13.0%), and 4 participants achieved SD (17.4%).

Based on the totality of data reviewed (including safety, efficacy, PK, PD, and nonclinical toxicology), the benefit/risk profile favors 65 mg QD. Therefore, the RP2D for nemtabrutinib is 65 mg QD. Further details are provided in Section 4.3.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. Current experience with nemtabrutinib in the clinical setting is summarized in Section 2.2.2.3 and the nemtabrutinib (MK-1026) IB.

The proposed study will evaluate the safety and the tolerability of nemtabrutinib in Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment. As described in Section 2.2.1, nemtabrutinib is a noncovalent ATP competitive inhibitor of BTK. Preclinical studies and clinical data (see Section 2.2.2) demonstrate encouraging antitumor activity of nemtabrutinib, which warrants further investigation. Given the high risk of progression of disease and development of resistance to currently available BTKi's in patients with hematological malignancies, there is an unmet medical need for more effective and tolerable treatment.

To date, 174 participants have received nemtabrutinib at various doses (5 mg to 80 mg). For MK-1026-001 (BELLWAVE-001), the most common (≥25%) TEAEs were fatigue (33.8%), constipation (33.1%), dysgeusia (31.6%), pyrexia (29.4%), peripheral edema, neutrophil count decreased, and cough (28.7% each), nausea and hypertension (both 27.2% each). For MK-1026-003 (BELLWAVE-003), the most common (≥15%) TEAEs were constipation (26.3%), oedema peripheral (21.1%), dysgeusia (18.4%), anemia and fatigue (both 15.8% each). Common SAEs included pyrexia (6.6%), pneumonia (6.6%), and febrile neutropenia (5.1%) in the MK-1026-001 (BELLWAVE-001) study; sepsis and COVID-19 (both 7.9% each), pneumonia, drug eruption and haematoma (5.3% each) in the MK-1026-003 (BELLWAVE-003) study.

Participants taking nemtabrutinib should be monitored for signs and symptoms of hemorrhages (including major and fatal bleeds), hematopoietic cytopenias, hypertension, infections, hypersensitivity, and cardiac arrhythmias. These events are considered either identified risks (based on available safety data for nemtabrutinib as per data cut off date for the IB) or potential risks (based on the class effects of BTK inhibitors). Other BTK inhibitors have reported life-threatening and fatal hemorrhagic AEs and infections.

Risks and benefits of anticoagulant or anti-platelet therapies should be considered when co-administered with nemtabrutinib due to risk of hemorrhage.

Additional details regarding specific benefits and risks for participants participating in this clinical study are summarized in the nemtabrutinib (MK-1026) IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypothesis testing will not be performed in this protocol.

All objectives and endpoints apply to Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of treatment with nemtabrutinib	Dose limiting toxicities (DLTs) Adverse events (AEs) Discontinuing study treatment due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the PK profile of nemtabrutinib	PK parameters including AUC, Cmax, Tmax and Cmin in plasma
To evaluate objective response rate (ORR) and duration of response (DOR) following administration with nemtabrutinib for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) participants per iwCLL criteria 2018, for Waldenström's Macroglobulinemia (WM) /Lymphoplasmacytic lymphoma (LPL) participants per International Workshop on WM (IWWM) 2014 and for mature B-cell neoplasms participants other than CLL/SLL/WM/LPL per Lugano criteria 2014 as assessed by investigator	CLL/SLL participants: - Objective response (OR): complete response (CR), or complete response with incomplete bone marrow recovery (CRi), or nodular partial response (nPR), or partial response (PR) WM/LPL participants: - OR: CR, very good partial response (VGPR), or PR Mature B-cell neoplasms participants other than CLL/SLL/WM/LPL: - OR: CR or PR All participants: - DOR, defined as the time from the first documented evidence of an objective response until disease progression or death due to any cause, whichever occurs first
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
For CLL/SLL participants: To evaluate the ORR including response category of partial response with lymphocytosis (PRL) following administration with nemtabrutinib per iwCLL criteria 2018 as assessed by investigator	Objective response including PRL, defined as CR, CRi, nPR, PR, or PRL

To evaluate progression-free survival (PFS) and overall survival (OS) following administration with nemtabrutinib for CLL/SLL participants per iwCLL criteria 2018, for WM/LPL participants per IWWM 2014 and for mature B-cell neoplasms participants other than CLL/SLL/WM/LPL per Lugano criteria 2014 as assessed by investigator	PFS, defined as the time from first dose to the first documented disease progression or death due to any cause, whichever occurs first OS, defined as the time from the first dose of study treatment to death due to any cause
For CLL/SLL participants: To investigate the relationship between clinical outcomes which includes ORR, DOR, PFS and OS following administration with nemtabrutinib per iwCLL criteria 2018 as assessed by investigator, and BTK-C481 mutation status	OR: CR, CRi, nPR, or PR DOR, PFS and OS BTK-C481 mutation status
For CLL/SLL participants: To evaluate undetectable minimal residual disease (MRD) following administration with nemtabrutinib per iwCLL criteria 2018 as assessed by investigator	Undetectable MRD is defined as <1 leukemia cell per 10,000 cells (MRD $<10^{-4}$) in peripheral blood or bone marrow
For WM/LPL participants: To evaluate ORR including response category of minor response (MR) following administration with nemtabrutinib per IWWM 2014 as assessed by investigator	Objective response including MR, defined as CR, VGPR, PR, or MR
To evaluate pharmacodynamics following administration with nemtabrutinib	Serum CCL3 concentration
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1, open-label, multisite, dose escalation study of nemtabrutinib in Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment. This study will evaluate the safety, tolerability, PK and preliminary efficacy of nemtabrutinib.

The study design is shown in Figure 1. This study will enroll patients according to a modified toxicity probability interval (mTPI) design and perform dose escalation of nemtabrutinib at each predetermined dose levels (45 mg QD or 65 mg QD). To evaluate the DLT, participants will be enrolled to one dose level at the same time. Study medication will be administered at the following dose levels;

– Dose level 1 (DL1): 45 mg QD

– Dose level 2 (DL2): 65 mg QD

Details of DLT assessment schedules and rules are described in Section 4.3.2. The definition of DLTs is provided in Section 4.3.1. In principle, during DLT assessment period, participants will be hospitalized.

AEs will be evaluated by the investigator, according to criteria outlined in the NCI-CTCAE, version 5.0, to establish the safety and tolerability of nemtabrutinib monotherapy per the primary objective of this study.

Secondary objectives of this study are to evaluate PK following administration of nemtabrutinib and to evaluate ORR and DOR assessed by the investigator using assessment criteria of each disease as a preliminary efficacy evaluation. PFS and OS assessed by the investigator using assessment criteria of each disease are evaluated as tertiary/exploratory objectives.

Treatment response assessments may include computed tomography (CT)/magnetic resonance imaging (MRI) and/or positron emission tomography (PET) imaging, and laboratory assessments. Treatment response assessments will be performed during screening, every 12 weeks (±7 days), and every 24 weeks (±7 days) after 4 years and should follow calendar days from C1D1.

Patients will continue taking nemtabrutinib 45 mg or 65 mg QD until unacceptable toxicity, disease progression, or another discontinuation criterion described in Section 7.1 is met.

In or after cycle 4, participants receiving 45 mg of nemtabrutinib may be escalated to the 65 mg if the tolerability is confirmed at the 65 mg of nemtabrutinib and at the discretion of the investigator after discussion with the participant, upon the consultation with the sponsor.

Participants who discontinue treatment for reasons other than confirmed progressive disease will have posttreatment follow-up for disease status (including imaging) until progressive

disease, initiating a new anticancer therapy, withdrawing consent for study participation, pregnancy, or becoming lost to follow-up.

Participants who experience the confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks (84±14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required.

No interim analysis is planned for this study.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This is a Phase 1, open-label, multisite, dose escalation study designed to evaluate the safety and tolerability of nemtabrutinib, a non-covalent irreversible inhibitor of BTK, in Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment (either at least 2 prior regimens given in combination or sequentially or 1 prior BTK-containing regimen when a BTK inhibitor is approved as first line therapy). BTK inhibitors are approved for the treatment of CLL/SLL; however, resistance is known to develop to these irreversible inhibitors, with one of prevalent mechanism being the acquisition of BTK-C481 mutations. There is a need for more effective therapies for patients who have failed 1 or more prior therapies. Nemtabrutinib can inhibit wild-type BTK as well as the BTK-C481 mutant form of the enzyme. In the CLL/SLL indication resistance mutations occur in approximately 40 to 80% of patients following treatment with covalent, irreversible inhibitors (e.g., ibrutinib) [Gango, A., et al 2020] [Quinquenel, A., et al 2019] [Woyach, J. A., et al 2017] [Kanagal-Shamanna, R., et al 2019]. Data from the first-in-human Phase 1 study of nemtabrutinib has shown response in a variety of hematological malignancies, including CLL/SLL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Endpoint definitions are provided in Section 9.4.1.

Objective Response

OR is the secondary efficacy endpoint.

Treatment effect measured by OR can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship.

Treatment effect measured by OR can be a surrogate endpoint to support accelerated approval according to FDA guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry, Dec 2018). Nodular partial remission (nPR) has all the features of a CR but has lymphoid nodules in the marrow, which should be further evaluated. If immunohistochemistry conclusively shows the nodules are CLL cells, a response of "nPR" should be assigned. If analysis shows them to be composed of other histological types, it should be considered CR [Hallek, M., et al 2018].

Each hematological malignancy has specific response criteria that will be applied in the assessment of OR as summarized in Section 3.

Duration of Response

DOR is a secondary efficacy endpoint.

Improved DOR can result in a meaningful delay in disease progression as opposed to a temporary response without lasting benefit.

Exploratory Efficacy Endpoints

OS represents a precise and reliable measure of time to event endpoint. PFS is a surrogate endpoint that reflects tumor growth and includes deaths and therefore correlates to OS. Undetectable MRD is a surrogate endpoint for CLL and current literature suggests that there is an association between MRD negativity and OS in patients with CLL treated with chemoimmunotherapy. The therapeutic paradigm with small molecule inhibitors of the B-cell receptor signaling pathway and other novel products continue to rapidly evolve in this area [Food and Drug Administration 2020]. PRL represents a reduction in lymph nodes, splenomegaly and other markers of response with no sign of progression other than lymphocytosis, and has been used in other BTKi studies. Partial response with lymphocytosis is defined as a >50% reduction in lymphadenopathy and splenomegaly, with persistent lymphocytosis; often the blood lymphocyte counts are equal to or greater than those observed prior to therapy [Kipps, T. J., et al 2017]. Minor response (MR) is defined as 25 to 49% reduction in serum IgM levels [Dimopoulos, M. A., et al 2014].

4.2.1.2 Safety Endpoints

The primary objective of this study is to evaluate the safety and tolerability of nemtabrutinib in patients with Mature B-cell neoplasms who have failed or are intolerant to previous treatment in Japanese patients. The primary safety analysis will be based on participants who experience toxicities as defined by NCI-CTCAE version 5.0 criteria. Safety will be assessed by evaluating the toxicities and grades of toxicities experienced by participants who have received nemtabrutinib.

For AEs, attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.1.3 Pharmacokinetic Endpoints

The secondary objective of this study is to assess PK profile with single administration of nemtabrutinib. PK variables determined will include AUC, Cmax, Cmin, Tmax. and when possible t1/2. Blood samples for PK analysis will be drawn during the first three cycles of nemtabrutinib administration for each dose level. Additional unscheduled blood sample(s) for PK may be collected on any study day(s) upon agreement between the investigator and Sponsor.

4.2.1.4 Pharmacodynamic Endpoints

The BTK signaling biomarkers and/or other BCR signaling pathway related cytokines will be evaluated.

4.2.1.5 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (eg, blood components, tumor material, etc.) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to the following:

Germline genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations.

4.3 Justification for Dose

The starting dose is 45 mg, which is the highest dose in which no DLTs were observed in MK-1026-001 (BELLWAVE-001) study, to evaluate the safety and tolerability of nemtabrutinib for Japanese participants as this study is a first clinical trial for nemtabrutinib in Japan. The dose level will be escalated to 65 mg QD based on the dose escalation design if the dose level of 45 mg QD is tolerable. Further information on dose modifications is provided in Section 6.6.1.

Part 1 of MK-1026-003 (BELLWAVE-003) study consisted of dose escalation and dose confirmation to establish the RP2D of nemtabrutinib. Dose escalation was based on a modified toxicity probability interval design. Dose escalation and de-escalation decisions were based on the number of participants enrolled and number of DLTs observed. PK, PD,

efficacy and safety data for 23 participants with CLL/SLL (dosed with 80 mg) in the BELLWAVE-003 study (24-MAY-2022 data cutoff), and 138 CLL/SLL and NHL participants enrolled in the BELLWAVE-001 study (doses ranging from 5 to 75 mg), including 112 participants enrolled in the 65 mg arm (08-APR-2022 data cutoff), were used to determine the RP2D.

An evaluation of efficacy showed a clear dose-dependent increase in the ORR with doses up to 75 mg QD in the BELLWAVE-001 and a similar benefit at a dose of 80 mg QD in the BELLWAVE-003 study. A total of 112 participants received at least 1 dose of 65 mg nemtabrutinib in the BELLWAVE-001 study. A total of 57 participants treated with 65 mg nemtabrutinib had CLL/SLL. The median follow-up for the 57 CLL/SLL treated with 65 mg nemtabrutinib was 8.1 months (range 0.1 to 38.8 months). The efficacy results showed ORR of 56.1% (95% CI: 42.4, 69.3). The ORR excluding PRL was 29.8%. Of the CLL/SLL participants, 2 (3.5%) achieved a complete remission, 15 (26.3%) achieved a PR and 16 (28.1%) achieved SD.

A total of 6 participants treated at 65 mg QD reported 8 DLTs, 7 were considered related to nemtabrutinib and 1 not related per investigator. Of these 6 participants, 1 participant experienced neutropenia (Grade 4), 1 participant experienced neutropenia twice (Grade 2 and Grade 3), 1 participant experienced thrombocytopenia (Grade 4), 1 participant experienced erythematous rash (Grade 3), 1 participant experienced pruritus (Grade 3) and maculopapular rash (Grade 3), and 1 participant experienced supraventricular tachycardia (Grade 3).

The most common (≥10%) treatment-related AEs observed across all doses included dysgeusia (18.4%), neutrophil count decreased (17.6%), nausea and fatigue (both at 12.5% each), and platelet count decreased (10.3%). SAEs were reported in 47.1% participants, of which, 8.1% were assessed by the investigator as treatment related. SAEs that were assessed by the investigator as related to nemtabrutinib included 2 cases of rash maculo-papular and singular events of febrile neutropenia, bradycardia, supraventricular tachycardia, diarrhea, cellulitis, blood creatinine increased, lipase increased, neutrophil count decreased, drug reaction with eosinophilia and systemic symptoms and rash erythematous. A total of 28 (20.6%) participants discontinued study treatment due to an AE; 16 (11.8%) were considered to be related to study treatment. There were 7 reported deaths; none were assessed as related to nemtabrutinib or met the definition of DLT. Of the 7 deaths, 3 were due to acute respiratory failure and 1 each from respiratory failure, dyspnea, fall and sepsis. Overall, no new safety issues were identified; observed events were consistent with the class and as expected in the underlying population.

Important potential AEs based on drug class (eg, hemorrhages, hypertension, atrial fibrillation, infection, cytopenias, and hypersensitivity) have been observed across the BELLWAVE-001 and BELLWAVE-003 studies and are generally seen at lower incidences compared to the frequencies, severity, and seriousness observed with ibrutinib. These observed events did not have significant impact on discontinuations and interruptions.

