Janssen Research & Development *

Clinical Protocol

A Randomized, Controlled, Open-label, Multicenter, Inferentially Seamless Phase 2/3 Study of Ibrutinib in Combination with Rituximab Versus Physician's Choice of Lenalidomide Plus Rituximab or Bortezomib Plus Rituximab in Participants with Relapsed or Refractory Mantle Cell Lymphoma

Study Name: VEGA

Short Title

Seamless Phase 2/3 Study of Ibrutinib With Rituximab in Relapsed/Refractory Mantle Cell Lymphoma

Protocol 54179060MCL3004; Phase 2/3 Seamless Design
Amendment 1

JNJ-54179060 (ibrutinib)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency identifier Number(s):
IND: 102688
EudraCT NUMBER: 2022-000364-21
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Status:	Approved
Date:	08 June 2023
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-641149, 2.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 1	All	08 June 2023
Original Protocol	All	21 July 2022

Amendment 1 (08 June 2023)

Overall Rationale for the Amendment: As a result of the decision for early study discontinuation, the overall reason for the amendment is to stop enrollment and to ensure that participants on the study benefiting from study treatment will continue to receive study treatment, either in this study, or rollover to a long-term extension study, or through commercial access. The electronic case report form (eCRF) collection period will end, and the clinical database will be closed as soon as possible but no later than when the last study participant has completed the first 6 cycles of study treatment or switched to ibrutinib monotherapy at 560 mg once daily, whichever occurs first. All eCRF data collected up to this timepoint will be included in the final Clinical Study Report.

All participants will be given the choice to either remain on the randomized treatment arm or switch to ibrutinib monotherapy at 560 mg once daily (unless ibrutinib dose was reduced for toxicity reasons**)**. All participants will also be given the option to drop rituximab treatment and continue with monotherapy.

Additionally, this amendment provides additional clarification that participants benefiting from study treatment, and for whom commercial access is not readily available due to local reimbursement regulation and access agreement, will be able to continue to receive treatment.

In the following table, new text added to the protocol is shown in **bold**. Deleted text is shown in ~~strike through~~.

Section Number and Name	Description of Change	Brief Rationale
Updates made as a result of early study discontinuation		
1.1 Synopsis	Updates made to harmonize with changes in the protocol body	For consistency with the protocol
Throughout protocol	Reference to the Phase 3 part of the study removed, where applicable	As a result of the early study discontinuation, the Phase 2 part of this study will not fully enroll, and the Phase 3 part will not start.
10.13 (Appendix 13): Continuation of Study Treatment After the End of eCRF Data Collection and Clinical Database Closure to the End of the Study	New Appendix describing the study procedures for participants who are continuing to receive study treatment after the end of eCRF data collection and clinical database closure until the end of the study	To reflect procedures to be followed
1.3 Schedule of Activities; 4.4 End of Study Definition; 6.2 Preparation /Handling/Storage/ Accountability; 6.4 Study Treatment Compliance; 6.7 Concomitant Therapy; 7.1 Discontinuation of Study Treatment; 7.2 Participant Discontinuation /Withdrawal From the Study; 8.1.1 Study Procedures (Overview); 8.1.3 Open-label Treatment Phase; 8.2.1 Efficacy Assessments; 8.3 Safety Assessments; 8.3.2 Clinical Laboratory Tests; 8.4.5 Pregnancy; 10.1 Clinical Laboratory Tests; 10.2.8 CRF Completion; 10.2.9 Source Documents, 10.2.10 Monitoring; 10.2.13 Study and Site Start and Closure; 10.3.1 Adverse Events Definitions and Classifications; 10.3.4 Special Reporting Situations; 10.3.5 Procedures	Cross-reference added to Section 10.13 (Appendix 13)	To provide a cross-reference to Section 10.13 (Appendix 13) for a description of study procedures for participants who continue to receive study treatment after data collection has ended and the clinical database has been closed

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema	Figure 1: Schematic Overview: Phase 2 Part of the Study for Dose Selection – revised. Text added: **Upon implementation of Protocol Amendment 1, investigators will discuss treatment options with the participants and will be given the choice to either remain on the randomized treatment arm or switch to ibrutinib monotherapy at 560 mg once daily (unless ibrutinib dose was reduced for toxicity reasons). All participants will also be given the option to drop rituximab treatment and continue with monotherapy** Details of post-treatment Follow-up removed Figure 2: Schematic Overview: Phase 3 Part of the Study for Safety and Efficacy - deleted	To provide updated schematic overview of the Phase 2 part of the study effective upon implementation of Protocol Amendment 1
1.3 Schedule of Activities	Revised to reflect procedures only for participants who have received <6 cycles of study treatment Note added: **Refer to Section 10.13 (Appendix 13) for a description of the study procedures for participants who continue to receive study treatment after eCRF data collection has ended and the clinical database has been closed**	To provide details of study procedures effective upon implementation of Protocol Amendment 1
1.3 Schedule of Activities, Clinical Laboratory Tests, Serum immunoglobulins 10.1 Appendix 1: Clinical Laboratory Tests	Lines deleted Text deleted: ~~Beta2-microglobulin and serum Ig levels (IgG, IgM, IgA).~~	No longer applicable following implementation of Protocol Amendment 1
1.3 Schedule of Activities, Clinical Laboratory Tests: PK blood samples; PD blood samples	Schedule for blood sample collections for PK and PD evaluations deleted Associated footnotes deleted	Only blood samples already received before implementation of Protocol Amendment 1 can be used for PK and PD analysis
2.1 Study Design	Section updated and text included: **As a result of the early study discontinuation, the Phase 2 part of this study will not fully enroll, and the Phase 3 part will not start. The objective of the study is to provide continued access to study treatment for participants who continue to benefit from treatment**	To update Study Design as a result of early study discontinuation
3. Objectives and Endpoints	Primary objective revised and text added: **As a result of the early study discontinuation, the primary objective of Protocol Amendment 1 is to provide continued access to treatment. The Phase 2 exploratory objectives and endpoints of characterization of PK and PD of ibrutinib may continue to be evaluated using blood samples already collected prior to implementation of Protocol Amendment 1**	Updated Objectives and Endpoints as a result of the early study discontinuation and implantation of Protocol Amendment 1

Section Number and Name	Description of Change	Brief Rationale
	Phase 2 primary objectives and endpoints deleted; Phase 3 Primary, Secondary and Exploratory objectives and endpoints deleted	
	Phase 2 PD endpoint updated: BTK **and/or ITK** occupancy at various doses of ibrutinib and at different timepoints to identify dose occupancy relationships. PK parameters removed and only system exposure will be evaluated	To update PD and PK evaluations. Included the option to also evaluate ITK occupancy
Hypothesis	Phase 2 hypothesis updated: No formal testing will be conducted **due to early study discontinuation and the primary purpose of Protocol Amendment 1 is continued access of study treatment.** Phase 3 hypothesis deleted	Hypothesis updated as a result of the early study discontinuation
4.1 Overall Design	Section updated with information regarding the option for all participants to switch to ibrutinib monotherapy at 560 mg QD (unless ibrutinib dose was reduced for toxicity reasons). Text updated: During the study, safety evaluations will include AE monitoring, physical examinations **per standard of care**, vital signs, 12-lead ECG **(as clinically indicated)**, concomitant medication usage, and clinical laboratory parameters (hematology, chemistry, coagulation, **as clinically indicated**). Text added: **an End of Treatment visit for a safety assessment should take place within 30 days (+14-day window) after the last dose of study treatment, or before the start of subsequent anti-cancer therapy, if earlier**	To provide details of updated study design and End of Study definition effective upon implementation of Protocol Amendment 1
4.4 End of Study Definition	Section updated and text added: **The clinical database will close and no further data will be collected in the eCRFs as soon as possible but no later than when the last study participant has completed the first 6 cycles of study treatment. Only data collected in the eCRF during the data collection period will be included in the final Clinical Study Report.** **The sponsor will ensure that participants benefiting from study treatment can continue to receive study treatment after this time until study treatment is available commercially, available from another source, or until study completion, whichever occurs earlier** **The study is considered completed once all participants still receiving study treatment have transitioned to commercial or alternative access, have stopped receiving study treatment, or upon a decision by the sponsor to terminate the study, whichever occurs earlier**	

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 8.1.4 Post-treatment Follow-up Phase; 6.6 Continued Access to Study Treatment After the End of the Study	Post-treatment Follow-Up Phase columns deleted Section deleted Section deleted	No longer applicable following implementation of Protocol Amendment 1
4.2 Scientific Rationale for Study Design	Section deleted and text added: **As a result of the early study discontinuation, the objective of the study is to provide continued access to study treatment for participants who continued to benefit from treatment**	
6.1 Study Treatment(s) Administered; 6.3 Measures to Minimize Bias: Randomization and Blinding	Sections revised and text deleted	Updated as the Phase 3 part of the study will not start
8.1 Study Procedures (8.1.1 Overview)	Text removed for approximate amount of blood drawn in the Phase 2 and Phase 3 parts of the study:	Blood sample volumes removed due to revised study assessments
8.1.3 Open-label Treatment Phase	Section amended to remove details of administration of the FACT-Lym and PRO questionnaire; evaluation of possible toxicities, dose modifications; and disease progression. Text added: **The sponsor recommends disease evaluations be performed per standard of care**	To update Treatment Phase procedures effective upon implementation of Protocol Amendment 1
8.2.1 Efficacy Assessments	Response assessments updated as follows: **To determine whether continued study treatment is warranted, investigators should monitor and assess participants for response to treatment or disease progression per standard of care preferably using the Lugano Criteria (Cheson 2014). Disease status and date of disease progression should be documented**	Following implementation of Protocol Amendment 1, these assessments will be performed per standard of care
8.2.1.1 PET Scan; 8.2.1.2 Radiographic Image assessments (CT/MRI); 8.2.1.3 Bone Marrow Assessment; 8.2.1.4 Endoscopy 8.2.1.5 Biopsies of Other Sites; 8.2.1.6 Physical Examination	Sections deleted	
8.2.1.7 Patient-Reported Outcomes	Section deleted	No longer required following implementation of Protocol Amendment 1

Section Number and Name	Description of Change	Brief Rationale
8.2.2.1 Assessment of Disease response and Progressive Disease	Details of IRC review of progressive disease deleted Text updated: For all participants with disease progression by the investigator, the investigator should notify the sponsor medical monitor ~~within 24 hours~~ **promptly when** ~~of~~ becoming aware of the progression **including after database closure.**	No longer required due to the early termination of the study To clarify the disease progression notification instructions
8.5 Pharmacokinetics	Section updated to remove details of the schedule for blood sample collection for PK analysis. Text added: **Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected (ibrutinib treatment arm only) may be used for further development of the existing population-based PK model. No further blood samples will be collected from participants for PK evaluation upon implementation of protocol Amendment 1**	Only blood samples already received before implementation of Protocol Amendment 1 can be used for PK analysis
8.6 Pharmacodynamic Evaluations	Section updated to remove details of the schedule for blood sample collection for PD analysis. Text added: **Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected may be used for BTK and/or ITK occupancy (free and total) evaluation. No further blood samples will be collected from participants for PD evaluation upon implementation of protocol Amendment 1**	Only blood samples already received before implementation of Protocol Amendment 1 can be used for PD analysis Included the option to also evaluate ITK occupancy
8.8 Sample Collection and handling (Study Specific Materials)	Text deleted: ~~Progressive disease notification form (see Section 8.2.2.1)~~ and ~~PRO questionnaires and user manuals: PRO questionnaires will include the FACT-Lym. Sample questionnaires are provided in Section 10.9 (Appendix 9).~~	No longer required following implementation of Protocol Amendment 1
8.3 Safety Assessments 1.3 Schedule of Activities; 8.1.3 Open-label Treatment Phase; 8.3 Safety Assessments; 8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting 10.3.1 Adverse Event Definitions and Classifications	Text included that safety evaluations should be performed as clinical indicated. Text included that safety data collection will be limited to SAEs, Grade ≥3 AEs and AEs leading to treatment discontinuation, and concomitant medications related to SAEs and Grade ≥3 AEs” Text updated: All **SAEs,** AEs, **Grade ≥3 AEs and AEs leading to treatment discontinuation**, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF	To clarify safety evaluations and safety data collection effective upon implementation of Protocol Amendment 1

Section Number and Name	Description of Change	Brief Rationale
6.7 Concomitant Therapy	Text added: **As of implementation of Protocol Amendment 1, only concomitant therapy related to SAEs and Grade ≥3 AEs up to 30 days after the last dose of study treatment, or until the start of subsequent anti-lymphoma, whichever is first, needs to be recorded**	To clarify safety evaluations and safety data collection effective upon implementation of Protocol Amendment 1
6.7 Concomitant Therapy; 8.3 Safety Assessments; 10.3 1 Adverse Events Definitions and Classifications	Text added: **For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, only SAEs and pregnancy information will be documented in the participant file/source notes and reported to the sponsor's Global Medical Safety database only until the end of the study (see Section 4.4) and as described in Section 10.13 (Appendix 13)**	To describe the SAE and pregnancy reporting procedures after the end of eCRF data collection and clinical database closure
8.4.5 Pregnancy (Lenalidomide)	Text added: **After the end of eCRF data collection and clinical database closure, pregnancy reporting will continue as described above and in Section 10.13 (Appendix 13)** Text updated: If pregnancy occurs, study treatment should be discontinued immediately and the participant should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling. **The sponsor will collect information on the outcome of the pregnancy and health of the baby for 1 year after birth or until the outcome of an adverse pregnancy event is known or resolved**	To describe the pregnancy reporting procedures after the end of eCRF data collection and database closure To clarify sponsor's responsibility should pregnancy occur for participants receiving lenalidomide
9 Statistical Considerations; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.3 Participant Analysis Sets; 9.4 Statistical Analyses; 9.4.1 General Considerations; 9.4.2 Primary Endpoint; 9.4.3 Secondary Endpoints; 9.4.3.1 Definitions; 9.4.3.2 Analysis; 9.4.4 Exploratory Endpoints; 9.5 Interim Analysis; 9.6 Independent Data Monitoring Committee; 10.2.6 Committees Structure	Sections deleted and text added to Section 9: **Due to the early termination of the study, an IDMC to monitor safety data, and to review efficacy data, is no longer required. Data will be summarized, and descriptive statistics will be presented.**	Statistical considerations and IDMC no longer required following implementation of Protocol Amendment 1
10.2.2 Financial Disclosure	Section deleted	No longer required following implementation of Protocol Amendment 1

Section Number and Name	Description of Change	Brief Rationale
10.2.10 Monitoring	Details of central monitoring deleted	Following implementation of Protocol Amendment 1, central monitoring will not be required
10.11 (Appendix 11): Disease Evaluation Schedule	Appendix deleted	Following implementation of Protocol Amendment 1, disease assessments will be performed per standard of care
Updates made to provide clarity and to align with current sponsor template		
1.3 Schedule of Activities, Clinical Laboratory Tests: Serum pregnancy test (female POCBP only)	New footnote (e) added: **For lenalidomide participants, pregnancy test is required at EOT. Medically supervised pregnancy test should be repeated every 4 weeks, including at least 4 weeks after last dose of treatment, except in case of tubal sterilization. If pregnancy occurs, the sponsor will collect information on the outcome of the pregnancy and health of the baby for 1 year after birth or until the outcome of an adverse pregnancy event is known or resolved**	To clarify pregnancy testing requirements for lenalidomide
1.3 Schedule of Activities, Clinical Laboratory Tests 5.3 Restrictions During Study Participation	Text updated for serum pregnancy test Notes: *For female POCBP randomized to lenalidomide, within 24 hours ~~of~~ **prior to** starting treatment for C1 (serum) and thereafter weekly **(±2 days)** (urine or serum) pregnancy tests are required during the first month, then monthly **(-2 days)** thereafter in females with regular menstrual cycles or every 2 weeks **(±2 days)** in females with irregular menstrual cycles.	Updated to be consistent with Section 5.3 (Restrictions During Study Participation); and to allow ± 2-day windows for pregnancy testing
1.3 Schedule of Activities, Study Drug Administration: Rituximab 375 mg/m^2 6.1 Study Treatment(s) Administered	Text added to footnote 'b' **It is recommended that ibrutinib is administered prior to rituximab** Text added to paragraph 1 and Table 4: **It is recommended that ibrutinib is administered prior to rituximab on Day 1 of Cycles 1 to 6**	To clarify dosing administration for rituximab in combination with ibrutinib
1.3 Schedule of Activities, Clinical Laboratory Tests: Hepatitis serologies PCR	Updated: To be performed **as clinically indicated** during the treatment phase	To clarify when hepatitis serologies PCR tests are to be performed
10.6 (Appendix 6): Calculating the Simplified MIPI for MCL	New appendix included for calculating the simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) (Hoster 2008) Link to Section 10.6 (Appendix 6) included in Section 4.1 Overall Design	To provide instructions for calculating the sMIPI