CCL3, a BCR-dependent chemokine shown to be downregulated upon inhibition of BTK, was used as a PD marker in both BELLWAVE-001 and BELLWAVE-003 studies. Analysis of the PD data showed a dose-dependent decrease in serum CCL3 concentrations with

increasing nemtabrutinib dose. PK data showed an increase in exposure across the nemtabrutinib dose range from 5 mg to 80 mg QD. The clearance following single and multiple dosing was generally similar across the dose range and also across days (Day 1 and Day 22) suggesting that nemtabrutinib exhibits linear PK. Also, considering the preclinical data obtained to date [Section 2.2.2.2] that CCI [redacted] here is unlikely to occur potential differences of PK in Japanese CCI [redacted] derived from ethnicity/race.

Based on the totality of data reviewed (including safety, efficacy, PK, PD, and nonclinical toxicology), the benefit/risk profile favors 65 mg QD. Therefore, the RP2D for nemtabrutinib is 65 mg QD.

4.3.1 Dose-limiting Toxicity Definition

All toxicities will be graded using NCI-CTCAE version 5.0 based on the investigator assessment. Hematologic toxicities in participants with CLL will be assessed according to the iwCLL criteria as described in Appendix 11.

The DLT window of observation will be during Cycle 1 (4 weeks).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration.

- Grade ≥3 nonhematologic toxicity with exception of Grade 3 nausea, vomiting, diarrhea, rash, fatigue, and uncontrolled hypertension which will not be considered a DLT unless lasting more than 72 hours despite optimal supportive care (not laboratory)
- Grade 4 hematologic toxicity lasting >7 days, OR
    - Grade 4 platelet count decreased of any duration
    - Grade 3 platelet count decreased if associated with bleeding

      Note: For participants with BM involvement, numerical value of decreased platelet count for Grade 3 or Grade 4 will not be considered DLT unless the participant developed new or worsening clinical symptoms based on investigator assessment as compared with baseline and associated with low platelet counts. Grade 3 lymphocytosis, considered to be an expected outcome of BTK inhibition, is not considered a DLT.
    - Grade 3 or higher febrile neutropenia of any duration

- Any Grade 3 or Grade 4 nonhematologic laboratory abnormality, if:
  - Values result in DILI (see Section 8.4.7 for laboratory criteria), or
  - Medical intervention is required, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week

    Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. (see Section 8.4.1).
- Missing >25% of nemtabrutinib doses as a result of drug-related AE(s) during the first 1 cycle (4 weeks)
- Grade 5 toxicity

4.3.2 Dose Finding Using a Modified Toxicity probability Interval Design

Further dose finding will follow the mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30%. Dose escalation and de-escalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of DLTs observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the actual DLT rate, 3 to 6 participants may be enrolled. In Table 2, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. Notably, given a flat non-informative prior Beta(1,1), the DU decision occurs when the posterior probability that the toxicity rate at the current dose level is larger than the target toxicity rate of 30% is greater than 95%.

When adding participants to a dose level in response to a “stay” decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 2). Second, to determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 2).

A D or DU decision at the lowest dose level will stop the enrollment and sponsor will discuss the continuation of the study. An E decision at the highest dose level will result in staying at that level.

If 1 out of initial 3 participants develop a DLT, it will be S, therefore 3 participants will be added. If 2 out of 3 participants develop a DLT, it will be D, where the dose should be reduced. If 2 out of 6 participants develop a DLT, sponsor and principal investigator will discuss path forward of further Japanese enrollment.

The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to the expansion cohort, and the escalation schedule may be adjusted based on pharmacodynamic, PK, and safety data emerging throughout the trial.

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 2, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%.

Table 2 Dose-finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose			
Number of participants with at least 1 DLT	N=3	N=4	N=5	N=6
0	E	E	E	E
1	S	S	S	E
2	D	S	S	S
3	DU	DU	D	D
4		DU	DU	DU
5			DU	DU
6				DU

Abbreviations: E=Escalate to the next higher dose; S=Stay at the current dose; D=De-escalate to the next lower dose; DU=The current dose is unacceptably toxic.

Target toxicity rate = 30%

Flat noninformative prior Beta (1,1) is used as a prior and ε1=0.03, ε2=0.01[Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010]

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Histologically confirmed B-cell malignancy failed or intolerant to either at least 2 prior regimens given in combination or sequentially OR have received 1 prior BTK-containing regimen when a BTK inhibitor is approved as first line therapy.

2. CLL/SLL participants:

   Active disease for CLL/SLL clearly documented to initiate therapy. The need for therapy should be evaluated by the investigator from a comprehensive perspective in reference to the following criteria.

   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cutoff levels of Hb <10 g/dL or platelet counts $<100 \times 10^9$/L are generally regarded as indication for treatment. However, in some patients, platelet counts $<100 \times 10^9$/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.

   - Massive (ie, >+6 cm below the left costal margin) or progressive or symptomatic splenomegaly.

   - Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.

   - Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or LDT, < 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; participants with initial blood lymphocyte counts $<30 \times 10^9$/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (eg, infections, steroid administration) should be excluded.

- Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
  - Unintentional weight loss ≥10% within the previous 6 months.
  - Significant fatigue (ie, cannot work or unable to perform usual activities).
  - Fever of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
  - Night sweats for ≥1 month without evidence of infection.

3. WM/LPL participants:

   Active disease is defined as 1 of the following:

   - Systemic symptoms – Fever, drenching night sweats, fatigue, weight loss, and/or severe neuropathy.
   - Physical findings – Symptomatic or bulky (≥5 cm in the longest diameter) lymphadenopathy, symptomatic hepatomegaly, and/or symptomatic splenomegaly.
   - Laboratory abnormalities – Hemoglobin <10 g/dL or platelet count <100,000/microL.
   - Coexisting disease – Immunoglobulin light chain amyloidosis with organ dysfunction, symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic anemia and/or thrombocytopenia, or nephropathy due to WM/LPL.

4. WM/LPL participants:

   Have measurable disease, satisfying any of the following for participants with WM/LPL

   - At least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan (minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis)
   - IgM ≥ 450 mg/dL
   - bone marrow infiltration of ≥ 10%.

5. Participants with B-cell malignancies except CLL/SLL/WM/LPL:

   Have measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan, except the participants with CLL/SLL/WM/LPL. A minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.

6. Performance status of 0-2 on the ECOG Performance Scale within 7 days prior to allocation.

7. Have a life expectancy of at least 3 months, based on the investigator assessment.

8. Have the ability to swallow and retain oral medication.

9. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to the first dose of study intervention.

   Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

   Hepatitis B screening tests are not required unless:

   - Known history of HBV infection
   - As mandated by local health authority

10. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to the first dose of study intervention.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

11. Adequate organ function as defined in Table 3. Specimens must be collected within 7 days prior to the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥750/µL
Platelets	≥50,000/µL[a]
Hemoglobin	≥8.0 g/dL[a, b]
Renal	
CrCL using the Cockcroft-Gault equation test[c] or a 24-hour urine test	≥30 mL/min
Hepatic	
Total bilirubin (serum)	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN In participants with documented liver metastases and/or Gilbert's syndrome, total bilirubin of ≤3 x ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × institutional ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT/PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT/PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: AIHA=autoimmune hemolytic anemia; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=Creatinine clearance; INR=International normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

[a] No requirement in participants with significant bone marrow involvement.

[b] Criteria must be stable for ≥1 week, with the exception of AIHA for CLL/SLL.

[c] Cockcroft-Gault:

$$\frac{([140\text{-age (years)}] \times \text{weight [kg]})}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

Note: This table includes eligibility-defining laboratory value requirements for intervention; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

12. Is Japanese male or female, from 18 years of age inclusive, at the time of providing informed consent.

Male Participants

13. If male, agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The

length of time required to continue contraception for each study intervention is as follows:

- Nemtabrutinib: 12 days

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

14. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Nemtabrutinib: 30 days

    The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.2.

  - Abstains from breastfeeding during the study intervention period and for at least 30 days after study intervention.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

15. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has active HBV/HCV infection or at study entry. See Inclusion Criteria 9 and 10 for the requirements.

2. History of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 3 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder.

3. Active central nervous system (CNS) involvement.

4. Active infection requiring systemic therapy.

5. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

6. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

7. QTc prolongation (defined as a QTcF > 450 msecs) or other significant electrocardiogram (ECG) abnormalities including 2nd degree atrioventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).

8. Has any clinically significant gastrointestinal abnormalities that might alter absorption (eg, gastric bypass surgery, gastrectomy).

9. Has a known severe hypersensitivity (≥Grade 3) to Nemtabrutinib, its active substance and/or any of its excipients. Refer to the Nemtabrutinib IB for a list of excipients.

10. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

11. Underlying history of severe bleeding disorders.

12. History or concurrent condition of pneumonitis/interstitial lung disease. Pneumonitis/interstitial lung disease also include radiation pneumonitis.

Prior/Concomitant Therapy

13. Has received prior systemic anticancer therapy within 5 half-lives or 4 weeks (if prior therapy was a monoclonal antibody) prior to allocation.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

    Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study intervention.

14. Currently being treated with the following drugs:

    a. P-gp substrates with a narrow therapeutic index

    b. CYP3A strong inducers

    c. CYP3A strong inhibitors

    Note: A washout period of at least 5 times the half-life after the last dose of any of the above treatments is required for a participant to be eligible for study enrollment.

    Note: Refer to Section 6.5.1 regarding prohibited concomitant medications and potential drug interactions during the study.

15. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention.

    Refer to Section 6.5.1 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

1. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

2. Prior exposure to non-covalent, reversible BTK inhibitors.

Diagnostic Assessments

Not applicable in this study.

Other Exclusions

Not applicable in this study.

5.3 Lifestyle Considerations

No specific lifestyle restrictions are required, with the exception to avoid drinking grapefruit juice and the use of St John's Wort.

5.3.1 Meals and Dietary Restrictions

Avoid drinking grapefruit juice.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

To adequately evaluate the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1. Participants are considered non-evaluable and will be replaced if:

- They are allocated but not treated.
- They discontinue from the study, without the occurrence of a DLT, prior to completing all the safety evaluations for reasons other than treatment-related AEs (eg, disease progression).
- They receive less than 75% of the total planned administration of nemtabrutinib in Cycle 1 and did not experience a DLT.

A minimum of 3 participants per dose level is required to evaluate whether the current dose may be escalated to the next higher dose level. Once this is satisfied, replacement participants are not required. Non-evaluable participants will not be counted toward the total number of participants for DLT evaluation. However, the Sponsor will assess the safety and tolerability of nemtabrutinib after considering all safety information, including information on adverse events that occurred in non-evaluable participants.

If a participant experiences a DLT in Cycle 1, study intervention may be discontinued after discussion between the sponsor and investigator. However, if the participant is deriving clinical benefit from the study intervention and is deemed clinically stable, the participant may be allowed to continue after discussion between the Sponsor and the investigator. Participants must meet the following criteria for clinical stability:

- Participants must have adequate organ function as indicated by the laboratory values in Table 3;
- Participants must have no evidence of disease progression; and
- Participants must have an ECOG performance status of 0 to 2.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study is outlined in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP / AxMP	Sourcing
Nemtabrutinib (MK-1026)	Experimental	Nemtabrutinib (MK-1026)	Drug	Tablet	5 mg or 20 mg	45 mg (DL 1)	Oral	QD	Test Product	IMP	Central
Nemtabrutinib (MK-1026)	Experimental	Nemtabrutinib (MK-1026)	Drug	Tablet	5 mg or 20 mg	65 mg (DL2)	Oral	QD	Test Product	IMP	Central

Abbreviations: DL=dose level; EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once daily.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 4 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.10 for details regarding administration of the study intervention.

6.1.1 Treatment

Nemtabrutinib is administered as a daily 45 mg or 65 mg dose, taken orally, until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

Each cycle consists of 4 weeks (28 calendar days). If a dose interruption or delay occurs or persists on Day 1 of planned next cycle the current cycle will be longer than 28 calendar days. If a dose interruption or delay occurs in the middle of the cycle and treatment can be resumed on Day 1 of planned next cycle, the current cycle will remain 28 days.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Nemtabrutinib will be administered QD by mouth under fasting conditions (either 1 hour prior to, or 2 hours after the meal). On visit days when PK and PD samples are scheduled, dosing should be delayed until the pre-dose PK and PD samples have been collected at the site.

For administrative reasons, the treatment period is divided into 4 week cycles (28 days).

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

An observation period of at least 24 hours will occur between intervention initiating treatment for the first and second participants enrolled within each new dose level. New dose level cohort will open for enrollment without delay once the DLT observation period (Cycle 1) of the current dose level cohort is completed and a dose-escalation decision is made.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Interruptions more than 21 consecutive days from the protocol-specified treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

- A record of the number of Nemtabrutinib dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccine rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

Severe (Grade 3 and above) skin rashes considered to be related to nemtabrutinib may be treated with systemic steroids. Further details are provided in Section 6.6.1.

Concomitant use of anticoagulant or antiplatelet agents with BTKi increases the risk of major hemorrhage. Consider the risks and benefits of anticoagulant or antiplatelet therapy during study treatment. If anticoagulant or antiplatelet agents are used, participants should be monitored for signs and symptoms of bleeding.

Participants who are receiving HBV antiviral therapy at the treatment allocation should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

6.5.1 Prohibited Concomitant Medications

The following medications are not allowed during the screening and treatment phase of the study:

- Primary prophylactic G-CSF during the DLT evaluation period.
- Immunosuppressive therapies including continuous high-dose corticosteroids (>30 mg prednisone equivalent per day).
- Any concurrent anticancer therapy including, but not limited to, chemotherapy, radiotherapy (except palliative radiotherapy for local pain control), hormonal therapy or immunotherapy.
- Other investigational agents.
- Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

  NOTE: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.
- Concomitant medications with the following characteristics are prohibited during the study (see Section 2.2.2.2 for DDI risk summary):
  - P-gp substrates with a narrow therapeutic index
  - CYP3A strong inducers
  - CYP3A strong inhibitors

    Note: If the participant requires short-term use of CYP3A strong inhibitors, consultation with the Sponsor is required and treatment interruption with nemtabrutinib may be permitted.

  Note: Detailed information of P-gp substrates with a narrow therapeutic index, CYP3A strong inducers and CYP3A strong inhibitors can be found at the following website:

  https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

6.5.2 Rescue Medications and Supportive Care

Rescue treatment and adjuvant therapy are not specified in this study.

6.6 Dose Modification (Escalation/Titration/Other)

Nemtabrutinib – any treatment interruption more than 21 consecutive days needs to be discussed with the sponsor.

In or after cycle 4, participants receiving 45 mg of nemtabrutinib may be escalated to the higher dose if the tolerability is confirmed at the 65 mg of nemtabrutinib and at the discretion of the investigator after discussion with the participant, upon the consultation with sponsor.

If the escalation is permitted, the higher dose can be utilized from the Day 1 of next cycle based on the approved date.

The participants who receive the higher dose of nemtabrutinib should perform site visit / telephone contact after 14 (±3) days and 28 (±3) days from the first dose of the escalated dose to assess adverse event. Refer to Section 1.3 for the detailed schedule.

6.6.1 Nemtabrutinib Dose Modification

At the occurrence of an adverse event, associated with study treatment, dose interruptions and/or reductions in nemtabrutinib administration are allowed. If dose reduction is indicated, the participants should be assigned to the lower dose. In the event of a dose modification, the dose change(s) must be captured in the electronic data collection (EDC) system.

A maximum of 1 dose reduction will be allowed before a participant is discontinued from study treatment. Dose delays/reductions/modifications are specified in the event of non-hematological and non-skin toxicity (Table 6), hematological toxicity (Table 7, Table 8), and for drug-related skin toxicities (Table 9). Hematologic toxicity in CLL participants will be assessed by the grading scale in the iwCLL guidelines Appendix 11. Grade 1 to 2 drug-related skin rashes may be treated with topical steroids and antihistamines. Severe (Grade 3 and above) drug-related skin rashes may be treated with systemic steroids. Nemtabrutinib treatment should be discontinued in the case of a Grade 4 skin-related event.

Although the MOA for BTKi associated skin toxicities is not fully elucidated, several types of manifestations have been observed, including acne-like rash/folliculitis and immune-mediated drug reaction [Sibaud, V., et al 2020]. For acne-like rash, including papulopustular rash, obtaining bacteria/mycological cultures is recommended. If no microorganisms are detected, administer tetracyclines or other antibiotics as needed. If *Staphylococcus aureus* is detected, begin oral and/or topical antibiotics with anti-*Staphylococcus aureus* coverage.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (eg, elective surgery, unrelated medical events, radiotherapy) not related to study intervention. Consider the benefit-risk of withholding nemtabrutinib for 3-7 days pre-and post-surgery depending upon the type of the surgery and the risk of bleeding. Participants should be placed back on study intervention within 21 days of the scheduled interruption unless discussed with Sponsor. The reason for interruption should be documented in the participant's CRF and medical notes.

Participants should be monitored for signs and symptoms of bleeding during nemtabrutinib treatment. Discontinue nemtabrutinib if severe hemorrhage occurs.

Table 5 Dose Modification for Nemtabrutinib

Dose Modification	Dose of Nemtabrutinib	
0	45 mg QD (2 × 20 mg tablets plus 1 × 5 mg tablet)	65 mg (3 × 20 mg tablets plus 1 × 5 mg tablet)
1	30 mg QD (1 × 20 mg tablet plus 2 × 5 mg tablets)	45 mg QD (2 × 20 mg tablets plus 1 × 5 mg tablet)

Abbreviation: QD=once daily.

Table 6 Dose Delays/Reductions of Nemtabrutinib for Drug-related Non-Hematological and Non-skin Toxicity

Event Grade	**Action**
Grade 1 or 2	Continue current dose level; however, at the discretion of the investigator, dose interruption/modification may be implemented
Grade 3 (except Grade 3 nausea, vomiting, diarrhea, or controlled hypertension)	Withhold nemtabrutinib until recovery to Grade 1 or baseline. • If recovery occurs within 21 days, restart nemtabrutinib at the same dose and schedule, unless further dose reduction is necessary in the opinion of the investigator. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to the dose modification 0 is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.
Grade 4 (except Grade 4 nausea, vomiting, or diarrhea)	Permanently discontinue nemtabrutinib.
Grade 3 or 4 nausea, vomiting, or diarrhea	Withhold nemtabrutinib until recovery to Grade 1 or baseline. • If recovery occurs within 24 hours, restart nemtabrutinib at the current dose level. • If recovery occurs after 24 hours and within 21 days, restart nemtabrutinib at dose modification 1. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. For any occurrence of nausea and vomiting, prophylactic anti-emetics may be used. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to the dose modification 0 is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.

Table 7 Dose Delays/Reductions of Nemtabrutinib for Drug-related Hematological Toxicity for All Participants Except Those with CLL

Event[a]	**Action**
Anemia (Hgb ≥ 8 g/dL) **Thrombocytopenia** (Platelet ≥ 50 $\times 10^9$/L)	Continue current dose level; however, at the discretion of the investigator, dose interruption/modification may be implemented.
Anemia (Hgb < 8 and ≥ 6 g/dL) **Thrombocytopenia** (Platelet < 50 to ≥ 25 $\times 10^9$/L)	<u>First occurrence of AE:</u> Withhold nemtabrutinib and monitor hematology and/or chemistry at least once a week until relevant lab value(s) recover to the values outlined below: • If the relevant laboratory value recovers within 7 days to baseline (if cytopenias present at the start of study) or ≥ 8 g/dL for Hgb, ≥ 50×10^9/L for platelets (if no cytopenias present at the start of study), resume nemtabrutinib treatment at the same dose level. • If the relevant laboratory value takes more than 7 days but within 21 days to recover with or without therapy to the level described above, restart nemtabrutinib administration at dose modification 1. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. <u>Second occurrence of the Same AE:</u> • If a second hold is required for the same event, administer nemtabrutinib at dose modification 1. • If a second hold is required for the same event at dose modification 1 and the event dose not recover within 21 days, permanently discontinue nemtabrutinib. <u>Third occurrence of the Same AE:</u> If a patient experiences a third occurrence of the same event at dose modification 1, permanently discontinue nemtabrutinib if not recovered within 21 days.

Event[a]	**Action**
Anemia (Hgb < 6 g/dL) **Thrombocytopenia** (Platelet < 25×10^9/L) **Neutropenia** (ANC < 0.5×10^9/L)	<u>First occurrence of AE:</u> Withhold nemtabrutinib and monitor hematology and/or chemistry at least once a week until relevant lab value(s) recover to the values outlined below: • If the relevant lab value recovers within 21 days to baseline (if cytopenias present at the start of study) or ≥ 8 g/dL for Hgb, ≥ 50×10^9/L for platelets, or ≥ 0.5×10^9/L for ANC (if no cytopenias present at the start of study), with or without the use of GCSF support, resume nemtabrutinib treatment at dose modification 1. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to dose modification 0 is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. <u>Second occurrence of the Same AE:</u> • If a second hold is required for the same event at the dose modification 0 or 1 and the event does not recover within 7 days, permanently discontinue nemtabrutinib.
[1] Abbreviations: AE=adverse event; ANC=absolute neutrophil count; CLL=chronic lymphocytic leukemia; GCSF=granulocyte colony-stimulating factor; Hgb=hemoglobin [a.] Applicable to participants who had new toxicities or participants with cytopenia at baseline that worsen.	

Table 8 Dose Delays/Reductions of Nemtabrutinib for Drug-related Hematological Toxicity for Participants With CLL

Event [a,b]	**Action**
<u>Grade ≤ 2</u> Anemia (Hgb <50% decrease from baseline) and ≥6g/dL Thrombocytopenia (platelet <50% decrease from baseline) and ≥25×10^9/L	Continue current dose level; however, at the discretion of the investigator, dose interruption/modification may be implemented.
<u>Grade 3</u> Anemia (Hgb 50% to 74% decrease from baseline) and <6 g/dL) Thrombocytopenia (platelet 50% to 74% decrease from baseline) and <25×10^9/L)	<u>First occurrence of AE:</u> Withhold nemtabrutinib and monitor hematology and/or chemistry at least once a week until relevant lab value(s) recover to the values outlined below: • If the relevant laboratory value recovers within 7 days to baseline (if cytopenias present at the start of study) or ≥8 g/dL for Hgb, ≥50×10^9/L for platelets (if no cytopenias present at the start of study), resume nemtabrutinib treatment at the same dose. • If the relevant laboratory value takes more than 7 days but within 21 days to recover with or without therapy to the level described above, restart nemtabrutinib administration at dose modification 1. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-

Event [a,b]	Action
	escalation to dose modification 0 is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. <u>Second occurrence of the Same AE:</u> • If a second hold is required for the same event at dose modification 0, administer nemtabrutinib at dose modification 1. Dose escalation to dose modification 0 is not permitted. • If a second hold is required for the same event at dose modification 1 and the event does not recover within 21 days, permanently discontinue nemtabrutinib. <u>Third occurrence of the Same AE:</u> If a patient experiences a third occurrence of the same event at dose modification 1 and recovery does not occur within 21 days on drug hold, permanently discontinue nemtabrutinib.
<u>Grade 4</u> Anemia (Hgb ≥75% decrease from baseline) and <6g/dL Thrombocytopenia (platelet ≥75% decrease from baseline) and <25 × 10^9/L Neutropenia (ANC <0.5 × 10^9/L)	<u>First occurrence of AE:</u> Withhold nemtabrutinib and monitor hematology and/or chemistry at least once a week until relevant laboratory value(s) recover to the values outlined below: • If the relevant lab value recovers within 21 days to baseline (if cytopenias present at the start of study) or ≥8 g/dL for Hgb, ≥50×10^9/L for platelets, >0.5×10^9/L for ANC (if no cytopenias present at the start of study), with or without the use of GCSF support following institutional standard practice, resume nemtabrutinib treatment at dose modification 1. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to dose modification 0 is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered. • If recovery occurs after more than 21 days on drug hold, permanently discontinue nemtabrutinib. <u>Second occurrence of the Same AE:</u> If a second hold is required for the same event at dose modification 0 or 1 and the event does not recover within 7 days, permanently discontinue nemtabrutinib.

[2] Abbreviations: AE=adverse event; ANC=absolute neutrophil count; CLL=chronic lymphocytic leukemia; GCSF=granulocyte colony-stimulating factor; Hgb=hemoglobin.

a. Applicable to participants who had new toxicities or participants with cytopenia at baseline that worsens.

b. For participants with CLL, grading of hematological toxicities will be according to Appendix 11. Refer to additional notes in Appendix 11 when assessing grades.

Table 9 Dose Modification for Nemtabrutinib Drug-related Skin Toxicities

Event	Action
Grade 1 and 2	Continue current dose level; however, at the discretion of the investigator, dose interruption/modification may be implemented. Grade 1 to 2 drug-related skin rashes may be treated with topical steroids and antihistamines. For papulopustular rash oral antibiotic prophylaxis is strongly recommend.
Grade 3	• First occurrence of AE: ➢ Withhold nemtabrutinib until recovery to Grade 1 or baseline; meanwhile treat the skin toxicity as clinically indicated; then restart nemtabrutinib at dose modification 1. ➢ If the event does not recur within 21 days after restarting the study treatment, the participant's treatment dose may be escalated to dose modification 0. ➢ If the event does not recur within 21 days after starting treatment, the participant may remain at this dose if, in the opinion of the investigator, the participant is getting clinical benefit at this dose level. • Second occurrence of AE: ➢ If a participant experiences a second occurrence of the event while at dose modification 1, which is considered to be related to nemtabrutinib treatment, this participant should be permanently discontinued. ➢ If a participant experiences a second occurrence of the event at dose modification 0, which is considered to be related to nemtabrutinib treatment, withhold nemtabrutinib until recovery to Grade 1 or baseline; meanwhile treat the skin toxicity as clinically indicated; then restart nemtabrutinib at dose modification 1. Dose escalation to dose modification 0 is not permitted. • Third occurrence of AE: ➢ Permanently discontinue study treatment. Grade 3 drug-related skin rashes may be treated with systemic steroids. For papulopustular rash oral antibiotic prophylaxis is strongly recommend. Note: Participants with any grade Steven-Johnsons Syndrome should permanently discontinue nemtabrutinib.
Grade 4	Permanently discontinue study treatment. Grade 4 drug-related skin rashes may be treated with systemic steroids. For papulopustular rash oral antibiotic prophylaxis is strongly recommend.
Abbreviations: AE=adverse event.	

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not Applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Confirmed disease progression outlined in Section 8.2.2.1 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study is outlined in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Missed or Vomited Doses

A missed (ie, >6 hours beyond scheduled dose) or vomited dose should not be replaced. The participant should be instructed to take the next schedule dose. If the participant vomits the first dose of nemtabrutinib, the participant may be rechallenged at the discretion of the investigator. If doses are missed or vomited, this must be indicated in the participants source documents and eCRF.

8.1.2 Informed Consent

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information

provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

Informed consent given by the participant (or their legally acceptable representative) must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the participant (or their legally acceptable representative) before participation in the study.

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.2.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

8.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.4 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

As part of medical history collection, known mutational status will be recorded.

For participants with WM/LPL, the presence of amyloid deposits will be recorded as part of medical history, if available.

Details regarding prognostic markers, current, and prior disease status will be obtained.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.6 Prognostic Profile

8.1.6.1 Molecular Genetics Profile of CLL/SLL

If available at Screening, test results should be provided to establish the molecular prognostic profile of CLL/SLL participants. The staging is assessed per Binet and Rai for CLL and Lugano Classification for SLL:

- Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), TP53 mutation, add (trisomy 12), del(6q) in peripheral blood lymphocytes
- Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)
- IGHV mutational status
- BTK mutation status on C481 residue
- Sequencing: TP53 point mutation
- Serum markers: serum β2 microglobulin, optional thymidine kinase
- Notes: Only β2 microglobulin must be tested by the site at screening and on an ongoing basis during the study. The other test results should be reported exclusively from the participant's medical records, if available.

8.1.6.2 Prognostic Risk Factors

At the time of study entry, disease subtype per WHO classification of lymphoid neoplasms [Swerdlow, S. H., et al 2016], staging per Ann Arbor and Lugano staging criteria 2014 [Cheson, B. D., et al 2014], tumor location, relevant prognostic factors will be obtained. The following prognostic factors will be collected at the time of study entry:

- CLL-IPI: for CLL [International CLL-IPI working group 2016]
- IPI and age adjusted IPI: for MZL, SLL and other NHL [International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993]
- MIPI and MIPI-c: for MCL [Hoster, E., et al 2016] [Hoster, E., et al 2008]
- FLIPI and FLIPI-2: for FL [Solal-Céligny, P., et al 2004] [Federico, M., et al 2009]
- ISSWM: for WM/LPL [Morel, P., et al 2009]
- NCCN IPI: for DLBCL [Zhou, Z., et al 2014]

8.1.7 Prior and Concomitant Medications Review

8.1.7.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention.

8.1.7.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

8.1.8 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.9 Assignment of Treatment/Allocation Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/allocation number.

8.1.10 Study Intervention Administration

The first dose of study intervention will be administered at the study site on C1D1. For the high-risk participants only, dosing will be witnessed at the study site on C1D2.Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day. Treatment will be continued until unacceptable toxicity, documented disease progression, or another discontinuation criterion is met.

For administrative reasons, the treatment period is divided into 4-week cycles (28 days).

A missed or vomited dose should not be replaced as summarized in Section 8.1.1.

The investigator/designee will be asked to check nemtabrutinib returned supplies for administration compliance.

8.1.10.1 Timing of Dose Administration

Nemtabrutinib is administered orally under fasted conditions (1 hour prior to or 2 hours after the meal) daily. All doses will be administered at the participants home, with the exception of the first day of drug administration at the study clinic and on study visit days when PK and/or PD samples are scheduled. On study visit days when PK and/or PD samples are scheduled, the investigator/designee will instruct the participant not to take their dose of nemtabrutinib until their assessments have been performed. Nemtabrutinib will be dispensed in the clinic on Day 1 of Cycles 1 to 28, and then every 3 cycles after Cycle 28.

8.1.11 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.12 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.13 Domiciling

As a general rule, a participant should be hospitalized during the DLT evaluation period (the first 4 weeks after the initiation of study medications, Cycle 1).

8.1.14 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

Treatment response assessments (including imaging, physical examinations, constitutional symptoms, hematological evaluations, and bone marrow as required) are required every 12 weeks (±7 days) and should follow calendar days from C1D1. The frequency of treatment response assessment can be decreased to every 24 weeks (±7 days) starting the fourth year on study. If dosing is delayed, treatment response assessments should continue as scheduled. For further details refer to the SoA in Section 1.3.

8.2.1 Criteria for Assessment of Disease

8.2.1.1 CLL/SLL

iwCLL Criteria

Participants with CLL/SLL will be assessed using response criteria defined in the 2018 iwCLL consensus (see Appendix 9). Assessment of response should include physical examination, constitutional symptoms, imaging, and evaluation of the blood (CBC) and bone marrow as summarized below:

- A thorough history, inclusive of constitutional symptoms
- Prognostic biomarkers and cytogenetics (screening only, based on historical data). See Section 8.1.6.1.
    - IGHV mutational status, metaphase karyotyping, FISH for del(17p) and/or sequencing for TP53 point mutations which indicate high-risk CLL.