Section Number and Name	Description of Change	Brief Rationale
5.3 Restrictions During Study Participation	Text revised: **For participants randomized to lenalidomide, ~~T~~t**wo negative pregnancy tests must be obtained prior to initiating study treatment. The first test should be performed at screening and the second test within 24 hours prior to the first dose of study treatment. ~~For participants randomized to lenalidomide, w~~**W**eekly pregnancy tests are required during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles.	To provide further clarity for pregnancy test requirements for participants receiving lenalidomide
6.1 Study Treatment(s) Administered	Table 4 Description of Ibrutinib, Rituximab, Lenalidomide, and Bortezomib, and Study Treatment Administration Instructions – text corrected: **IV infusion -** rituximab Authorization status of ibrutinib, Rituximab, Lenalidomide, and Bortezomib in the EU added	To clarify that rituximab is administered as an IV infusion and not as an IV injection Required as this study will be performed under the EU CTR
6.5.3 Dose Modifications (Lenalidomide)	Table 9 Lenalidomide Dose Modifications for Hematologic Toxicities Text added for recommended course for platelets ≥50,000/µL and neutrophils ≥1,000/µL: **If previous dose was 5 mg, reduce dose to 2.5 mg daily or 5 mg every other day[a]**; Do not dose below **2.**5 mg daily **or 5 mg every other day[a]**: Footnote added: **[a]If using locally sourced lenalidomide, refer to local label for lowest dose level allowed**	To clarify dose reduction instructions if previous lenalidomide dose was 5 mg
8.8 Sample Collection and Handling (Study-specific Materials)	Text modified: IWRS ~~manual~~ **instructions and guidance** and supplies	Text amended as there is no official IWRS manual available
9.4.5 Safety Analyses (Statistical Considerations)	Text updated: Any **new or worsening** AE occurring at or after the initial administration of study treatment through the day of last dose plus 30 days, or ~~until~~ **prior to** the start of a subsequent anticancer therapy, ~~if~~ **whichever is** earlier, **or any follow-up AE (linked to an existing TEAE) with onset date and time beyond 30 days after the last dose of study treatment but prior to the start of subsequent therapy, or any AE that is considered treatment-related regardless of the start date of the event,** is considered to be treatment-emergent	To update the definition of a treatment emergent AE and to align the Statistical Analysis Plan and protocol
10.1 (Appendix 1): Clinical Laboratory Tests	Text updated: Screening for Hepatitis B and C will include the following evaluations: **Hepatitis B surface antigen**, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody	To include Hepatitis B surface antigen evaluation

Section Number and Name	Description of Change	Brief Rationale
10.3.3 (Appendix 3): Severity Criteria (Adverse Events)	Text updated: ~~Any AE will be graded as per the above. Should an AE become fatal or have a fatal outcome, the original grade is not changed but "fatal" shall be reported as an outcome.~~ ~~Only in the following cases a Grade 5 event is to be reported:~~ ~~• Death NOS: Only for deaths due to unknown reason (pending follow-up information; if further information becomes available this should be adapted as adequate)~~ ~~• Sudden death: A sudden (defined as instantaneous or within 1 hour of the onset of symptoms) cessation of life that cannot be attributed to a CTCAE term~~ The investigator ~~should~~ **must** use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities),	To align with the current sponsor protocol template
Throughout the protocol	Protocol template-driven updates were made where applicable.	To align with updates to the sponsor's oncology protocol template.
Title page; 1.1 Synopsis	Added the EU CTR number	To add the EU CTR registry number for this study
Throughout the protocol	Revisions and modifications were made throughout the protocol to increase clarity, for consistency within this protocol, or to correct omissions and errors. Links and cross-references were corrected/updated.	Minor errors were noted.

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LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
B-cell	B-lymphocyte
BID	twice daily
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
BTKi	inhibitor of Bruton's tyrosine kinas
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography (scan)
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	US Food and Drug Administration
FDG	[18F]-fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded tumor (tissue)
FL	follicular lymphoma
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAB	hepatitis B core antibody
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
HEV	hepatitis E virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ITK	Interleukin-2-inducible T-cell kinase
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat (population)
IV	intravenous
IWRS	interactive web response system
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin Lymphoma
NONMEM	nonlinear mixed-effects modeling

ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
POD	progression of disease
POCBP	Participants of Childbearing Potential
PPP	Pregnancy Prevention Plan
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
QD	once daily
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
ROW	Rest of the World
r/r	relapsed or refractory
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
sMIPI	simplified Mantle Cell Lymphoma International Prognostic Index
SC	subcutaneous
SIPPM	Site Investigational Product and Procedures Manual
SmPC	Summary of Product Characteristics
TFR	tumor flare reaction
TLS	tumor lysis syndrome
TP53	tumor protein 53
TTNT	time-to-next treatment
ULN	upper limit of normal
US	United States
USPI	United States Package Insert

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Controlled, Open-label, Multicenter, Inferentially Seamless Phase 2/3 Study of Ibrutinib in Combination With Rituximab Versus Physician's Choice of Lenalidomide Plus Rituximab or Bortezomib Plus Rituximab in Participants with Relapsed or Refractory Mantle Cell Lymphoma

Short title: Seamless Phase 2/3 Study of Ibrutinib with Rituximab in Relapsed/Refractory Mantle Cell Lymphoma

IND: 102688
EudraCT NUMBER: 2022-000364-21
EU CTR NUMBER: 2023-503618-64

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is a first-in-class, potent, orally administered, covalently-binding small molecule Bruton's Tyrosine Kinase inhibitor (BTKi) currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC (an AbbVie company) for the treatment of B-lymphocyte (B-cell) malignancies and chronic graft-versus-host disease. Ibrutinib is approved in many countries globally for the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) as a monotherapy. Due to the sponsor's decision for early study discontinuation, major changes are incorporated throughout this Protocol Amendment 1 to reflect this.

RISK/BENEFIT

Management of r/r MCL can be challenging due to advanced patient age and increased aggressiveness of disease over time. Phase 2 studies of ibrutinib in combination with rituximab resulted in higher response rates and longer progression-free survival (PFS) and overall survival (OS) in subjects with r/r MCL compared with historical data from ibrutinib monotherapy studies. Risks associated with ibrutinib treatment include hemorrhage, atrial fibrillation and hypertension, and measures will be taken in this study to minimize risks to participants, including close monitoring and dose modifications. The potential risks are justified by the anticipated benefits that may be afforded to participants with r/r MCL. Bortezomib and lenalidomide are approved agents for the treatment of MCL and are to be given with or without rituximab. The overall benefit-risk assessment in this study is expected to be positive for the study participants.

OBJECTIVES

The primary objective is to provide continued access to study treatment for participants who continued to benefit from treatment.

HYPOTHESIS

Phase 2: No formal statistical hypothesis testing will be conducted.

OVERALL DESIGN

This study was designed as a randomized, open-label, international, multicenter, inferentially seamless Phase 2/3 adaptive study. As a result of the early study discontinuation, the Phase 2 part of this study will not fully enroll, and the Phase 3 part will not start.

Participants will be randomized 1:1:1:1 to Treatment Arm A1 (ibrutinib 560 mg once daily [QD] + rituximab) or Treatment Arm A2 (ibrutinib 420 mg QD + rituximab) or Treatment Arm A3 (ibrutinib 140 mg twice daily [BID] + rituximab) or Treatment Arm B (physician's choice of lenalidomide + rituximab or bortezomib + rituximab). Upon implementation of Protocol Amendment 1, all participants will be given the option to switch to ibrutinib 560 mg QD monotherapy (unless ibrutinib dose

was reduced for toxicity reasons). All participants will also be given the option to drop rituximab treatment and continue with monotherapy.

Randomization will be stratified by sMIPI score, prior lines of therapy, and geographical region. Selection of physician's choice of comparator must be made for every participant prior to randomization. The study will include a Screening Phase (up to 30 days prior to randomization), and a Treatment Phase (from randomization until study treatment discontinuation). An End-of-Treatment visit for a safety assessment should take place within 30 days (+14-day window) after the last dose of study treatment or before the start of subsequent anti-cancer therapy, if earlier. The electronic case report form (eCRF) data collection period will end, and the clinical database will be closed. All eCRF data collected up to this timepoint will be included in the final Clinical Study Report.

Participants benefiting from study treatment may continue to receive study treatment after the end of eCRF data collection and clinical database closure until study treatment is commercially available, available from another source, or until study completion, whichever occurs earlier.

The study is considered completed when all participants still receiving study treatment have transitioned to commercial or alternative access to study treatment, have stopped receiving study treatment, or upon a decision by the sponsor to terminate the study, whichever occurs earlier.

TREATMENT GROUP AND DURATION

Participants in Treatment Arms A1, A2 and A3 will receive ibrutinib orally (560 mg QD, 420 mg, QD, or 140 mg BID, respectively, 28-day cycle) until disease progression or unacceptable toxicity. Participants in Treatment Arm B will receive either lenalidomide (20 mg [or 10 mg if creatinine clearance (CrCl) is 30 to <60 mL/min] orally QD on Days 1 through 21 of a 28-day cycle) or bortezomib (1.3 mg/m^2 intravenously [IV] or subcutaneously [SC] on Days 1, 4, 8, and 11 of a 21-day cycle) until disease progression or unacceptable toxicity. Participants in all treatment arms will have the choice to also receive rituximab (375 mg/m^2 IV) on Day 1 of Cycles 1 to 6.

Upon implementation of Protocol Amendment 1, all participants will be given the choice to either remain on the randomized treatment arm or switch to ibrutinib monotherapy at 560 mg QD (unless ibrutinib dose was reduced for toxicity reasons). Participants will continue with the chosen dosing regimen (the regimen they were assigned to during randomization, or the ibrutinib 560 mg monotherapy dose regimen) until the investigator determines that the participant is no longer benefiting from treatment (ie, disease progression or unacceptable toxicity has occurred), the participant withdraws consent, alternative access to study treatment is available and feasible (eg, rollover to a long-term extension study, patient assistance program, or commercial source of study treatment) or until the end of the study, whichever occurs earlier. The sponsor will ensure that participants enrolled in the study who are benefiting from study treatment can continue to receive treatment after study end through alternative access.

EFFICACY EVALUATIONS

Assessment of tumor response and progression will be conducted in accordance with the Lugano Criteria (Cheson 2014). The investigator will evaluate sites of disease by radiological imaging, physical examination, bone marrow biopsy, or other procedures as per standard of care.

To determine whether continued study treatment is warranted, investigators should monitor and assess participants for response to treatment or disease progression per standard of care preferably using the Lugano Criteria (Cheson 2014). Only disease status and date of disease progression should be documented in the eCRF. After the eCRF data collection period has ended, notification of progressive disease should be sent to the medical monitor via email. Refer to the Appendix (Continuation of Study Treatment After the End of eCRF Data Collection and Clinical Database Closure to the End of the Study) for further guidance on study procedures after the end of eCRF data collection.

PHARMACOKINETIC EVALUATIONS

Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected (ibrutinib treatment arm only) may be used for further development of the existing population-based PK model.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected may be used for Bruton's Tyrosine Kinase (BTK) and/or Interleukin-2-inducible T-cell kinase (ITK) occupancy (free and total) evaluation. A portion of the formalin-fixed paraffin-embedded tumor (FFPE) block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments (eg, Ki-67, and tumor protein 53 [*TP53*], and other genes).

SAFETY EVALUATIONS

Safety evaluations should be performed as clinically indicated and can include physical examinations and relevant clinical laboratory tests. Participants should be periodically monitored clinically for atrial fibrillation, and electrocardiograms (ECGs) should also be performed at the investigator's discretion, particularly in participants with arrhythmic symptoms (eg, palpitations, lightheadedness, or new onset dyspnea).

All serious adverse events (SAEs) occurring during the study must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event. The sponsor will collect SAE data by the SAE reporting process. Safety data collection will be limited to SAEs, Grade ≥3 AEs, and AEs leading to treatment discontinuation; and concomitant medications related to SAEs and Grade ≥3 AEs.

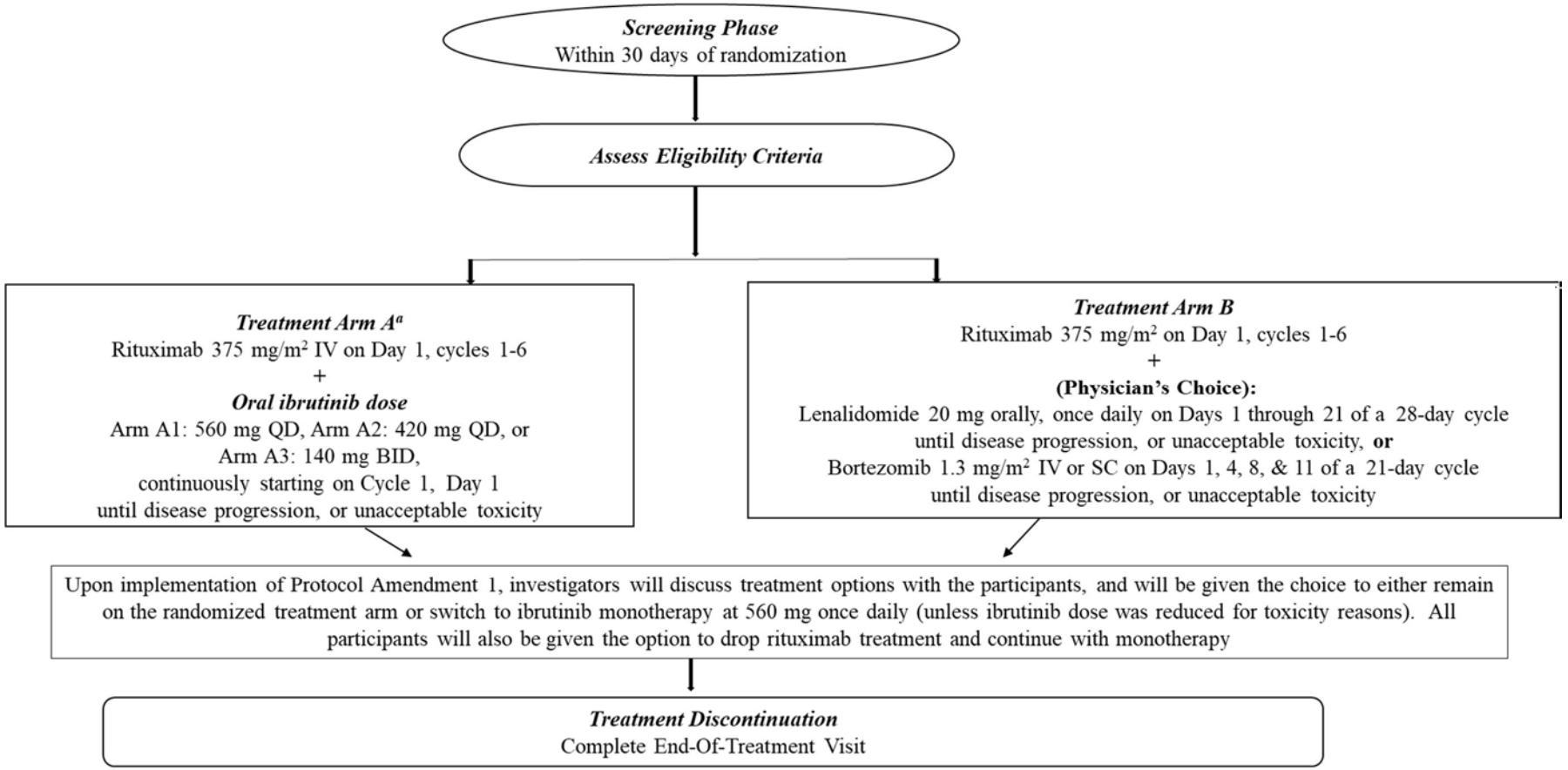
For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, only SAEs and pregnancy information will be documented in the participant file/source notes and reported to the sponsor's Global Medical Safety database only until the end of the study. The sponsor will no longer perform on-site monitoring visits (unless specifically required) but will perform remote monitoring visits.

STATISTICAL METHODS

Due to the early termination of the study, an Independent Data Monitoring Committee (IDMC) to monitor safety data, and to review efficacy data, is no longer required. Data will be summarized, and descriptive statistics will be presented.

1.2. Schema

Figure 1: Schematic Overview: Phase 2 Part of the Study



BID twice daily;-IV intravenous; MCL mantle cell lymphoma; QD once daily; SC subcutaneous

[a.] A cycle is defined as 28 days.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Note: Refer to Section 10.13 (Appendix 13) for a description of the study procedures for participants who continue to receive study treatment after eCRF data collection has ended and the clinical database has been closed.