- Staging (screening only).
  - CLL: Rai and Binet
  - SLL: Lugano
- Physical examination including palpable cervical, axillary, and inguinal lymphadenopathy, and hepatomegaly or splenomegaly.
- CBC and differential count.
- Serum β2 microglobulin.
- CT of neck, chest, abdomen, and pelvis as defined in the iwCLL guidelines (see Appendix 9).
- Marrow aspirate and/or biopsy: in the event of a CR, as defined in the iwCLL guidelines (see Appendix 9), or for cytopenias of uncertain cause.
- MRD (in peripheral blood and if available, BM) in the event of a CR– using a suitably sensitive technique such as 6-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using an assay comparable to ClonoSEQ with minimum sensitivity, <1 CLL cells in 10,000 leukocytes.

Response definitions are summarized in 2018 iwCLL publication in Appendix 9, except for PRL. PRL will not be considered for ORR but may preclude PD due to lymphocytosis alone. Partial response with lymphocytosis is defined as a >50% reduction in lymphadenopathy and splenomegaly, with persistent lymphocytosis [Kipps, T. J., et al 2017].

8.2.1.2 Mature B-cell neoplasms participants other than CLL/SLL/WM/LPL

Lugano Criteria (Primary)

Participants with Mature B-cell neoplasms participants other than CLL/SLL/WM/LPL will be assessed using the 2014 Lugano Classification (see Appendix 9). Assessment of response should include:

- A thorough history of disease burden and constitutional symptoms.
- Lugano staging (screening only).
- Whole-body PET and CT of neck, chest, abdomen, and pelvis.
- Marrow aspirate and biopsy (screening only for participants with non-FDG-avid lymphoma).
- For participants who have non-FDG-avid lymphomas, bone marrow aspirate and/or biopsy should be performed to confirm CR (if participant had bone marrow

involvement) and as clinically indicated. For FDG-avid lymphoma subtypes, PET may replace bone marrow sample.

Response definitions are summarized in 2014 Lugano publication [Cheson, B. D., et al 2014] in Appendix 9.

8.2.1.3 WM/LPL

IWWM criteria

Participants with WM/LPL will be assessed using the 2014 IWWM Classification. Assessment of response should include:

- A thorough history, inclusive of pathognomonic as well as constitutional symptoms
- The presence of amyloid deposits (if applicable)
- IgM immunofixation and serum level
- CT for assessment of extramedullary disease (ie, lymphadenopathy/splenomegaly) if recorded at screening or if subsequently observed on physical examination
- New signs/symptoms on physical examination
- Bone marrow aspirate and/or biopsy in the event of CR
- Kappa-light chains, Lambda light chains, and Kappa/Lambda ratio (or Free light chain ratio) (if applicable)
- Serum viscosity when clinically indicated
- Report the use of any extracorporeal therapies that might impact immunoglobulin assays (eg, plasmapheresis)

In addition to the above, cryoglobulins will be tested at each response assessment visit and if clinically indicated.

Response definitions are summarized in 2014 IWWM publication in Appendix 9.

8.2.2 Tumor Response Assessments

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. Disease response assessments may use CT/MRI and/or PET imaging, laboratory studies, and physical examination. The same imaging technique should be used in

a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility. Other imaging modalities that may be collected and included in response assessment include bone scans and dedicated brain imaging. Other types of medical imaging (such as ultrasound) should not be included in response assessment.

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. Any imaging obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening images to confirm the participant with other than CLL/SLL has measurable disease.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of allocation.

The first on-study imaging assessment and tumor response assessment should be performed at 12 weeks (84±7 days) from the date of Cycle 1 Day 1. Subsequent tumor imaging and tumor response assessment should be performed every 12 weeks (84±7 days) or more frequently if clinically indicated. Imaging and tumor response assessment frequency can be decreased to every 24 weeks (168±7 days) starting the fourth year on study, regardless of dose interruption or delays.

Treatment effect measured by ORR can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship. Disease response assessments and imaging should continue to be performed until documented disease progression by local investigator, the start of new anticancer treatment, withdrawal of consent, death, pregnancy, or the end of the study, whichever occurs first.

ORR will be evaluated in each of the following cohorts:

- CLL/SLL participants: per iwCLL criteria 2018 (Appendix 9).
- WM/LPL participants: per IWWM 2014 (Appendix 9)
- Mature B-cell neoplasms participants other than above: per the Lugano Classification 2014 (Appendix 9)

8.2.2.1 Disease Progression Assessment

8.2.2.1.1 Imaging Assessment

If an investigator concludes the participant's disease has progressed, study treatment must be discontinued unless confirmation is required for clinically stable participants. The participant will enter post-treatment follow-up; ie, 30-day Safety Follow-up and Survival Follow-up. For participants who discontinue study intervention, tumor imaging should be performed at the

time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of Cycle 1 Day 1 until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

It is at the discretion of the investigator to stop study treatment or to keep a clinically stable participant on study treatment until repeat imaging performed 4 to 6 weeks later confirms progression. Participants that are deemed clinically unstable should not have repeat imaging for confirmation. Clinical stability may be defined as:

- Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values).
- No decline in ECOG performance status.
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites requiring urgent medical intervention (eg, cord compression).

If progression is confirmed by subsequent imaging, then the participant will be discontinued from study treatment. If progression is not confirmed, then the participant should resume/continue study treatment provided:

- The Sponsor is consulted and provides approval to continue treatment.
- No other antitumor therapy (eg, chemotherapy, radiation, etc.) has been administered.

The participant will be asked to reconsent to continue treatment beyond initial progression. Participants should have their next scan according to the every 12-week schedule from the first dose of study treatment. When feasible, participants should not be discontinued until progression is confirmed. Treatment with nemtabrutinib must stop at any time a disease response assessment is confirmed as PD.

8.2.2.1.2 Non-imaging Assessment

In disease indications where progression can be based on non-imaging parameters (eg, laboratory studies, physical examination and bone marrow examination), it is at the discretion of the investigator to stop study treatment or to keep a clinically stable participant on study treatment until repeat assessment performed 4 to 6 weeks later confirms progression. For WM/LPL, a repeat assessment is preferred after a result suggests progression due to the potential impact to disease measures attributable to treatment initiation, or due to alternate etiologies. WM/LPL participants may experience disease flare (ie, a rapid rise in serum IgM level or an increase in known extramedullary disease) during

study treatment interruption. Follow-up assessment after treatment re-initiation should be taken into consideration in assessing disease flare. Participants that are deemed clinically unstable should not have repeat assessment for confirmation.

If progression is confirmed, then the participant will be discontinued from study treatment. If progression is not confirmed, then the participant should resume/continue study treatment provided:

- The Sponsor is consulted and provides approval to continue treatment.
- No other antitumor therapy (eg, chemotherapy, radiation, etc.) has been administered.

8.2.3 Non-Hodgkin's Lymphoma B Symptoms

These symptoms include the following:

- Unintentional weight loss ≥10% within the previous 6 months.
- Significant fatigue (ie, ECOG performance score 2 or worse; cannot work or unable to perform usual activities).
- Fevers of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
- Night sweats for ≥1 month without evidence of infection.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be measured after 5 minutes rest and will include temperature (method must be kept consistent throughout study), systolic and diastolic blood pressure, pulse, and respiratory rate, as defined in Section 1.3.

8.3.3 ECOG Performance Status

ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with grade 0 to 5.

The investigator or qualified designee will assess ECOG Performance Status (Appendix 8) at screening and each visit prior to administration, and at the end of treatment visit as specified in the SoA.

8.3.4 Electrocardiograms

12-lead ECG in triplicate will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA and in Table 1 using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Measured ECG data will be used for safety assessment and exploratory evaluation of the relationship between PK and QT interval. At each time point when triplicate ECG are required, ECG is to be taken after the participant has been in a recumbent position for at least 10 minutes. Three individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

Participant should refrain from foods from ECG assessment at pre-dose on Day 1 of each Cycle until the completion of ECG assessment at 2 hour (C1D1 and C2D1) or 4 hour (C3D1) post-dose.

8.3.5 SpO_2 Measurement

The measurement of SpO_2 is performed by the investigator or designee by the standard method in each study site as per SoA.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- HIV screening will follow local regulations.
- HBV Monitoring

Tests should be aligned with study intervention visits.

If participant has history of HBV, then monitoring is required if clinically indicated until EOT.

8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.6.2 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

- Pregnancy tests should be performed monthly and/or as per local regulations. Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test.

8.3.7 Tumor Lysis Syndrome

8.3.7.1 Tumor Lysis Syndrome for CLL/SLL

Assessment of tumor lysis syndrome in CLL/SLL is based on [Fischer, K., et al 2019].

Definition of High Risk for TLS in CLL/SLL:

- The high-risk category for developing tumor lysis syndrome in CLL/SLL is any measurable lymph node with the largest diameter ≥10 cm or the presence of both ≥25×109/L ALC AND any measurable lymph node with the largest diameter ≥5 cm but <10 cm. Lymph node size will be determined by radiologic assessment.

Prophylaxis for TLS in High Risk CLL/SLL:

- Oral uric acid reducer (eg, allopurinol 300 mg/day) beginning ≥72 hours before dose and continued per local institutional guidelines and then discontinued per investigator discretion. Rasburicase may be administered per regional/institutional standards. Oral hydration of 1.5 to 2 L/day beginning ≥48 hour before dose and continuing for ≥24 hour.

Monitoring for TLS in High Risk CLL/SLL:

- Hematology and chemistry samples will be taken predose on C1D1 and at 8 and 24 hours (C1D2) postdosing. The investigator or subinvestigator must review the 8-hour and 24-hour (C1D2) laboratory results before dosing on the next day. Post Cycle 1 monitoring is only required if clinically indicated.

8.3.7.2 Tumor Lysis Syndrome for NHL

Assessment of tumor lysis syndrome in NHL is based on [Howard, S. C., et al 2011].

Definition of High Risk for TLS in NHL:

- The high-risk category for developing tumor lysis syndrome in NHL is any measurable lymph node with the largest diameter ≥10 cm.

Prophylaxis for TLS in High Risk NHL:

- Oral uric acid reducer (eg, allopurinol 300 mg/day) beginning ≥72 hour before dose and continued per local institutional guidelines and then discontinued per investigator discretion. Rasburicase may be administered per regional/institutional standards. Oral hydration of 1.5 to 2 L/day beginning ≥48 hour before dose and continuing for ≥24 hour.

Monitoring for TLS in High Risk NHL:

- Hematology and chemistry samples will be taken predose C1D1 and at 8 and 24 hours (C1D2) postdosing. The investigator or subinvestigator must review the 8-hour and 24-hour (C1D2) laboratory results before dosing on the next day. Post Cycle 1 monitoring is only required if clinically indicated.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-

specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.6.2, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified AE Collection Period**	**Reporting Time Period: After the Protocol-specified AE Collection Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Potential DILI events meeting biochemical criteria of Hy's Law (requires regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified AE Collection Period	**Reporting Time Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor:
ECI (requires regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - requires regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
AE=adverse event; DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical event; SAE=serious adverse event.				

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. SAEs and other reportable safety events, including potential DILI events meeting biochemical criteria of Hy's Law, pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

ECIs for this study include:

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
- An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,
- At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

Additional ECIs for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5.
- Major hemorrhage: all ≥ Grade 3 hemorrhages, all serious hemorrhages, and CNS hemorrhages of any grade.
- Atrial fibrillation and atrial flutter of any grade, and ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmia, ventricular fibrillation, ventricular tachyarrhythmia, and ventricular tachycardia) of any grade.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for nemtabrutinib. No specific information is available on the treatment of overdose of nemtabrutinib. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an AE is associated with an overdose of, nemtabrutinib the AE must be reported as a SAE, even if no other seriousness criteria are met. All reports of overdose associated with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. If a dose of nemtabrutinib meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

8.6 Pharmacokinetics

To evaluate the pharmacokinetic profile of nemtabrutinib, sample collections for analysis of PK is currently planned as shown in Section 1.3 and in Table 1. Blood samples will be obtained to measure plasma PK of nemtabrutinib.

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in the Central Laboratory Manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in the SoA:

- Blood for BTK C481 mutation status. (CLL/SLL participants only)
- Blood for genetic analysis.

Sample collection, storage and shipment instructions for the exploratory biomarker specimens will be provided in the Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 28 days prior to intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention.

Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis testing, which may be done up to 28 days prior to the first dose of study intervention.

Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria with the agreement of the sponsor. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria are met. Participants who are rescreened will retain their original screening number.

8.11.2 Treatment Period Visit

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

Unless otherwise specified, assessments/procedures are to be performed prior to the first dose of study intervention for each cycle, and the window for each visit as defined in the SoA.

In or after cycle 4, participants receiving 45 mg of nemtabrutinib may be escalated to 65 mg if the tolerability is confirmed at 65 mg of nemtabrutinib and at the discretion of the investigator after discussion with the participant, upon the consultation with sponsor. If the escalation is permitted, the higher dose can be utilized from the Day 1 of next cycle based on the approved date. The participants who receive the higher dose of nemtabrutinib should perform site visit / telephone contact after 14 (±3 days) days and 28 (±3 days) days from the first dose of the escalated dose. Refer to Section 1.3 for the detailed schedule.

In or after cycle 28, the participants will visit the site every 3 cycles. Between these 3 cycles, the site visit / telephone contact is required when each cycle (e.g., cycle 29 and cycle 30) will start.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.11.4 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

All AEs that occur before the Safety Follow-up Visit should be recorded (up to 30 days after the end of treatment).

8.11.5 Efficacy Follow-up Visits

Participants who discontinue study intervention for reasons other than PD should continue with imaging assessments per the protocol-defined schedule until: (1) site assessed initial PD or further confirmed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, (5) pregnancy, or (6) study conclusion or early termination, whichever occurs first. All new anticancer therapy initiated after the study intervention discontinuation must be recorded in the CRF. If a participant initiates another anticancer therapy other than the assigned study intervention, the study intervention should be discontinued. If a participant initiates a new anticancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up visit should occur before the first dose of the new therapy.

NOTE: Efficacy follow-up assessments should follow calendar days from allocation. If dosing is delayed, efficacy assessments should continue as scheduled.

8.11.6 Survival Follow-up Contacts

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The Sponsor may request survival status be assessed at additional time points during the course of the study. All participants who are not known to have died before the request for these additional survival status time points will be contacted at that time.

After approval of Protocol amendment 04, participants in the Survival Follow-up phase will be discontinued from the study and no further visits will be required.

8.11.7 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate sSAP.

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in the sSAP as needed and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	This is an open-label, multicenter, dose escalation, phase I study of nemtabrutinib in Japanese participants with Mature B-cell neoplasms who have failed or are intolerant to previous treatment.
Intervention Assignment	A minimum of 3 participants up to a maximum 6 participants per dose level will be enrolled.
Analysis Populations	Safety: All-Participants-as-Treated (APaT) and Dose limiting toxicity-evaluable Efficacy: All-Participants-as-Treated (APaT) Pharmacokinetic: Per-Protocol (PP)
Primary Endpoint(s)	Dose-limiting toxicity (DLT) Adverse event (AE) Discontinuing study treatment due to an AE
Secondary Endpoints	PK parameters (AUC, Cmax, Tmax and Cmin) Objective response as assessed by investigator Duration of response as assessed by investigator
Statistical Methods for Key Efficacy Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) together with its 95% confidence interval.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm [Ji, Y., et al 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate by dose level and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.
Statistical Methods for Key Pharmacokinetic Analyses	The plasma concentrations of nemtabrutinib will be summarized by planned visit and time for each dose separately. PK parameters will be summarized by dose.