		Treatment Phase 2/3 From randomization until study treatment discontinuation				EOT visit	Notes
	Screening (-30 days)	**Arms A1, A2, A3: 28-day cycle (±2 days) Arm B (len): 28-day cycle (±2 days) Arm B (bor): 21-day cycle (±2 days)**				**30 days (+7 days)**	Upon implementation of Protocol Amendment 1, all participants will have the option to switch to ibrutinib 560 mg monotherapy QD (unless ibrutinib dose was reduced for toxicity reasons)
		Day 1	**Day 4**	**Day 8**	**Day 11**		
Screening/Administrative							
Informed consent (ICF)	X						Must be signed before first study related activity
Demographics	X						
Weight	X	X				X	C1-6; All. After C6: bor pts only[a]
ECOG PS Score	X						
Study Drug Administration							
Arm A: ibrutinib[b,c]		Continuous (28-day cycle)					
Arm B: Lenalidomide 20 mg daily **(Arm B - len pts only)**[b,c]		Day 1 through 21 of 28-day cycle					Daily len 10 mg if CrCl 30 to <60 mL/min
Arm B: Bortezomib 1.3 mg/m^2 **(Arm B - bor pts only)**[a,b,c]		X	X	X	X		At least 72 hours should elapse between consecutive doses
Rituximab 375 mg/m^2 **(All treatment arms)**[a,b,c]		C1 through 6 only [c]					
Study drug accountability		X				X	
Disease Assessments							
CT/MRI scan	X	Per SOC (preferably every 4-6 months) until treatment discontinuation					SOC CT/MRI, PET and bone marrow may be used for screening if performed up to 60 days before randomization.
PET	X	Per SOC					
Bone marrow aspirate and biopsy	X	Per SOC					

		Treatment Phase 2/3 From randomization until study treatment discontinuation				EOT visit	Notes
	Screening (-30 days)	**Arms A1, A2, A3: 28-day cycle (±2 days) Arm B (len): 28-day cycle (±2 days) Arm B (bor): 21-day cycle (±2 days)**				**30 days (+7 days)**	Upon implementation of Protocol Amendment 1, all participants will have the option to switch to ibrutinib 560 mg monotherapy QD (unless ibrutinib dose was reduced for toxicity reasons)
		Day 1	**Day 4**	**Day 8**	**Day 11**		
Endoscopy		Per SOC					
Physical examination	X	Per SOC					Including height (Screening only)
B-symptoms	X						
Safety Assessments							
Vital signs	X	X				X	
12-lead ECG	X					X	
Clinical Laboratory Tests							
Hematology[d]	X	X				X	D4, D8 and D11 for Bor pts when clinically indicated. For Len pts weekly hematology tests are required for the first 8 weeks (Section 8.3.2)
Coagulation studies	X	As clinically indicated					
Serum Chemistry[d]	X	X				X	
Hepatitis serologies/PCR	X	As clinically indicated					see Section 5.2
Serum pregnancy test (female POCBP only)	X	X*				X[e]	*For female POCBP randomized to lenalidomide, within 24 hours prior to starting treatment for C1 (serum) and thereafter weekly (±2 days) (urine or serum) pregnancy tests are required during the first month, then monthly (-2 days) thereafter in females with regular menstrual cycles or every 2 weeks (±2 days) in females with irregular menstrual cycles.
Tumor tissue sample[f]	X						FFPE tumor slides or blocks may be either newly obtained or from previous biopsy
Ongoing Participant Review							
Concomitant therapy		Safety data collection will be limited to SAEs, Grade ≥3 AEs and AEs leading to treatment discontinuation; and concomitant medications related to SAE and Grade ≥3 AEs, from signing ICF and up to 30 days after the last dose of study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier					
Adverse events (AE)							
New malignancies		<----------Continuous ---------->					

bor=bortezomib; C=cycle; CR=complete response; CrCl=creatinine clearance; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End of Treatment; FACT-Lym= Functional Assessment of Cancer Therapy-Lymphoma; FFPE=formalin-fixed

paraffin-embedded; POCBP Participants of Childbearing Potential; GI=gastrointestinal; h=hour(s); ICF=informed consent form; len=lenalidomide; min=minutes; MCL=mantle cell lymphoma; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PET= positron emission tomography; POD=progression of disease; PD=pharmacodynamics; PK=pharmacokinetics; Pts=participants; SoA=schedule of activities; SOC=standard of care; wk=week

Note: Guidelines for study intervention administration affected by the Coronavirus Disease 2019 (COVID-19) pandemic are found in Section 10.10 (Appendix 10).

a. If a participant's weight changes by more than 10% from baseline, the weight used for calculating the dose of bortezomib and rituximab should be re calculated
b. Rituximab: 28-day cycle in combination with ibrutinib or lenalidomide, and 21-day cycle in combination with bortezomib. It is recommended that ibrutinib is administered prior to rituximab.
c. Randomization to Arm A (A1: ibrutinib 560 mg QD, or A2: ibrutinib 420 mg QD, or A3: ibrutinib 140 mg BID); randomization to Arm B (selection must be made prior to randomization).
d. Must be obtained within 48 hours of Day 1 of each cycle and reviewed prior to dosing.
e. For lenalidomide participants, a pregnancy test is required at EOT. A medically supervised pregnancy test should be repeated every 4 weeks, including at least 4 weeks after last dose of treatment, except in case of tubal sterilization. If pregnancy occurs, the sponsor will collect information on the outcome of the pregnancy and health of the baby for 1 year after birth or until the outcome of an adverse pregnancy event is known or resolved.
f. Buccal swab should be submitted with tumor samples (archival or fresh biopsy) at Screening. Only 1 set of buccal swab is needed.

2. INTRODUCTION

Ibrutinib (IMBRUVICA®, PCI-32765; JNJ-54179060) is a first-in-class potent, orally administered, covalently-binding small molecule BTKi currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC (an AbbVie company) for the treatment of B-cell malignancies and chronic graft-versus-host disease. Ibrutinib is approved in many countries globally for the treatment of adult patients with r/r MCL as a monotherapy, with accelerated approval in the United States (US) for the treatment of adult patients with MCL who have received at least one prior therapy. Ibrutinib was first recommended for r/r MCL per national Comprehensive Cancer Network (NCCN) guidelines in 2014.

Relevant clinical information is discussed within this section. For the most comprehensive clinical and nonclinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure and Addenda/Supplements for ibrutinib and product label (IMBRUVICA® USPI 2022; IMBRUVICA® SmPC 2022). The term “study treatment” throughout the protocol, refers to ibrutinib and rituximab, lenalidomide and rituximab, and bortezomib and rituximab, as defined in Section 6.1, Study Treatments Administered. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term “participant” refers to a subject in the study.

2.1. Study Rationale

Since the initial approval in the US on 13 November 2013, subsequent addition to the NCCN guidelines (version 1, 2014) and approval in the European Union (EU) (2014) and other countries worldwide, ibrutinib has become an established standard of care for r/r MCL which has brought significant benefit as a chemotherapy-free, targeted, oral therapy to patients suffering from this aggressive lymphoma. A program of Phase 2 and 3 studies have established ibrutinib monotherapy treatment as an effective standard therapy in r/r MCL. However, results from a single arm Phase 2 investigator-initiated study demonstrated higher response rates and longer PFS with ibrutinib + rituximab compared with historical data for ibrutinib monotherapy (Section 2.2.7).

This study was designed as a randomized, multicenter, open-label, inferentially seamless Phase 2/3 study to determine the recommended daily dosage of ibrutinib when administered in combination with rituximab (Phase 2) and to evaluate whether the combination of ibrutinib + rituximab will result in superior efficacy, compared with the combination of physician’s choice of either lenalidomide + rituximab or bortezomib + rituximab, in participants with r/r MCL who are BTKi naïve (Phase 3).

As a result of the early study discontinuation, the Phase 2 part of this study will not fully enroll, and the Phase 3 part will not start. The objective of the study is to provide continued access to study treatment for participants who continue to benefit from treatment.

2.2. Background

2.2.1. Mantle Cell Lymphoma

Mantle cell lymphoma is an uncommon and incurable clinicopathologic subtype of B-cell non-Hodgkin Lymphoma (NHL), and accounts for about 6-9% of all NHL cases in the Western world (Lai 2000). The annual incidence of MCL has increased during recent decades to 4-8/1000,000 and occurs more frequently in older adults (Zhou 2008).

Most patients with MCL are male (median age: 65 years) who present with advanced stage disease (ie, Stage III or IV) with most cases following an aggressive clinical course (Dreyling 2014). In the US, the MCL incidence rate is highest in non-Hispanic whites (0.73, 95% CI 0.71-0.76) significantly higher than those of the other races (Wang 2014). For the 40 64 and 65+ age groups, non-Hispanic whites have the highest MCL incidence rates, which does not translate in a significant difference in 5-year relative survival rates. When stratified by age, for the 40 64 years group, non-Hispanic whites have a higher survival rate (63.1%) than Hispanic whites (51.4%). For the 65+ years group, non-Hispanic whites have the best survival rate (44.4%), while blacks have the worst (34.9%). However, these racial differences were found to be not significant in a multivariate analysis.

Though the clinical course of MCL may be somewhat indolent at diagnosis, the course invariably becomes aggressive over time and is considered incurable with standard therapies. Some patients with MCL may achieve long-term, disease-free survival after allogenic stem cell transplantation, but in general, the disease is characterized by a series of relapses with a median OS of 8 to 10 years (Wu 2020).

2.2.2. Treatment for Relapsed or Refractory Mantle Cell Lymphoma

Management of MCL at relapse can be very challenging due to advanced patient age and increased aggressiveness of disease over time. The number of treatment options have increased over the last decade, and treatment choice is dependent on patient factors, prior therapy, and remission duration. Approved therapy options at relapse which are preferred per NCCN version 3 2022 guidelines (NCCN 2022) include the BTKi ibrutinib, acalabrutinib and zanubrutinib (all accelerated approvals by the Food and Drug Administration [FDA]). Other approved targeted agents include bortezomib (full approval) and an immunomodulating drug, lenalidomide (full approval), and are recommended to be administered with or without rituximab (bortezomib) and with rituximab (lenalidomide).

Additional suggested regimens considered useful in certain circumstances include bendamustine + rituximab or bendamustine + rituximab and cytarabine (RBAC500) if not previously given, ibrutinib with rituximab and lenalidomide, ibrutinib with venetoclax, venetoclax with or without rituximab, and rituximab with dexamethasone, cisplatin, cytarabine (DHAP), or with dexamethasone, cytarabine, oxaliplatin (DHAX) or gemcitabine, oxaliplatin (GemOx). Most recently, brexucabtagene autoleucel, a CAR-T-cell therapy, received accelerated approval for r/r MCL. However, current therapies for r/r MCL are infrequently curative and unable to overcome

high-risk disease features. The proposed study is hypothesized to improve the depth and duration of response.

2.2.3. Investigational Product Name and Description

Ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral capsule formulation containing micronized ibrutinib.

2.2.4. Nonclinical Studies With Ibrutinib

For the most comprehensive nonclinical information regarding ibrutinib, refer to the latest version of the Investigator's Brochure and product label (IMBRUVICA® USPI 2022; IMBRUVICA® SmPC 2022).

2.2.5. Clinical Pharmacokinetic Data With Ibrutinib

For the most comprehensive clinical PK information regarding ibrutinib, refer to the latest version of the Investigator's Brochure and product label (IMBRUVICA® USPI 2022; IMBRUVICA® SmPC 2022).

2.2.6. Clinical Efficacy of Ibrutinib in Mantle Cell Lymphoma

Efficacy data from studies of ibrutinib as monotherapy in subjects with r/r MCL are presented in Table 2. Efficacy results from Studies PCYC-04753, PCYC-1104-CA, PCI-32765MCL2001, and PCI-32765MCL3001 demonstrate that ibrutinib has activity as a single agent in treatment of subjects with r/r MCL.

Table 2: Clinical Efficacy of Ibrutinib Monotherapy in Relapsed or Refractory Mantle Cell Lymphoma

Study	Description	No. of Subjects	Efficacy Results (Final Analysis)
PCYC-04753	Phase 1, open-label, dose-escalation, monotherapy, multicenter study in subjects with r/r B-cell malignancies	9 with a diagnosis of MCL	Median time on study: 8.0 mo Median PFS: 11.6 mo Objective response: 7 of 9 subjects (78%) CR: 3 of 9 subjects PR: 4 of 9 subjects
PCYC-1104-CA (Wang 2015)	Phase 2, open-label, monotherapy, multicenter study in subjects with r/r MCL	111	Median time on study: 26.7 mo Median PFS: 13.0 mo CR rate: 23% ORR: 66.7% Median DOR: 17.5 mo Median OS: 22.5 mo
PCI-32765 MCL2001	Phase 2, single-arm, monotherapy, multicenter study in subjects with relapsed MCL	120	Median time on study: 25.3 mo Median PFS: 10.1 mo CR rate: 24.5% ORR:66.4% Median DOR: 21.3 mo Median OS: 25.4 mo

Study	Description	No. of Subjects	Efficacy Results (Final Analysis)
PCI-32765 MCL3001	Phase 3, randomized, open-label, comparator (ibrutinib vs temsirolimus), monotherapy, multicenter study in subjects with r/r MCL	ibrutinib (n=139) temsirolimus (n=141)	Median time on study: 38.7 mo ibrutinib vs 38.7 mo tem PFS: HR 0.45 (95% CI: 0.35, 0.60), p<0.0001 Median PFS: 15.6 mo ibrutinib vs 6.2 mo tem CR rate: 23.0% ibrutinib vs 2.8% tem ORR: 77.0% ibrutinib vs 46.8% tem, p<0.0001 OS: HR 0.74 (95% CI: 0.54, 1.02), p=0.0621

CI=confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; MCL=mantle cell lymphoma; mo=months; No.=number; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; r/r=relapsed or refractory; tem=temsirolimus; vs=versus

For further details on the efficacy and safety data from these studies, refer to the ibrutinib Investigator's Brochure.

2.2.7. Studies of Ibrutinib in Combination With Rituximab in Subjects with MCL

Following on from Study PCYC-1104-CA (Section 2.2.6), it was hypothesized that by adding rituximab to ibrutinib, MCL cells associated with the ibrutinib redistribution lymphocytosis could be targeted, leading to more potent antitumor activity (Jain 2018; Wang 2016). Fifty participants with r/r MCL were enrolled in an open-label, Phase 2 investigator-initiated study. Participants received ibrutinib (560 mg daily administered orally) until progressive disease or unacceptable toxic effects, in combination with rituximab. Participants received rituximab at 375 mg/m² IV once weekly for 4 weeks during Cycle 1 (one cycle was 28 days), then on Day 1 of Cycles 3 8, and thereafter once every other cycle for up to 2 years. Median age was 67 years (range: 45-86 years), and the median number of previous treatment regimens was 3 (range: 1 9). At a median follow-up of 16.5 months, 44 (88%) participants achieved an objective response, with 22 (44%) participants achieving a CR, and 22 (44%) a partial response (PR). The only Grade 3 AE in ≥10% of participants was atrial fibrillation in 6 (12%) participants. Grade 4 diarrhea and neutropenia occurred in 1 participant each. Adverse events that led to discontinuation of therapy were atrial fibrillation in 3 (6%) participants, liver infection and bleeding in 1 (2%) participant each. Two participants died while on-study from cardiac arrest and septic shock.

Long-term follow-up from this study showed continued efficacy with the combination of ibrutinib + rituximab in participants with r/r MCL (Jain 2018). At a median follow-up time of 47 months (range: 1 52 months), median duration on treatment was 16 months (range: 1-53 months) with a median number of 17 treatment cycles (range: 1 56). Twenty-nine participants (58%) achieved complete remission and of these, 12 participants continued study treatment. The median PFS was 43 months, and median OS was not reached. The most frequent Grade 1 and Grade 2 toxicities were fatigue, diarrhea, nausea, arthralgias and myalgias. No participant had long term toxicities.

The combination of ibrutinib + rituximab was assessed in a Phase 2 investigator-initiated study in previously untreated elderly (≥65 years) participants with MCL (Jain 2020). Participants received ibrutinib (560 mg orally daily administered orally) until disease progression or unacceptable toxicity, and rituximab 375 mg/m^2 IV on Days 1, 8, 15 and 22 in Cycle 1, followed by rituximab

on Day 1 of Cycles 3-8, then on Day 1 every 2 months for up to 2 years. The median follow-up was 36.2 months (range: 6-48 months). The ORR was 96% (66% CR, 30% PR, and 4% stable disease). Median number of ibrutinib + rituximab cycles to reach CR was 8 (range: 3-51 cycles). The Median PFS and OS were not reached. The most frequent Grade 3-4 toxicities were atrial fibrillation (22%), fatigue (18%), diarrhea, myalgias, and shortness of breath (each 14% of participants), neutropenia and pain (each 8% of participants). There were no Grade 5 toxicities.

The sponsor-initiated Study PCI-32765MCL3002 was a Phase 3, placebo-controlled study that evaluated the efficacy and safety profile of therapy with ibrutinib in combination with bendamustine and rituximab (BR) in elderly participants (≥65 years) with newly diagnosed MCL. Participants received ibrutinib (N 261) 560 mg orally once daily on a 28-day cycle, or placebo (N 262). until disease progression, unacceptable toxicity, or study end, in combination with BR background therapy (bendamustine: 90 mg/m^2 IV on Days 1 and 2 of Cycles 1-6, for a maximum of six 28-day cycles, and rituximab: 375 mg/m^2 IV on Day 1 of Cycles 1-6 unless disease progression or unacceptable toxicity). After Cycle 6, participants with CR or PR continued to receive rituximab on Day 1 of every second cycle for a maximum of 12 additional doses unless progression of disease or unacceptable toxicity.

At the primary analysis, with a median follow up of 84.7 months, the study met its primary endpoint of investigator-assessed PFS, with ibrutinib + BR significantly reducing the risk of disease progression or death by 25% compared with placebo + BR (HR 0.75; 95% CI: 0.59, 0.96; p 0.011]). The median PFS was 80.6 months for ibrutinib + BR and 52.9 months for placebo + BR. The CR rate was higher for ibrutinib + BR than placebo + BR (65.5% vs 57.6%) but did not reach statistical significance (p 0.0567). With a median follow-up of 84.7 months, OS similar between ibrutinib + BR and placebo + BR (104 and 107 deaths, respectively), with a HR of 1.07 (95% CI: 0.81, 1.40; p 0.648). Median OS was not reached for either treatment group; the estimated 60-month OS rates were 65% for ibrutinib + BR and 67% for placebo + BR. This study is ongoing for collection of additional survival data.