Interim Analyses	No interim analysis is planned. Data will be examined on a continuous basis to allow for dose finding decisions.
Multiplicity	There will be no multiplicity control in this study since no hypothesis testing is planned.
Sample Size and Power	Each dose level assessed will have a minimum of 3 participants. Based on the occurrence of DLTs, up to 6 participants may enroll per dose level. The actual sample size is dependent on the number of dose levels tested and emerging safety data.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as an open-label study, i.e., participants, investigators, and sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Safety Endpoints

The primary safety endpoints are the number/proportion of participants with DLTs, with AEs, and who discontinue study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3 and Section 8.4.

9.4.2 Efficacy Endpoints

- Objective Response (OR)

OR is defined as participants who achieve at least a PR, per disease-specific criteria (see Section 8.2.1) as assessed by investigator. Objective response rate (ORR) is the proportion of participants in the analysis population with objective response.

- Duration of Response (DOR)

For participants who demonstrate an objective response as assessed by investigator, per disease-specific criteria, duration of response is defined as the time from the first documented evidence of an objective response until disease progression or death due to any cause, whichever occurs first.

9.4.3 Pharmacokinetic Endpoints

Pharmacokinetic endpoints include plasma concentrations of nemtabrutinib, as well as any derived PK parameters. PK parameters include nemtabrutinib AUC, Cmax, Tmax and Cmin after the first dose (at Cycle 1 Day 1) and at steady-state.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study treatment.

The DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability. See Section 4.3.1 and Section 5.5 for details.

At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.2 Efficacy Analysis Population

Efficacy analyses will be conducted in the APaT population.

9.5.3 Pharmacokinetic Analysis Populations

The Per-Protocol (PP) population will be used for analysis of PK data in this study. The PP population consists of the subset of subjects who complied with the protocol sufficiently to ensure that the data they generated will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. Major protocol violators will be identified prior to the database lock, by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with the reasons for exclusion, in the CSR.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Analysis by dose level will be performed by the initially assigned dose level. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Safety Analysis

The broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a SAE, an AE which is both drug-related and serious, who discontinued due to an AE, and who discontinued due to a drug-related AE will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

DLT will be listed and summarized by dose level. The pool adjacent violators-algorithm, which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses. The estimate of the DLT rate by dose level and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.2 Statistical Methods for Efficacy Analysis

- Objective Response (OR)

The point estimate and exact 95% Clopper-Pearson CI for response rates will be provided. Participants with missing data will be considered non-responders. This analysis will also be performed based on data pooled across all participants who eventually receive 65 mg.

- Duration of Response (DOR)

If the number of participants who achieve an objective response permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who achieve an objective response will be included in this analysis. Details will be documented in sSAP as appropriate.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 11.

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
OR per disease-specific criteria† by investigator	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders
DOR per disease-specific criteria† by investigator	Summary statistics using Kaplan-Meier method	Responders in APaT population	Details will be documented in sSAP

Abbreviations: APaT=all-participants-as-treated; CI=confidence interval; DOR=duration of response; OR=objective response; sSAP=supplemental statistical analysis plan.

† See Section 8.2.1

9.6.3 Statistical Methods for Pharmacokinetic Analysis

Plasma concentrations of nemtabrutinib will be summarized by planned visit and time for each dose level separately. PK parameters will be summarized by dose level. Details of statistical analysis of pharmacokinetic analyses will be documented in the sSAP as appropriate.

9.6.4 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized in the population which consists of all allocated participants. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed.

9.7 Interim Analyses

No interim analysis will be performed. Data will be examined on a continuous basis to allow for dose finding decisions.

9.8 Multiplicity

There will be no multiplicity control in this study since no hypothesis testing is planned.

9.9 Sample Size and Power Calculations

Each dose level assessed will have a minimum of 3 participants. Based on the occurrence of DLTs, up to 6 participants may enroll per dose level. The actual sample size is dependent on the number of dose levels tested and emerging safety data. The estimated DLT rate among 3 or 6 participants in the DLT evaluable population and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) are provided in Table 12.

Table 12 Precision of the Estimated DLT Rates

Number of DLT events	N=3		N=6	
	DLT rate	90% credible interval	DLT rate	90% credible interval
0	0.000	(0.013, 0.527)	0.000	(0.007, 0.348)
1	0.333	(0.098, 0.751)	0.167	(0.053, 0.521)
2	0.667	(0.249, 0.902)	0.333	(0.129, 0.659)
3	1.000	(0.473, 0.987)	0.500	(0.225, 0.775)
4	NA	NA	0.667	(0.341, 0.871)
5	NA	NA	0.833	(0.479, 0.947)
6	NA	NA	1.000	(0.652, 0.993)

9.10 Subgroup Analyses

No subgroup analyses will be performed.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in days.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power, randomization, and blinding) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of

stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source records according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are

intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central

contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- The following laboratory samples will also be collected as indicated in the SOA (Section 1.3):
  - Serum β2-microglobulin.
  - Serum immunoglobulin IgA, IgG, and IgM.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential [a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen or urea [b]	Potassium	Aspartate Aminotransferase /Serum Glutamic-Oxaloacetic Transaminase	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate) [c]	Chloride	Magnesium
	Creatinine or creatinine clearance [d]	Sodium	Alanine Aminotransferase /Serum Glutamic-Pyruvic Transaminase	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Lactate dehydrogenase
	Phosphorous	Lipase	Uric acid	
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte (esterase) by dipstick or urinalysis Microscopic examination (if blood or protein is abnormal, or per local standard of care)			
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Serum or urine pregnancy test (as needed for WOCBP) Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, hepatitis B surface antibody, HCV RNA and HBV DNA) as required by local health authority or institutional regulations. Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

Abbreviations: aPTT=activated partial thromboplastin time; BUN=blood urea nitrogen; GFR=glomerular filtration rate; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; WBC=white blood cell; WOCBP=woman of childbearing potential.

NOTES:

a. Absolute number is required and % differential is requested if available.
b. BUN is preferred; if not available, urea may be tested.
c. Performed only if considered the local standard of care.
d. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
   - All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study).
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. For hematologic toxicities in participants with CLL, assessment of intensity will be according to iwCLL in Appendix 11. Any AE that changes CTCAE/iwCLL grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - 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 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 AE.

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
    - Yes, there is a reasonable possibility of study intervention relationship:
        - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
    - No, there is not a reasonable possibility of study intervention relationship:
        - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
ECOG = Eastern Cooperative Oncology Group Adapted from [ECOG ACRIN Cancer Research Group 2016]	

10.9 Appendix 9: Disease Response Criteria

10.9.1 Application of the iwCLL Classification for Treatment Response Assessment

iwCLL Criteria 2018 are available in [Hallek, M., et al 2018].

10.9.1.1 Overview

This appendix describes the process for assessing treatment response according to the iwCLL Criteria for CLL/SLL [Hallek, M., et al 2018]. Focal lesions (lymph nodes and others), spleen, and liver will be assessed along with constitutional symptoms, hematologic parameters (lymphocytes, neutrophils, platelets, hemoglobin), and bone marrow.

Anatomic imaging may include CT, MRI, or some combination of the 2. CT is the most common modality used, and for the purposes of this document the term "CT" will be used to represent all anatomic imaging, no matter which imaging modality is used.

Before treatment ("baseline"), on CT, all malignant lymph nodes ("nodal lesions") will be classified as "target" (selected for quantitative assessment) or as "non-target" (selected for qualitative assessment). All focal non-nodal lesions are followed as non-target. The spleen will be assessed quantitatively (by measuring the craniocaudal length), and the liver will be assessed qualitatively. If biopsy is performed, or if there are any physical examination findings that cannot be evaluated by imaging, these should be documented.

After therapy has begun, target lesions, non-target lesions, and the presence of new lesions in images will be assessed to provide a collective response in focal lesions (usually referred to as the "lymph node response" because the great majority of the focal lesions are lymph nodes). The spleen and liver will be assessed separately from focal lesions for an organomegaly response. Lymph node response, spleen and liver response, and specific pieces of clinical information will be combined to produce the overall response for each timepoint. The criteria are summarized in the tables below and detailed in the following sections.

10.9.1.2 Anatomic Disease Assessment

Anatomic assessment specifically refers to the size of focal lesions or organs, assessed using computed tomography or magnetic resonance imaging. As stated previously, for simplicity the term "CT" will be used to represent all anatomic imaging.

10.9.1.2.1 Screening (Baseline) Assessment

Documentation of focal lesions

All focal lesions are identified at screening and classified as measurable or non-measurable. Up to 6 of the measurable nodal lesions are selected as "target" lesions, which are then followed quantitatively throughout the study. All other focal lesions (including non-nodal lesions) are documented as "non-target" lesions and evaluated qualitatively thereafter.

Measurable and non-measurable lesions

Malignant lymph nodes (nodal lesions) are considered measurable if they are considered to be due to CLL, are clearly and reproducibly measurable in 2 dimensions in the axial plane, and measure >1.5 cm in LDi when assessed by CT/MRI scan, irrespective of scanner type and slice thickness/interval.

Lesions considered non-measurable include:

- Uni-dimensionally measurable lesions (clearly measurable in only 1 dimension)
- Extranodal lesions which are considered to be clearly due to CLL

Target and Non-target Lesions

Up to 6 target lesions will be selected from among the measurable lesions and documented as target lesions. Target lesions should be selected based on their size (largest lesions preferred) and suitability for reproducible measurements. Measurements of the LDi and longest perpendicular, or "SDi" should be made in the axial plane on the slice of the lesion with the longest in-plane diameter. Calculate the product of PPD for each target lesion and the SPD for all target lesions.

Non-target lesions will be all focal (nodal or extranodal) lesions not chosen as target lesions, whether they were measurable or not.

Once lesions are designated as target or non-target, those designations may not change during later assessments.

Spleen Assessment at Baseline

Splenic disease will be assessed quantitatively, independent of the assessment of measurable and non-measurable focal lesions. The spleen will be measured in the cranial to caudal axis, and all spleen measurements referred to hereafter will refer to this craniocaudal length. The spleen is considered normal if the length is less than 13 cm (or if the spleen has been removed surgically). It is considered enlarged if it is greater than or equal to 13 cm in length. The portion of the measurement that exceeds 12.9 cm will be referred to as the abnormal portion, or the excess length.

Liver Assessment at Baseline

Hepatic enlargement will be assessed qualitatively, separately from the assessment of focal disease. At baseline, the liver will be assessed as either normal or enlarged (qualitatively enlarged based on expert judgment on CT scans, without a benign explanation of the enlargement).

10.9.1.2.2 Post-baseline Assessment

Target lesions

At each follow-up visit, target, non-target lesions and the presence of new lesions in images will be assessed to provide a collective lymph node response.

- CR: All target lymph nodes must have regressed to normal size defined as ≤1.5 cm in LDi. Target extranodal sites must be absent (0 by 0 cm).
- PR: ≥50% decrease in SPD of target lesions from baseline, and no individual lesion meets the criteria for progression.
- PD: Target lesion progression is based on the growth of any single target lesion (not a change in the SPD) from its nadir (smallest size previously seen, which can include the baseline if that is the smallest), which meets all of the following requirements:
  - The lesion must have increased by ≥50% from its nadir in PPD
  - It must be >1.5 cm in LDi
  - And 1 of the following:
    - For lesions <2 cm at nadir, the lesion's LDi or SDi must have increased by ≥0.5 cm at the current timepoint from its nadir.
    - For lesions ≥2 cm at nadir, the lesion's LDi or SDi must have increased by ≥1 cm at the current timepoint from its nadir.
- SD: A target lesion assessment of SD requires all of the following:
  - Target lesions do not meet the criteria for CR or PR
  - No individual lesion meets the criteria for progression
- NE: When any target lesion identified at baseline cannot be evaluated at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy or other procedures that change the lesion size, the target lesion assessment will be NE, unless progression is identified in another target lesion.

Non-target lesions

Non-target lesions will be assessed at each post-baseline timepoint individually and as a group. Response categories are as defined below:

- Absent/Normalized (CR): All individual non-target nodal lesions must have returned to normal size. All extranodal lesions must have disappeared.

- Unequivocal Progression (PD): Any individual non-target lesion must unequivocally progress in the context of the overall disease burden to be assessed as PD. For increased thickening of the wall of a hollow viscus, the reviewer will use their cautious judgment to determine whether the increase is most likely caused by disease progression.

PD should not be called based solely on enlarging pleural effusions or ascites, or enlarging lytic bone lesions. Rather, the overall assessment should be based on the rest of the disease burden.

- SD: At least 1 non-target lesion is still present, or a lymph node enlarged, without any individual lesions showing unequivocal progression.

- NE: When an individual non-target lymph node, extranodal lesion, or non-measurable disease manifestation cannot be assessed at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy to a lesion, the individual non-target lesion will be assessed as NE. The assessment of the non-target lesions as a whole will be NE if any of the non-target lesions are NE and none are PD.

New lesions

Lesions will be considered new if they were not present at the baseline timepoint but are visible at the current timepoint.

A node will be recorded as a new lesion if it was previously normal in size and is now >1.5 cm in LDi. An unequivocal, new extranodal lesion of any size is considered a new lesion. If multiple new lesions are noted, at least one should be documented individually as a new lesion.

New lesions must be strongly believed to be due to CLL rather than another etiology (eg, infection, inflammation).

Some types of truly non-measurable lesions generally require further verification that they are attributable to CLL through biopsy or cytology. These include ascites, pleural or pericardial effusions, and lytic bone lesions. They should be recorded as new lesions only when there is other evidence of progression.

Other truly non-measurable lesions will not require verification to be considered a new lesion, as long as their appearance is unequivocal in the judgment of the reviewer:

- Non-measurable lesions in the central nervous system, attributable to CLL
- Non-measurable nodal masses such as infiltrative mesenteric or retroperitoneal masses

Extranodal lesions which disappeared and then reappeared at a later timepoint will cause a determination of progression, just like a new lesion, but are not designated "new".

The combined focal lesion response will be determined as follows:

Lymph Node Response

Target	Non-target	New lesions	Lymph Node Response
CR	CR	No	CR
CR	SD	No	PR
PR	CR/SD	No	PR
SD	CR/SD	No	SD
Any non-PD	NE	No	NE
NE	Any non-PD	No	NE
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
NA	NA	No	NED

Abbreviations: CR=complete response; NA=not applicable – (no lesions of this type present at baseline); NE=not evaluable; NED=no evidence of disease – (no lesions of any kind seen at baseline, and none present at visit being evaluated); PD=progressive disease; PR=partial response; SD=stable disease.

Spleen response

The spleen will be measured in the craniocaudal length as at baseline, and the enlarged portion calculated by subtracting 12.9 cm. Response categories for the spleen are as defined below:

- Normal (CR): Spleen was enlarged at baseline and has regressed to <13 cm at the current timepoint, or the spleen was assessed as normal at baseline and is still normal, or there is radiological evidence of splenectomy at baseline, or the spleen was normal at baseline, and there has been a splenectomy since then.
- PR: Spleen was assessed as enlarged at baseline, and its excess length has decreased by ≥50%.
- SD: No decrease consistent with PR and no increase consistent with progression.

- PD: The spleen is assessed as showing PD if any of the following are true:

  - Recurrent splenomegaly: A spleen which was abnormal at baseline (≥13 cm) first returned to normal, but at the current timepoint the spleen has increased by ≥2 cm from its nadir and the length is ≥13 cm.

  - New splenomegaly: No prior splenomegaly. The spleen has increased by ≥2 cm from baseline and the length is ≥13 cm.

  - Progression of existing splenomegaly: A spleen which was abnormal at baseline has the enlarged portion increase by ≥50% at the current timepoint from its nadir value, and ≥1 cm in absolute length.

Liver response

The liver will be assessed qualitatively. Response categories are defined below:

- Normal (CR): Liver was assessed as enlarged at baseline and has regressed to a normal size, OR liver was assessed as normal at baseline and continues to be normal in size.

- SD: Liver is considered stable when it is qualitatively enlarged, without unequivocal increase, on the basis of CT and/or MRI scans.

- Unequivocal increase (PD): New hepatomegaly, recurrent hepatomegaly, or clear progression of existing hepatomegaly.

Liver and Spleen Response

The liver and spleen should be assessed together for a response at each post-baseline timepoint based on the following table.

Post-baseline Liver and Spleen Assessment

Liver	**Spleen**	**Liver & Spleen Response**
Normal	Normal (<13 cm)	CR
Normal Enlarged but stable	PR (enlarged portion decreased ≥50%)	PR
Enlarged but stable	CR (spleen went from enlarged to normal)	PR
Enlarged but stable	Remains normal	SD
Went from enlarged to normal	Stably enlarged	PR
Remains normal or Enlarged but stable	Stably enlarged	SD
Any except progression	NE	NE (extremely unlikely)
NE	Any except progression	NE (extremely unlikely)
Progression Newly enlarged or Definite growth from prior timepoint	Any	PD
Any	Progression 50% increase from baseline (≥1 cm increase) Regrowth of prior splenomegaly (≥2 cm increase) New splenomegaly (≥13 cm and ≥2 cm increase)	PD
Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease. Note: To be considered "enlarged" for the purposes of this assessment, the liver must be enlarged (qualitative assessment by experienced reviewer) without any non-malignant explanation for the enlargement.		

Clinical data

At each follow-up timepoint, constitutional symptoms, circulating lymphocyte count, platelet count, neutrophil count, hemoglobin, and bone marrow will also be considered as part of the response assessment.

Constitutional Symptoms

Participants will be evaluated for the presence of fever (≥38.0^{0}C), night sweats, weight loss and significant fatigue at every follow up timepoint.

Blood Count and Bone Marrow Assessments

Hemoglobin, platelets, neutrophils, lymphocytes will be assessed at each follow up timepoint and results will be incorporated into the overall response. At certain protocol-specified time points, additional tissue biopsies may be collected and incorporated into the response assessment.

Physical examination findings

On rare occasions, lesions may be present on physical examination that are not seen on imaging at all. An example might be lymphadenopathy in the popliteal fossa, when the "whole body" imaging includes only anatomy to the mid femur. Such lesions should be documented as non-target lesions in study forms. They can contribute to progression if new lesions appear this way, and if any were present at baseline, they must disappear for an overall response of CR. If imaging was not performed, but the spleen and liver were assessed by physical examination, they can be used to contribute to the response assessment, in a qualitative manner only.

10.9.1.3 Overall Response

The imaging and clinical parameters are classified into 2 groups (A and B) and these groups will be assessed for response. Group A includes lymph node response, liver and spleen response, constitutional symptoms, and lymphocyte count. Group B includes platelet count, hemoglobin and bone marrow assessment.

Response Category Definitions

Complete Response (CR): All criteria from both groups have to be met.

- Group A:
  - All lymph nodes (none ≥1.5 cm)
  - Liver and spleen are normal
  - Participant should have no constitutional symptoms
  - Circulating lymphocyte count is normal ($<4 \times 10^9$/L)
- Group B:
  - Platelet count $\geq 100 \times 10^9$/L
  - Hemoglobin ≥11.0 g/dL (untransfused and without erythropoietin)

- Neutrophils ≥1.5 × 10^9/L (without exogenous growth factors)
- Normocellular marrow with no CLL cell or B-Lymphoid nodules

Complete Response with Incomplete Marrow Recovery (CRi)

CRi is defined as a CR with an incomplete recovery of the study participant's bone marrow. Study participants who have a CRi fulfill the criteria for a CR (including bone marrow examinations), but continue to have persistent anemia, thrombocytopenia, and/or neutropenia apparently unrelated to CLL, but related to drug toxicity.

Nodular Partial Response (nPR)

nPR is assessed when criteria for CR are met, except that bone marrow biopsy shows lymphoid nodules, reflecting residual disease (normocellular or hypocellular, <30% lymphocytes and lymphoid nodules present).

Partial Response (PR): At least 2 parameters from Group A and 1 parameter from Group B improve from screening if they were abnormal at previous timepoints. If only 1 of the parameters in each group was abnormal, only one needs to improve. Improvement is described as the following:

- Group A:
  - PR in lymph nodes (≥50% decrease in SPD)
  - PR in liver/spleen size (see above)
  - ≥50% decrease in circulating lymphocyte count from baseline
  - Resolution of constitutional symptoms
- Group B:
  - Platelet counts should be ≥100 × 10^9/L or increase ≥50% from baseline
  - Hemoglobin ≥11 g/dL or ≥50% increase from baseline
  - Marrow: Presence of CLL cells, or of B-lymphoid nodules, or not done

Partial Response with Lymphocytosis (PRL)

The overall response will be PRL when ALL of the following criteria are met:

- Lymphocyte count is stable or increased from baseline
- All other criteria for PR or better are met.

An increase in blood lymphocyte count by itself does not uniformly indicate an increased tumor burden but may reflect redistribution of leukemia cells from lymphoid tissues to the blood. In such cases, increased lymphocytosis alone is not a sign of treatment failure.

Progressive Disease (PD) if any of the parameters in group A or B indicate progression

- Group A:
  - Lymph node response is PD
  - Liver and spleen assessment shows PD
  - Circulating lymphocytes increase ≥50% from nadir (unless PRL, as above)

Elevation of treatment-related lymphocytosis, particularly during the initial phase of treatment, will not be considered PD unless at least 1 other feature shows worsening (ie, lymphadenopathy, splenomegaly, anemia or thrombocytopenia meet criteria for disease progression) at the same evaluation or the next evaluation.

- Group B:
  - Platelet count decreases ≥50% from baseline secondary to CLL
  - Hemoglobin decrease of ≥2 g/dL from baseline secondary to CLL
  - Marrow shows increase of CLL cells by ≥50% on successive biopsies

Transformation to a more aggressive histology (Richter syndrome or Richter transformation) is also considered PD. The diagnosis of Richter transformation should be established by lymph node or other tissue biopsy.

Stable Disease (SD): if participant parameters do not meet criteria for PR, PD or CR

Not evaluable (NE): if any of the imaging, constitution and blood parameters cannot be assessed and criteria for PD are not met:

Note: Missing or inconclusive bone marrow data will not drive an assessment of NE by itself.

10.9.1.4 iwCLL Summary Table

The following table summarizes the assessments based on both imaging and hematological parameters [Hallek, M., et al 2018].

Group	Parameter	Complete Response	Partial Response	Progressive Disease	Stable Disease
A	Lymph nodes	CR (see lymph node response table)	PR (see lymph node response table)	PD (see lymph node response table)	SD (see lymph node response table)
	Liver and/or spleen size	CR (see liver and spleen response table)	PR (see liver and spleen response table)	PD (see liver and spleen response table)	SD (see liver and spleen response table)
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% (from screening)	Increase ≥50% (from nadir)	Change of -49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 x 10^9/L or increase ≥50% over screening	Decrease ≥50% (from screening secondary to CLL)	Change of -49% to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11.0 g/dL or increase ≥50% over screening	Decrease ≥2 g/dL (from screening secondary to CLL)	Increase <11 g/dL or <50% over screening or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate
	Neutrophils	≥1.5 × 10^9/L (no exogenous growth factors)	Non-CR (Not meeting criteria for CR)	Non-CR (Not meeting criteria for CR)	Non-CR (Not meeting criteria for CR)

Abbreviations: CLL=chronic lymphocytic leukemia; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

10.9.2 Application of the Lugano Classification for Treatment Response Assessment

10.9.2.1 Overview

This appendix describes the process for assessing treatment response according to the Lugano Classification [Cheson, B. D., et al 2014] for malignant lymphoma ("Lugano" from now on). This assessment includes anatomic imaging with CT or MRI (size assessments of lymph nodes, extranodal lesions, spleen, and liver), metabolic imaging (whole body assessment with FDG-PET), and clinical findings (physical examination and bone marrow biopsy results), when these are available and appropriate.

Anatomic imaging may include CT, MRI, or some combination of the 2. CT is the most common modality used, and for the purposes of this document the term "CT" will be used to represent all anatomic imaging, no matter which imaging modality is used.

Before treatment ("baseline"), on CT all focal lesions (nodal and extranodal) will be classified as "target" (selected for quantitative assessment) and "non-target" (selected for qualitative assessment). The spleen will be assessed quantitatively (by measuring the vertical length), and the liver will be assessed qualitatively. The FDG-PET will be assessed using the 5-point scale (a method similar to the older Deauville criteria). If bone marrow biopsy is performed, or if there are any physical examination findings that cannot be evaluated by imaging, these should be documented.

After therapy has begun, response assessment will include anatomic response based on CT (when a CT is available), which includes target, non-target, and new focal lesions, as well as spleen and liver size assessment. Metabolic response, when an FDG-PET is available, will be based on the 5-point scale along with qualitative assessment of changes in FDG uptake from preceding timepoints. Anatomic response, metabolic response, and clinical information will be combined to produce the overall response for each timepoint. The criteria are summarized in the table below, and detailed in the following sections.

10.9.2.2 Lugano Summary Table

The following tables summarize the assessments based on both CT and PET, as described in the summary table in the original publication [Cheson, B. D., et al 2014]. For details about implementation, please see the sections following the tables.

Complete Response

Complete Response	PET-Based Response – CMR	CT/MRI-Based Response – CR
Target lesions	Score 1, 2, or 3	Target nodes/nodal masses regress to <1.5 cm in LDi; no extranodal sites of disease remain
Non-target lesions	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, negative by immunohistochemistry
Abbreviations: CMR=complete metabolic response; CR=complete response; CT=computed tomography; FDG=2 fluorodeoxyglucose; LDi=longest diameter; MRI=magnetic resonance imaging; PET=positron emission tomography.		

Partial Response

Partial Response	PET-Based Response – PMR	CT/MRI-Based Response – PR
Target lesions	Score 4 or 5 without new lesions Reduced overall uptake (extent and/or intensity) compared with baseline	≥50% decrease from baseline in SPD of target lymph nodes and extranodal sites (up to 6)
Non-target lesions	Not applicable	Anything other than progression
Organ enlargement	Not applicable	Spleen must have regressed by ≥50% in excess length
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline. If there are persistent focal changes in the marrow in the context of a nodal response and without recent growth factor use, perform biopsy, or consider MRI, or an interval scan.	Not applicable
Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; PMR=partial metabolic response; PR=partial response; SPD=sum of products of diameters.		

Stable Disease

Stable disease	PET-Based Response – SMD	CT/MRI-Based Response – SD
Target lesions	Score 4 or 5 (without new lesions) No significant change in FDG uptake from baseline or nadir	<50% decrease from baseline in SPD of target lesions. No lesion shows progression
Non-target 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
Abbreviations: CT=computed tomography; FDG=2 fluorodeoxyglucose; MRI=magnetic resonance imaging; PET=positron emission tomography; SD=stable disease; SMD=stable metabolic disease; SPD=sum of products of diameters.		

Progressive Disease

Progressive disease	PET-Based Response – PMD	CT/MRI-Based Response – PD
Target lesions	Score 4 or 5 with an increase in overall uptake (extent and/or intensity) compared within nadir	Growth of any target lesion: Increase ≥50% from nadir PPD and Increase in LDi or SDi from nadir of: ≥0.5 cm for lesions <2 cm ≥1.0 cm for lesions ≥2 cm and Current LDi >1.5 cm for a lymph node or ≥1.0 cm for an extranodal lesion
Non-target lesions	Not applicable	Clear progression of pre-existing non-target lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another cause (eg, infection, inflammation). If uncertain regarding cause of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node >1.5 cm in LDi A new extranodal site of any size so long as its presence is unequivocal and attributable to lymphoma
Organ enlargement	Not applicable	When splenomegaly was already present, the excess length must increase by ≥50% (≥1 cm absolute increase) from nadir. If no prior splenomegaly, or prior splenomegaly had resolved, spleen length must increase by ≥2 cm to >13 cm.
Bone marrow	New or recurrent FDG-avid foci, confirmed by biopsy	New or recurrent involvement
Abbreviations: CT=computed tomography; FDG=2 fluorodeoxyglucose; LDi=longest diameter; MRI=magnetic resonance imaging; PET=positron emission tomography; PD=progressive disease; PMD=progressive metabolic disease; PPD=product of perpendicular diameters; SDi=short axis diameter.		

10.9.2.3 Anatomic Disease Assessment

Anatomic assessment specifically refers to the size of focal lesions or organs, assessed using computed tomography or magnetic resonance imaging. As stated previously, for simplicity the term “CT” will be used to represent all anatomic imaging.

10.9.2.3.1 Screening (Baseline) Assessment

Documentation of focal lesions

All focal lesions caused by lymphoma are identified at baseline and classified as measurable or non-measurable. Up to 6 of the measurable lesions are selected to serve as “target” lesions,

which are then followed quantitatively throughout the study. All other focal lesions are documented as "non-target" lesions, and evaluated qualitatively thereafter.

Measurable and non-measurable lesions

Malignant lymph nodes (nodal lesions) are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice, and measure >1.5 cm in LDi when assessed by CT/MRI scan, irrespective of scanner type and slice thickness/interval. Extranodal lesions are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice, and are ≥1.0 cm in both LDi and SDi when assessed by CT/MRI scan, regardless of slice thickness. In lymphomas that are FDG-avid, a lesion must be PET positive (show FDG uptake greater than the surrounding tissue) to be measurable.

Lesions considered non-measurable include:

- Lymph nodes and nodal masses that are PET positive and considered consistent with lymphoma, but that do not meet the size and reproducibility requirements to be considered measurable, and lesions visible on PET but not CT
- PET-negative lesions which meet the size criteria for measurability, and are considered consistent with lymphoma, in lymphoma that shows FDG avidity in other lesions
- Uni-dimensionally measurable lesions (clearly measurable in only 1 dimension)
- Extranodal lesions which do not meet the requirements for measurability, but are considered to be clearly due to lymphoma
- Truly non-measurable/assessable sites of disease, including:
    - Effusions and ascites
    - Bone lesions
    - Brain lesions, CNS lesions, leptomeningeal disease
    - Mucosal lesions in the gastrointestinal tract
    - Pleural, peritoneal or bowel wall thickening

Target and Non-target Lesions

Up to 6 target lesions will be selected from among the measurable lesions and documented as target nodal and target extranodal lesions. Target lesions should be selected based on their size (largest lesions preferred) and suitability for reproducible measurements. Measurements of the LDi and SDi should be made in the axial plane on the slice of the tumor with the

longest in-plane diameter. Calculate the product of PPD for each target lesion and the SPD for all target lesions.

Non-target lesions will be all focal (nodal and extranodal) lesions that are consistent with lymphoma, but not chosen as target lesions, whether they were measurable or not.

Once lesions are designated as target or non-target, those designations may not change during later assessments.

Spleen Assessment at Baseline

Splenic involvement will be assessed quantitatively, as a separate category from the assessment of measurable or non-measurable focal lesions. The spleen length will be measured from cranial to caudal. All spleen measurements referred to hereafter will refer to this craniocaudal measurement. The spleen is considered normal if it is less than 13 cm, or if the spleen has been removed surgically. It is considered enlarged if it is greater than 13 cm in length. The portion of the measurement that exceeds 13 cm will be considered the abnormal portion.