The overall safety profile of ibrutinib + BR was consistent with the known safety profiles of ibrutinib and BR. There was a higher incidence of AEs in the ibrutinib + BR arm than the placebo + BR arm as follows: Grade 3 or higher AEs (92.7% vs 84.6%), serious adverse events (SAEs) (76.1% vs 60.0%), AEs leading to study drug discontinuation (45.2% vs 26.5%), AEs leading to study drug dose reduction (23.2% vs 10.0%), and AEs leading to death (11.2% vs 7.3%). Major hemorrhage events were generally comparable between the ibrutinib + BR and placebo + BR arms (5.8% vs 4.2%), and atrial fibrillation occurred more frequently in the ibrutinib + BR arm (36 [13.9%] participants) than the placebo + BR arm (17 [6.5%] participants).

2.2.8. Study Drugs Used in Combination With Ibrutinib and Comparator Therapies

2.2.8.1. Rituximab

Rituximab is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with NHL, including r/r CD20-positive follicular B-cell NHL as a single agent, and previously untreated CD20-positive diffuse large B-cell NHL in combination with cyclophosphamide,

doxorubicin, vincristine, and prednisone (CHOP) (RUXIENCE® USPI 2021; RUXIENCE® SmPC 2022).

2.2.8.2. Lenalidomide

Lenalidomide is an immunomodulatory agent that has demonstrated clinical benefit for patients with r/r MCL. Lenalidomide as monotherapy, is indicated for the treatment of adult patients with r/r MCL, and in combination with rituximab for adult patients with previously treated follicular lymphoma (FL) (Lenalidomide Accord SmPC 2022 [or local label if locally sourced]).

An open-label, Phase 1/2 trial in participants with r/r MCL was conducted to identify the maximum tolerated dose (MTD) of lenalidomide when combined with rituximab (Phase 1, N 14), and the efficacy and safety of the lenalidomide + rituximab combination (Phase 2, N 44). In Phase 1, participants received 10, 15, 20, and 25 mg of daily oral lenalidomide on Days 1 21 of each 28-day cycle. Rituximab 375 mg/m² IV was also administered in 4 weekly doses during Cycle 1 only. In Phase 2, participants received rituximab plus the MTD of lenalidomide, following the same cycles as for Phase 1. Treatment in both phases continued until disease progression, stem-cell transplantation, or severe toxicity. The MTD was 20 mg lenalidomide when combined with rituximab. Among 44 participants in Phase 2, 25 (57%) had an overall response: 16 (36%) had a CR and 9 (20%) had a PR. The median response duration was 18.9 months, median PFS was 11.1 months, and the median OS was 24.3 months (Wang 2012).

For details of studies with single agent lenalidomide in r/r MCL, refer to the product label (Lenalidomide Accord SmPC 2022 [or local label if locally sourced]).

2.2.8.3. Bortezomib

Bortezomib is a first in class proteasome inhibitor. Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated MCL who are unsuitable for hematopoietic stem cell transplantation (VECLADE® USPI 2021; VELCADE® SmPC 2021).

In a Phase 3, randomized, open-label study in r/r B-cell NHL, participants received bortezomib + rituximab (N 336) or rituximab alone (N 340). Participants were randomly assigned (1:1) to receive five 35-day cycles consisting of rituximab 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1, and on Day 1 of Cycles 2-5, either alone or with bortezomib 1.6 mg/m^2 IV on Days 1, 8, 15, and 22 of all cycles. With a median follow-up of 33.9 months, median PFS per IRC assessment was significantly longer with bortezomib + rituximab than with rituximab alone, 12.8 months versus 11.0 months, respectively; p 0.039. The HR was 0.82, corresponding to a 22% improvement in PFS with bortezomib + rituximab compared with rituximab alone (Coiffier 2011).

The efficacy and safety of bortezomib in combination with rituximab was demonstrated in a Phase 2 open-label, single-arm study in 155 participants with r/r MCL. With a median follow-up of more than 13 months, the ORR (CR+CRu+PR) was 31.0% (N 48), the CR rate (CR+CRu) was 8.0% (N 120 and the median duration of response (CR+CRu+PR) was 9.3 months (N 48) (VELCADE® USPI 2021).

2.3. Benefit-Risk Assessment

2.3.1. Risks for Study Participation

2.3.1.1. Risks Relevant With Ibrutinib

Mitigation strategies for risks associated with ibrutinib are presented in Table 3.

Table 3: Mitigation Strategies for Risks Associated with Ibrutinib

Risks[a]	Mitigation Strategies
Bleeding-related events	Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding Supplements such as fish oil and vitamin E preparation should be avoided Ibrutinib should be held for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding Guidance for participants who require surgical intervention or an invasive procedure while receiving ibrutinib is provided in Section 6.7.4. Guidance on use of antiplatelet agents and anticoagulants is provided in Section 6.7.2.2
Lymphocytosis	Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/μL), often associated with reduction of lymphadenopathy, has been observed in some subjects (35%) with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves withing a median of 8 weeks in subjects with MCL
Leukostasis	A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. Consider temporarily withholding ibrutinib. Participants should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated
Infections	Consider prophylaxis according to standard of care in participants who are at increased risk for opportunistic infections (see Section 6.7.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in participants treated with ibrutinib. Cases of hepatitis E, which may be chronic, have occurred in participants treated with ibrutinib. Participants should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting, jaundice, and abnormal liver function tests) and appropriate therapy should be instituted as indicated
Cytopenias	Monitor complete blood counts monthly
Interstitial lung disease	Monitor participants for pulmonary symptoms indicative of interstitial lung disease. If symptoms develop, follow the protocol dose modification guidelines (see Section 6.5.1). If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (see Section 6.5.1)
Cardiac arrhythmias and cardiac failure	Fatal and serious cardiac arrhythmias or cardiac failure have occurred in participants treated with ibrutinib. Participants with significant cardiac comorbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure, have been reported, particularly in participants with acute infections, or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Participants should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (eg, ECG, echocardiogram) as indicated for participants in whom there are cardiovascular concerns. Consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (Section 6.5.1)
Tumor lysis syndrome (TLS)	Participants at risk of TLS are those with high tumor burden prior to treatment. Monitor participants closely and take appropriate precautions

Table 3: Mitigation Strategies for Risks Associated with Ibrutinib

Risks[a]	Mitigation Strategies
Non-melanoma skin cancer	Monitor participants for the appearance of non-melanoma skin cancer
Hypertension	Regularly monitor blood pressure in participants treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate
Cardiovascular accidents	Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended
Diarrhea	These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Participants should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluations should be made to rule out other etiologies such as *Clostridium difficile* or other infections agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in Section 6.5.1
Rash	Participants should be closely monitored for signs and symptoms suggestive of severe cutaneous adverse reactions, including Stevens-Johnson syndrome. Participants receiving ibrutinib should be observed closely for rashes and treatment symptomatically, including interruption of the suspected agent as appropriate

[a] Source: Ibrutinib Investigator's Brochure, Edition 15, 2021.

2.3.1.2. Risks Relevant With Rituximab

For full details of warnings, precautions and AEs associated with treatment with rituximab, refer to the product label (RUXIENCE® USPI 2021; RUXIENCE® SmPC 2022).

2.3.1.3. Risks Relevant With Lenalidomide

Lenalidomide is an analog of thalidomide, which is a known human teratogen that causes severe birth defects or embryo-fetal death. Due to the embryo-fetal risk associated with immunomodulatory drugs, all participants receiving lenalidomide must adhere to the applicable Pregnancy Prevention Program (PPP) for lenalidomide (see Section 5.3 and Section 10.4 [Appendix 4] for further details).

For further details of the warnings, precautions and AEs associated with treatment lenalidomide, refer to the product label (Lenalidomide Accord SmPC 2022 [or local label if locally sourced]).

2.3.1.4. Risks Relevant With Bortezomib

For full details of warnings, precautions and AEs associated with treatment with bortezomib, refer to the product label (VELCADE® USPI 2021; VELCADE® SmPC 2021).

2.3.2. Benefits for Study Participation

In the Phase 2 studies described in Section 2.2.7, treatment with ibrutinib in combination with rituximab resulted in higher response rates and longer PFS and OS in subjects with MCL compared with historical data from ibrutinib monotherapy studies. Considering the results from these studies, participants may benefit from this combination treatment in this study. Bortezomib and lenalidomide are approved agents for the treatment of MCL and to be given with or without rituximab.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the risks and the measures taken to minimize risks to participants, such as periodic monitoring and dose modifications, the potential risks identified in association with ibrutinib + rituximab are justified by the anticipated benefits that may be afforded to participants with r/r MCL. The overall benefit-risk assessment in this study is expected to be positive for the participants in this study.