Liver Assessment at Baseline

Hepatic involvement will be assessed qualitatively, separately from the assessment of measurable or non-measurable disease. At baseline, the liver will be assessed qualitatively as either normal or enlarged, and should only be documented as enlarged if there is clear evidence (based on biopsy or imaging) that the enlargement is due to infiltration by lymphoma, and not to benign causes.

10.9.2.3.2 Post-baseline Assessment

Target lesions

At every timepoint after screening, each target lesion is measured. Calculate the PPD for each target lesion and the SPD for all target lesions together. Response categories are as defined below:

- Complete Response (CR): All target lymph nodes must have regressed to normal size defined as ≤1.5 cm in LDi. Target extranodal sites must be absent (0 by 0 cm).
- Partial Response (PR): ≥50% decrease in SPD of target lesions from baseline, and no individual lesion meets the criteria for progression.
- Progressive Disease (PD): Target lesion progression is based on the progression of any single lesion (not a change in the SPD), which meets all of the following requirements:
  - The lesion must have increased by ≥50% from its nadir in PPD.
  - For a lymph node, it must be >1.5 cm in LDi, and for an extranodal lesion it must be ≥1.0 cm in LDi.

- And one of the following:
    - For lesions <2 cm at nadir, the lesion's LDi or SDi must have increased by ≥0.5 cm at the current timepoint from its nadir.
    - For lesions ≥2 cm at nadir, the lesion's LDi or SDi must have increased by ≥1 cm at the current timepoint from its nadir.

- Stable Disease (SD): A target lesion assessment of SD requires all of the following:
    - Target lesions do not meet the criteria for CR or PR
    - No individual lesion meets the criteria for progression
- Not Evaluable (NE): When a target lesion identified at baseline cannot be evaluated at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy or other procedures that change the lesion size, the target lesion assessment will be NE, unless progression is assessed in another target lesion.

Non-target lesions

Non-target lesions will be assessed at each post-baseline timepoint individually and as a group. Response categories are as defined below:

- Absent/Normalized (CR): All individual non-target nodal lesions must have returned to normal size. All extranodal lesions must have disappeared.
- Unequivocal Progression (PD): Any individual non-target lesion must unequivocally progress in the context of the overall disease burden to be assessed as PD. For increased thickening of the wall of a hollow viscus, the reviewer will use their cautious judgment to determine whether the increase is most likely caused by disease progression.
    - PD should not be called based on enlarging pleural effusions or ascites, or enlarging lytic bone lesions, and rather, the overall assessment should be based on the rest of the disease burden.
- Stable Disease (SD): At least 1 non-target lesion is still present, or a node enlarged, without any individual lesions showing unequivocal progression.
- Not Evaluable (NE): When an individual non-target lesion lymph node, extranodal lesion, or non-measurable disease cannot be assessed at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy to a lesion, the individual non-target lesion will be assessed as NE. The assessment of the non-target lesions as a whole will be NE if any of the non-target lesions are NE and none are PD.

New lesions

Lesions will be considered new if they were not present at the baseline timepoint, but are visible at the current timepoint.

A node consistent with lymphoma will be recorded as a new lesion if it was previously normal in size and is now >1.5 cm in LDi. An unequivocal, new extranodal lesion consistent with lymphoma of any size is considered a new lesion. If multiple new extranodal lesions are noted, at least one should be recorded as a new lesion.

New lesions must be consistent with lymphoma rather than another etiology (eg, infection, inflammation) and must be PET-positive, if PET is available. New lesions will be treated as PET-positive when PET is not available to confirm avidity.

Some types of truly non-measurable lesions generally require further verification that they are attributable to lymphoma through biopsy or cytology. These include ascites, pleural or pericardial effusions, and lytic bone lesions. They may be recorded as new lesions only when there is other evidence of progression.

Other truly non-measurable lesions will not require verification to be considered a new lesion, as long as their appearance is unequivocal in the judgment of the reviewer:

- Non-measurable lesions such as brain and CNS lesions including leptomeningeal disease attributable to lymphoma

- Non-measurable nodal masses such as infiltrative mesenteric masses or retroperitoneal masses

Extranodal lesions which disappeared and then reappeared at a later timepoint will be considered indicators of progression.

Spleen response

The spleen will be measured in the craniocaudal length as at baseline, and the enlarged portion calculated by subtracting 13 cm. Response categories for the spleen are as defined below:

- Normal (CR): Spleen was enlarged at baseline and has regressed to ≤13 cm at the current timepoint or the spleen was assessed as normal at baseline and is still normal, or there is radiological evidence of splenectomy at baseline.

- Partial Resolution (PR): Spleen was assessed as enlarged at baseline, and its excess length has decreased by ≥50%.

- Stable Splenomegaly (SD): No decrease consistent with PR and no increase consistent with progression

- Unequivocal increase (PD): The spleen is assessed as PD if any of the following are true:

  - Recurrent splenomegaly: A spleen which was abnormal at baseline (>13 cm) first returned to normal, but at the current timepoint the spleen increases by >2 cm from its nadir and the length is >13 cm.

  - New splenomegaly: No prior splenomegaly and spleen increases by >2 cm from baseline and the length is >13 cm.

  - Progression of existing splenomegaly: A spleen which is abnormal at baseline has the enlarged portion increase by ≥50%, and by ≥1 cm in absolute measurement, at the current timepoint from its nadir value.

Liver response

The liver will be assessed qualitatively. Response categories are as defined below:

- Non-pathological: Liver was assessed as enlarged at baseline and has regressed to a normal size, or still enlarged but without evidence of lymphoma involvement, OR the liver was assessed as normal at baseline and continues to be normal.

- Enlargement: Liver is considered stable if there is persistent liver involvement with evidence based on imaging (CT or MRI) or biopsy that there is infiltration by lymphoma of the entire organ.

Anatomic Response

The anatomic response should be assessed at each post-baseline timepoint based on the criteria below. Liver size alone should never be the basis for response determination by itself, but only support the assessment as supplemental information.

Target	Non-Target	Spleen	New Lesions	Anatomic Response
CR	CR	CR	No	CR[a]
CR	CR	PR	No	PR[b]
CR	SD	CR	No	PR [b]
PR	CR/SD	CR/PR	No	PR
PR	CR/SD	SD	No	SD
SD	CR/SD	CR/PR	No	SD
SD	CR/SD	CR/PR/SD	No	SD
Any non-PD	NE	CR/PR/SD	No	NE
NE	Any non-PD	CR/PR/SD	No	NE
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
Any	Any	Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

[a] If the liver shows lymphoma involvement, it must resolve to allow CR.

[b] Spleen can drive PR on its own if no target lesions were identified at baseline.

10.9.2.4 Metabolic Response

In addition to anatomic imaging, metabolic imaging using FDG-PET can contribute to the assessment, if it is available, or may form the sole basis for response if no anatomic imaging is performed at a time point. An FDG-PET is required at screening. Subsequent time points that require PET are shown in the schedule of assessments. If lesions are not FDG-avid at baseline, PET is not required at follow-up timepoints unless clinically indicated.

PET Assessment

For every FDG-PET scan, a 5PS score is obtained by comparing the maximum standard uptake value of the lesion that shows the greatest tracer uptake (the “hottest” lesion) to surrounding normal tissue, to a ROI placed over blood in the heart or major vessels of the mediastinum (the “mediastinal blood pool”) and to an ROI placed over normal liver.

Depending on the uptake, a score between 1 and 5 will be assigned as follows:

Score	Definition
1	No uptake above background
2	Uptake above background, but below mediastinal blood pool
3	Uptake >mediastinal blood pool, but ≤uptake in liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver (maximum standard uptake value >2 × normal liver) OR (after treatment has started) New FDG-positive lymphoma lesions

After screening, in addition to the 5-point scale score the assessment of the FDG-PET also involves an assessment of the overall uptake (a combination of extent and intensity) by tissue consistent with lymphoma, and comparison of this uptake to the baseline and to the scan on which the overall uptake was lowest (nadir).

Metabolic response determination

Metabolic response categories are defined as follows:

Metabolic Response	Definition
Complete metabolic response (CMR)	A score of 1, 2, or 3.
Partial metabolic response (PMR)	A score of 4 or 5 (without new lesions), AND Overall uptake decreased compared with baseline
Stable metabolic disease (SMD)	A score of 4 or 5 (without new lesions), AND Overall uptake unchanged compared with baseline and nadir
Progressive metabolic disease (PMD)	A score of 4 or 5 with overall uptake increased compared with nadir, OR with new FDG-positive lesions consistent with lymphoma

In Waldeyer's ring or extranodal sites with high 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, CMR 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.

Clinical Data

Bone marrow assessment

To allow an overall response of CR, the bone marrow must be clear of lymphoma (negative for lymphoma).

Lugano allows assessment of bone marrow based on FDG-PET if the lymphoma type is FDG-avid. Bone marrow on FDG-PET may be normal, may show diffuse uptake (clinical judgment is required, because this is also compatible with reactive changes due to chemotherapy or colony-stimulating factors), or may show focal increased uptake that is strongly indicative of lymphoma.

Note: In this protocol, if there is bone marrow involvement, bone marrow is required to confirm CR, regardless of FDG-avidity.

A negative PET allows the bone marrow to be declared negative, even without biopsy, and would support a CR overall (diffuse uptake compatible with reactive changes from chemotherapy or growth factor use can fall into this category). A PR may occur with residual uptake higher than uptake in normal marrow but reduced compared with baseline. 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.

Bone marrow aspirate or biopsy is required only as clinically indicated, or if FDG-PET evaluation of bone marrow is judged inconclusive. For lymphoma that is shown at baseline to be non FDG-avid, both aspiration and biopsy are required to declare marrow to be negative. If bone marrow biopsy is performed and shows lymphoma, the bone marrow is considered positive, regardless of the results of the PET.

Physical examination findings

On rare occasions, lesions may be present on physical examination that are not seen on imaging at all. An example might be lymphadenopathy in the popliteal fossa, when the "whole body" imaging includes only anatomy to the mid femur. Such lesions should be documented as non-target lesions in study forms. They can contribute to progression if new lesions appear this way, and if any were present at baseline, they must disappear for an overall response of CR.

Other clinical data

Information on the use of hematopoietic growth factors and other medications can affect the response assessment as described above.

At certain protocol-specified time points, additional tissue biopsies may be collected and incorporated into the response assessment.

10.9.2.5 Overall Response

Overall response at each timepoint is determined by combining the anatomic response, metabolic response, and clinical data. When both CT and FDG-PET are available, the overall response is driven primarily by the metabolic response. When only one imaging modality is available at a given timepoint, that modality is the main determinant of overall response.

Metabolic Response	Anatomic Response	Bone Marrow	Physical Examination	Overall Response
CMR	CR, PR, or SD	Negative	No lesions	CR
PMR	CR, PR, or SD	Any	No new lesions	PR
SMD	CR, PR, or SD	Any	No new lesions	SD
PMD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Abbreviations: CMR=complete metabolic response; CR=complete response; PD=progressive disease; PMD=progressive metabolic disease; PMR=partial metabolic response; PR=partial response; SD=stable disease; SMD=stable metabolic disease.				

During determination of overall response, if no FDG-PET was performed at the timepoint in question, the results of a preceding PET may be "carried forward", unless there has been worsening of disease on the CT. For example, if a post-baseline assessment shows a CMR on the PET, and PR on the CT, the overall response is CR. If the next timepoint shows continued PR on the CT, but there is no PET available, the overall response for that visit is still CR.

Lugano Classification 2014 [Cheson, B. D., et al 2014]

Barrington, SF et al 2014 [Barrington, S. F., et al 2014]

10.9.3 Application of the IWWM Classification for Treatment Response Assessment

IWWM Criteria 2014 are provided in [Dimopoulos, M. A., et al 2014].

10.9.3.1 Overview

This appendix describes the process for assessing treatment response according to the IWWM Criteria for WM [Dimopoulos, M. A., et al 2014]. Assessments include:

- Imaging of abnormal lymph nodes
- Imaging of spleen and liver
- Measurements of serum IgM
- Detection of IgM by immunofixation
- Measurements of cryoglobulins
- Bone marrow biopsy
- Constitutional symptoms

- Plasmapheresis
- Amyloid (if applicable)

At baseline/screening, the participant should be assessed for the presence of extramedullary disease. If extramedullary disease is present, imaging should be used to assess the disease at baseline and follow-up timepoints. If there is no extramedullary disease at screening/baseline, then imaging does not need to be repeated at subsequent follow-up timepoints, unless clinically indicated.

Anatomic imaging may include CT, MRI or some combination of the 2. CT is the most common modality used, and for the purposes of this document the term "CT" will be used to represent all anatomic imaging, no matter which imaging modality is used.

Before treatment ("baseline"), if extramedullary disease is present on CT, all malignant lymph nodes ("nodal lesions") will be classified as "target" (selected for quantitative assessment) or as "non-target" (selected for qualitative assessment). All focal non-nodal lesions are followed as non-target. The spleen will be assessed quantitatively (by measuring the craniocaudal length). If biopsy is performed, or if there are any physical examination findings that cannot be evaluated by imaging, these should be documented.

After therapy has begun, target lesions, non-target lesions, and the presence of new lesions in images will be assessed to provide a collective response in focal lesions (usually referred to as the "lymph node response" because the great majority of the focal lesions are lymph nodes). The spleen size will be assessed separately from focal lesions for an organomegaly response. Imaging responses (when applicable) are combined with changes in the clinical data (including serum IgM, immunofixation, cryoglobulinemia, bone marrow, constitutional symptoms, plasmapheresis, and amyloidosis) to produce an overall response at each timepoint.

10.9.3.2 Anatomic Disease Assessment

Anatomic assessment specifically refers to the size of focal lesions or organs, assessed using computed tomography or magnetic resonance imaging. As stated previously, for simplicity the term "CT" will be used to represent all anatomic imaging.

10.9.3.2.1 Screening (Baseline) Assessment

Documentation of focal lesions

If extramedullary disease is present, all focal lesions are identified at screening and classified as measurable or non-measurable. Up to 6 lesions are selected as "target" lesions, which are then followed quantitatively throughout the study. All other focal lesions are documented as "non-target" lesions and evaluated qualitatively thereafter.

Measurable and non-measurable lesions

Malignant lymph nodes (nodal lesions) are considered measurable if they are considered to be due to WM/LPL, are clearly and reproducibly measurable in 2 dimensions in the axial plane, and measure >1.5 cm in LDi when assessed by CT/MRI scan, irrespective of scanner type and slice thickness/interval.

Lesions considered non-measurable include:

- Uni-dimensionally measurable lesions (clearly measurable in only one dimension)
- Extranodal lesions which are considered to be clearly due to WM/LPL

Target and Non-target Lesions

Up to 6 target lesions will be selected from among the measurable lesions and documented as target lesions. Target lesions should be selected based on their size (largest lesions preferred) and suitability for reproducible measurements. Measurements of the LDi and longest perpendicular, or "SD1" should be made in the axial plane on the slice of the lesion with the longest in-plane diameter. Calculate the product of PPD for each target lesion and the SPD for all target lesions.

Non-target lesions will be all focal (nodal or extranodal) lesions not chosen as target lesions, whether they were measurable or not.

Once lesions are designated as target or non-target, those designations may not change during later assessments.

Spleen Assessment at Baseline

Splenic disease will be assessed quantitatively, independent of the assessment of measurable and non-measurable focal lesions. The spleen will be measured in the cranial to caudal axis, and all spleen measurements referred to hereafter will refer to this craniocaudal length. The spleen is considered normal if the length is less than 13 cm (or if the spleen has been removed surgically). It is considered enlarged if it is greater than or equal to 13 cm in length. The portion of the measurement that exceeds 12.9 cm will be referred to as the abnormal portion, or the excess length.

10.9.3.2.2 Post-baseline Assessment

Target lesions

At each follow up visit, target, non-target lesions and the presence of new lesions in images will be assessed to provide a collective lymph node response.

- Complete Response (CR): All target lymph nodes must have regressed to normal size defined as ≤1.5 cm in LDi. Target extranodal sites must be absent (0 by 0 cm).

- Partial Response (PR): ≥1% decrease in SPD of target lesions from baseline, and no individual lesion meets the criteria for progression.

- Progressive Disease (PD): Target lesion progression is based on either a ≥50% increase in the SPD of all target lesions, or a ≥50% an increase in the LDi of any single target lesion from its nadir (smallest size previously seen, which can include the baseline if that is the smallest), which meets all of the following requirements

    - The final size of the individual lesion must be >1.5 cm in LDi

    - And one of the following:

        - For lesions <2 cm at nadir, the lesion's LDi must have increased by ≥0.5 cm at the current timepoint from its nadir.

        - For lesions ≥2 cm at nadir, the lesion's LDi must have increased by ≥1 cm at the current timepoint from its nadir.

- Stable Disease (SD): A target lesion assessment of SD requires all of the following:

    - Target lesions do not meet the criteria for CR or PR

    - No individual lesion meets the criteria for progression

- Not Evaluable (NE): When any target lesion identified at baseline cannot be evaluated at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy or other procedures that change the lesion size, the target lesion assessment will be NE, unless progression is identified in another target lesion.

Non-target lesions

Non-target lesions will be assessed at each post-baseline timepoint individually and as a group. Response categories are as defined below:

- Absent/Normalized (CR): All individual non-target nodal lesions must have returned to normal size. All extranodal lesions must have disappeared.

- Unequivocal Progression (PD): Any individual non-target lesion must unequivocally progress in the context of the overall disease burden to be assessed as PD. For increased thickening of the wall of a hollow viscus, the reviewer will use their cautious judgment to determine whether the increase is most likely caused by disease progression.

- PD should not be called based solely on enlarging pleural effusions or ascites or enlarging lytic bone lesions. Rather, the overall assessment should be based on the rest of the disease burden.

- Stable Disease (SD): At least 1 non-target lesion is still present, or a lymph node enlarged, without any individual lesions showing unequivocal progression.

- Not Evaluable (NE): When an individual non-target lymph node, extranodal lesion, or non-measurable disease manifestation cannot be assessed at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy to a lesion, the individual non-target lesion will be assessed as NE. The assessment of the non-target lesions as a whole will be NE if any of the non-target lesions are NE and none are PD.

New lesions

Lesions will be considered new if they were not present at the baseline timepoint but are visible at the current timepoint.

A node will be recorded as a new lesion if it was previously normal in size and is now >1.5 cm in LDi, and the change in size and the node morphology indicate malignancy. An unequivocal, new extranodal lesion of any size is considered a new lesion. If multiple new lesions are noted, at least one should be documented individually as a new lesion.

New lesions must be strongly believed to be due to WM/LPL rather than another etiology (eg, infection, inflammation).

Some types of truly non-measurable lesions generally require further verification that they are attributable to WM/LPL through biopsy or cytology. These include ascites, pleural or pericardial effusions, and lytic bone lesions. They should be recorded as new lesions only when there is other evidence of progression.

Other truly non-measurable lesions will not require verification to be considered a new lesion, as long as their appearance is unequivocal in the judgment of the reviewer:

- Non-measurable lesions in the central nervous system, attributable to WM/LPL

- Non-measurable nodal masses such as infiltrative mesenteric or retroperitoneal masses

Extranodal lesions which disappeared and then reappeared at a later timepoint will cause a determination of progression, just like a new lesion, but are not designated “new”.

Spleen response

The spleen will be measured in the craniocaudal length as at baseline, and the enlarged portion calculated by subtracting 12.9 cm. Response categories for the spleen are as defined below:

- Normal (CR): Spleen was enlarged at baseline and has regressed to <13 cm at the current timepoint, or the spleen was assessed as normal at baseline and is still normal, or there is radiological evidence of splenectomy at baseline, or the spleen was normal at baseline, and there has been a splenectomy since then.

- Partial Response (PR): Spleen was assessed as enlarged at baseline, and its excess length has decreased by ≥1%.

- Stable Disease (SD): No decrease consistent with PR and no increase consistent with progression.

- Progressive Disease (PD): The spleen is assessed as showing PD if any of the following are true:

    - Recurrent splenomegaly: A spleen which was abnormal at baseline (≥13 cm) first returned to normal, but at the current timepoint the spleen has significantly increased as judged by reviewer(s) and the length is ≥13 cm.

    - New splenomegaly: No prior splenomegaly. The spleen has increased significantly as judged by reviewer(s) from baseline and the length is ≥13 cm.

    - Progression of existing splenomegaly: A spleen which was abnormal at baseline has the significantly enlarged as judged by reviewer(s)

The combined radiology response will be determined as follows:

Radiology Response

Target	Non-target	New lesions	Spleen Response	Radiology Response
CR	CR	No	CR	CR
CR	SD	No	PR/CR	PR
PR	CR/SD	No	PR/CR	PR
PR	CR/SD	No	SD	SD
SD	CR/SD	No	Any but PD	SD
Any non-PD	NE	No	Any but PD	NE
NE	Any non-PD	No	Any but PD	NE
Any non -PD	Any non-PD	No	NE	NE
PD	Any	Yes/No	Any	PD
Any	PD	Yes/No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes/No	PD	PD
NA	NA	No	Normal (CR)	NED

Abbreviations: CR=complete response; NA=not applicable; NE=not evaluable; NED=no evidence of disease; PD=progressive disease; PR=partial response; SD=stable disease.

NA – No lesions of this type present at baseline.

NED – No lesions of any kind seen at baseline, and none present at visit being evaluated.

Clinical data

At each follow-up timepoint, serum IgM measurements, detection of IgM by immunofixation, cryoglobulin measurements, physical exams, bone marrow biopsy assessments, constitutional symptoms, plasmapheresis, and amyloid (if applicable) are assessed and will also be considered as part of the response assessment.

10.9.3.3 Overall Response

Overall response for each timepoint is defined below.

Response category definitions

Overall Timepoint Assessment

Response and Sub-categories for assessment	Overall Timepoint Assessment
Complete Response (CR)	**Complete resolution of disease (all of the following)**
Serum IgM	CR (Normal Serum IgM from baseline)
Serum M-Protein Immunofixation	Negative If immunofixation status is not reported/not interpretable for any available timepoints, the best possible response is VGPR. One negative immunofixation is sufficient to be called CR for a particular visit. Once a negative immunofixation has been reported for a visit, any subsequent visits with immunofixation status not reported or not interpretable can be CR as long as all remaining data supports a continued CR status.
Extramedullary Disease by Physical Examination	No EMD Present
Cryoglobulinemia	• Negative cryoglobulinemia if cryoglobulinemia was Positive at baseline. • If cryoglobulinemia was negative or not available at baseline, a negative cryoglobulinemia assessment at post-baseline is not required for an overall timepoint assessment of CR.
Radiology Overall Response	CR or NED
Bone Marrow	Negative Negative assessment of bone marrow is required to confirm CR even if bone marrow is negative at baseline. Once a CR has been confirmed by bone marrow then repeat bone marrow is not required.
Other Confounding Factors	No If amyloidosis was present at baseline, then it must be absent. No new symptomatic disease should be observed.
Very Good Partial Response	**At least one sub-category does not meet the criteria for CR; none of the sub-categories meet the criteria for PD; and responses are described below:**
Serum IgM	VGPR or CR (≥90% reduction in Serum IgM or normal from baseline)
Radiology Overall Response	CR or PR
Extramedullary Disease by Physical Examination	• Spleen and/or Lymph nodes which were assessed as Enlarged at baseline are assessed as Normal/Not Enlarged or • No EMD is present at baseline and post-baseline
New Symptomatic Disease	Absent

Response and Sub-categories for assessment	**Overall Timepoint Assessment**
Partial Response	**All criteria have to met**
Serum IgM	PR (≥50% and <90% reduction in Serum IgM from baseline)
Extramedullary Disease by Physical Examination	• Spleen and/or Lymph nodes which were assessed as Enlarged at baseline are assessed as Normal/Not Enlarged or • No EMD is present at baseline and post-baseline
Radiology Overall Response	• Any but PD
New Symptomatic Disease	Absent
Minor Response	**No new signs of active disease or progression**
Serum IgM	MR (≥25% and <50% reduction in Serum IgM from baseline)
Extramedullary Disease by Physical Examination	• Spleen and/or Lymph nodes which were assessed as 'Enlarged at baseline' are assessed as 'Normal/Not Enlarged' or 'Enlarged – Reduction from baseline' or • No EMD is present at baseline and post-baseline
Radiology Overall Response	• Any but PD
New Symptomatic Disease	Absent
Stable Disease	**Not meeting the criteria for CR, VGPR, PR, MR, PD, NE or NED**
Progressive Disease (PD)	**Any of the categories meet the criteria for progression**
Serum IgM	• PD unconfirmed, or • PD confirmed if serum IgM is the only indicator of PD (≥25% in serum IgM from nadir) • Absolute increase of >5 g/L is required when increase of IgM is the only applicable criterion
Extramedullary Disease by Physical Examination	Either spleen or lymph nodes are assessed as 'Enlarged New/recurrent' or 'Enlarged- Unequivocal Progression' Progression due to lymph node/spleen enlargement by PE only should be unequivocal, and cannot drive progressive disease unless supported by other data (eg, IgM meets the criteria for PD as defined above)
Radiology Overall Response	PD
Bone Marrow	Positive (New or recurrent involvement in bone marrow associated with WM)
New Symptomatic Disease	Yes
Not evaluable	**NE require AT LEAST ONE of the following, and no evidence of PD**
Serum IgM	Not available/evaluable or All available IgM values are confounded by plasmapheresis
Extramedullary Disease by Physical Examination	Spleen and/or Lymph nodes were assessed as Enlarged at baseline and follow-up assessments are not performed
Radiology Overall Assessment	NE
Cryoglobulinemia	If cryoglobulinemia is present, the overall tumor response can be NE based on the independent reviewer's oncological judgment.
New lesions	None

Response and Sub-categories for assessment	Overall Timepoint Assessment
No Evidence of Disease (NED)	**All criteria have to be met**
Serum IgM	Serum IgM or Serum M-Protein SPED was assessed as Normal at baseline and CR at Post-baseline
Extramedullary Disease by Physical Examination	No EMD at baseline and Post-baseline
Radiology Overall Assessment	NED
Bone Marrow	Negative at baseline and post-baseline
New Symptomatic Disease	None
Abbreviations: CR=complete response; EMD=extramedullary disease; IgM=immunoglobulin M; MR=minor response; NA=not applicable; NE=not evaluable; NED=no evidence of disease; PD=progressive disease; PE=physical examination; PR=partial response; SPED=serum protein electrophoresis; VGPR=very good partial response; WM=Waldenström's macroglobulinemia.	

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ABC	Activated B-cell
ADL	Activities of daily living
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransaminase
ATP	Adenosine triphosphate
AUC	Area under the curve
AV	Atrial ventricular
BCL-6	B-cell lymphoma 6
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BM	Bone marrow
BSEP	Bile salt export pump
BTK	Bruton's tyrosine kinase
BTKi	BTK inhibitor
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood cell
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	Maximum concentration
Cmin	Minimum concentration
CMR	Complete metabolic response
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case Report Form
CRi	Complete response with incomplete bone marrow recovery
CrCl	Creatinine clearance

Abbreviation	Expanded Term
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome P450
D	De-escalate to the next lower dose
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DU	The current dose is unacceptably toxic
E	Escalate to the next higher dose
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
EMD	Extramedullary disease
EOT	End of treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG	2 fluorodeoxyglucose
FISH	Fluoro in situ hybridization
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FLIPI-2	Follicular Lymphoma International Prognostic Index-2
FSH	Follicle-stimulating hormone
GCB	Germinal center B-cell
GCP	Good Clinical Practice

Abbreviation	Expanded Term
GCSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA/IgG/IgM	Immunoglobulin A, G, and M
IGHV	Immunoglobulin heavy chain variable region gene
INR	International normalized ratio
IPI	International Prognostic Index
IRB	Institutional review board
ISSWM	International Prognostic Scoring System for Waldenström Macroglobulinemia
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWWM	International Workshop on Waldenström's macroglobulinemia
L	Liter(s)
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
LDi	Longest diameter
LDT	Lymphocyte doubling time
LPL	Lymphoplasmacytic lymphoma
MCH	Mean corpuscular hemoglobin
MCL	Mantle-cell lymphoma

Abbreviation	Expanded Term
MCV	Mean corpuscular volume
MIPI	Mantle-cell Lymphoma International Prognostic Index
MIPI-c	Combined Mantle-cell Lymphoma International Prognostic Index
MOA	Mechanism of action
MR	Minor response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
mTPI	Modified Toxicity Probability Interval
MZL	Marginal zone lymphoma
N/n	Number
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NF-κB	Nuclear factor kappa-light chain-enhancer of activated B-cells
NHL	Non-Hodgkin's Lymphoma
nPR	Nodular partial response
NSAE	Nonserious adverse event
OME	Other important medical event
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PB	Peripheral blood
PD	Progression disease
PD	Pharmacodynamics
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PMD	Progressive metabolic disease
PMR	Partial metabolic response

Abbreviation	Expanded Term
PO	Orally
PPD	Product of perpendicular diameters
PR	Partial response
PRL	Partial response with lymphocytosis
PT	Prothrombin time
PTT	Partial thromboplastin time
q12w	Every 12 weeks
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
ROI	Region of interest
RP2D	Recommended Phase 2 dose
S	Stay at the current dose
SAE	Serious adverse event
SD	Stable disease
SDi	Short axis diameter
SLL	Small lymphocytic lymphoma
SMD	Stable metabolic disease
SoA	Schedule of activities
SPD	Sum of products of diameters
SPED	Serum protein electrophoresis
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumor lysis syndrome
UGT	Uridine-5'-diphospho-glucruonosyltransferase
ULN	Upper limit of normal
US	United states
VGPR	Very good partial response
WBC	White blood cell
WHO	World Health Organization
WM	Waldenström's macroglobulinemia
WOCBP	Woman/women of childbearing potential

10.11 Appendix 11: iwCLL Criteria for Assessment of Hematologic Toxicities

In participants with CLL, hematologic toxicities will be assessed according to the following table (Table 14), based on the iwCLL Guidelines [Hallek, M., et al 2018].

Table 14 Chronic Lymphocytic Leukemia Hematologic Toxicity

Grade[a]	Decrease in Platelets[b] or Hemoglobin[c] (Nadir) From Treatment Value (%)	Absolute Neutrophil Count (u/L) (Nadir)[d]
0	No change to 10	≥2000
1	11 to 24	≥1500 and <2000
2	25 to 49	≥1000 and <1500
3	50 to 74	≥500 and <1000
4	≥75	<500

Source: [Hallek, M., et al 2018].

[a] Grades: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as Grade 5.

[b] Platelet counts must be below normal levels for Grades 1 through 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L, this will be considered Grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L) was present at baseline, in which case the participant is not evaluable for toxicity referable to platelet counts.

[c] Hemoglobin levels must be below normal levels for Grades 1 through 4. Baseline and subsequent hemoglobin determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

[d] If the absolute neutrophil count (ANC) reaches $< 1 \times 10^9$/L, it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell (WBC) count or in circulating granulocytes are not to be considered because a decrease in the WBC count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9$/L before therapy, the participant is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented.

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