3. OBJECTIVES AND ENDPOINTS

As a result of the early study discontinuation, the primary objective of Protocol Amendment 1 is to provide continued access to treatment for participants who continue to benefit from treatment. The Phase 2 exploratory objectives and endpoints of characterization of PK and PD of ibrutinib may continue to be evaluated using blood samples already collected prior to implementation of Protocol Amendment 1.

Objectives	Endpoints
Exploratory	
• To characterize the pharmacokinetics of ibrutinib when administered in combination with rituximab • To assess the pharmacodynamics of ibrutinib when administered in combination with rituximab	• Systemic exposure • BTK and/or ITK occupancy at various doses of ibrutinib and at different timepoints

BTK=Bruton's Tyrosine Kinase; ITK= Interleukin-2-inducible T-cell kinase

HYPOTHESIS

Phase 2

No formal statistical hypothesis testing will be conducted.

4. STUDY DESIGN

4.1. Overall Design

This study was designed as a randomized, controlled, open-label, international, multicenter, inferentially seamless Phase 2/3 adaptive study. As a result of the early study discontinuation, the Phase 2 part of this study will not fully enroll, and the Phase 3 part will not start.

Participants will be randomized 1:1:1:1 to Treatment Arm A1 (ibrutinib 560 mg QD + rituximab) or Treatment Arm A2 (ibrutinib 420 mg QD + rituximab) or Treatment Arm A3 (ibrutinib 140 mg BID + rituximab), or Treatment Arm B (physician's choice of lenalidomide + rituximab or bortezomib + rituximab).

Randomization of the study will be stratified by simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) score (low/intermediate vs high) (Hoster 2008; Section 10.6 [Appendix 6]), prior lines of therapy (1 prior line with progression of disease [POD]24 [POD within 24 months of diagnosis] vs 1 prior line with POD>24 [POD >24 months after diagnosis] vs

>1 prior line), and by geographical region (US/EU vs Rest of the World [ROW]). Selection of physician's choice must be made for every participant prior to randomization.

This study will include a Screening Phase, and a Treatment Phase. The Screening Phase will be up to 30 days prior to randomization. The Treatment Phase will extend from randomization until study treatment discontinuation.

To determine whether continued treatment is warranted, investigators should monitor and assess participants for response to treatment or disease progression per standard of care preferably using the Lugano Criteria (Cheson 2014). Disease status and date of disease progression before the completion of 6 cycles of study treatment should be documented in the electronic case report form (eCRF). After 6 cycles of study treatment, the eCRF data collection period will end so notification of progressive disease to the medical monitor should be via email.

During the study, safety evaluations will include AE monitoring, physical examinations per standard of care, vital signs, 12-lead ECG, as clinically indicated, concomitant medication usage, and clinical laboratory parameters (hematology, chemistry, coagulation, as clinically indicated). At each site visit, participants will be evaluated for toxicity. All study evaluations will be conducted per the Schedule of Activities (Table 1).

Upon implementation of Protocol Amendment 1, all participants will be given the choice to either remain on the randomized treatment arm or switch to ibrutinib monotherapy at 560 mg QD (unless ibrutinib dose was reduced for toxicity reasons). All participants will also be given the option to drop rituximab treatment and continue with monotherapy.

Participants will continue with the chosen dosing regimen (the one to which they were assigned to during randomization or the ibrutinib 560 mg dose regimen) until the investigator determines that the participant is no longer benefiting from treatment (ie, disease progression or unacceptable toxicity has occurred), the participant withdraws consent, alternative access to study treatment is available and feasible (eg, rollover to a long-term extension study, patient assistance program or commercial source of ibrutinib), or until the end of the study, whichever occurs earlier.

An End-of-Treatment visit for a safety assessment should take place within 30 days (+14-day window) after the last dose of study treatment or before the start of subsequent anti-cancer therapy, if earlier. The eCRF data collection period will end, and the clinical database will be closed. All eCRF data collected up to this timepoint will be included in the final Clinical Study Report. Participants benefiting from study treatment may continue to receive study treatment after the end of eCRF data collection and clinical database closure until study treatment is commercially available, available from another source, or until study completion, whichever occurs earlier (see Section 4.4).

The study is considered completed when all participants still receiving study treatment have transitioned to commercial or alternative access to study treatment, have stopped receiving study treatment, or upon a decision by the sponsor to terminate the study, whichever occurs earlier. A diagram of the study design for the Phase 2 part of the study is provided in Section 1.2 (Figure 1).

4.2. Scientific Rationale for Study Design

As a result of the early study discontinuation, the original objective of the study no longer applies. The aim of the sponsor with Protocol Amendment 1 is to provide continued access to study treatment for participants who continued to benefit from treatment.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences. Following the implementation of Protocol Amendment 1, the total blood volume to be collected will be minimal, and only for the purpose of study procedures including safety.

4.3. Justification for Dose

Data from Study PCYC-04753 showed that although ibrutinib is rapidly eliminated from the plasma after oral administration, QD dosing is adequate to sustain maximal BTK occupancy for 24 hours postdose at dose levels ≥2.5 mg/kg. Although the BTK occupancy was above 90% at ibrutinib doses ≥2.5 mg/kg in this study, the data are from combined B-cell malignancy cohorts containing small numbers of subjects with MCL (ie, 9 subjects with r/r MCL). Based on these data, simulations on BTK occupancy were performed with a maximal efficacy (E_{max}) model at different dose levels (140 mg, 280 mg, 420 mg, and 560 mg once daily) in a population of virtual subjects. The results showed a higher percentage of subjects with occupancy of >90% at 560 mg compared with 280 mg QD (91.9 % for 560 mg vs 75.7% for 280 mg). Moreover, the dose of 560 mg QD appeared to have a manageable safety profile and objective responses were observed in MCL patients.

Further exposure-response analyses in subjects with MCL receiving single-agent ibrutinib 560 mg/day (Studies 1104, MCL2001, MCL3001, and 04753) did not reveal an exposure-response relationship for efficacy (ORR) across the observed exposure range. In addition, no clear exposure-response relationship for PFS was observed in study MCL3002, in which ibrutinib was combined with chemoimmunotherapy (bendamustine-rituximab). With regards to safety, ibrutinib exposure was associated with the incidence of atrial fibrillation and any hemorrhage within the exposure range obtained in the ibrutinib treatment arm in Study MCL3002. The predicted incidence of atrial fibrillation decreased from 11.9% for an ibrutinib area under the plasma concentration-time curve (AUC) of 349 h.ng/mL (median AUC associated with 560 mg QD dosing) to 10.9% for an AUC of 262 h.ng/mL (median AUC predicted for 420 mg QD dosing). Similarly, the incidence of any hemorrhage decreased with a 25% reduction in 560 mg QD dose from 29.4% to 27.4% for subjects receiving no CYP3A inhibitor comedication and from 43.8% to 41.3% for subjects receiving

CYP3A inhibitor comedication. The exposure-response relationship for atrial fibrillation was not observed in Studies 1104, MCL2001, MCL3001 and 04753.

Recently, a new covalent binding time-dependent PK/PD model was built using published data to describe the BTK occupancy in CLL patients. Due to limited data from MCL patients and lack of information on BTK dynamics between MCL and CLL biology, this model was adapted to reflect the biology of MCL. BTK dynamics in the more aggressive MCL biology assumed faster BTK turnover (Scenario 1) or higher baseline free BTK concentrations (Scenario 2). The results for the first scenario showed 96.2%, 91.6%, 78.1%, and 98.7% of subjects with occupancy of >90% for the 560 mg, 420 mg, 280 mg QD, and 140 mg BID, respectively, at trough plasma concentrations (C_{trough}). The results for the second scenario showed 100% of subjects with occupancy of >90% for all 4 dose levels. Given the uncertainty in BTK assumptions in the MCL population, and to ensure maximum BTK occupancy in the majority of the subjects, 420 mg QD and 140 mg BID were selected for the lower doses to be evaluated in this study. Using these doses, the currently labelled dose (560 mg/day) is evaluated side-by-side with 420 mg/day which is 25% lower and predicted to have lower overall exposure (free maximum observed plasma concentration [C_{max}], AUC, and minimum plasma drug concentration [C_{min}]). The 140 mg BID dose is 50% lower (280 mg total daily dose) compared with 560 mg/day and is predicted to have lower (free) C_{max} and AUC. However, (free) C_{min} is similar to the 420 mg/day dose level, which may be important for efficacy (maintaining BTK occupancy). With these dose levels, certain AE rates may be positively impacted with the resulting lower exposures.

Furthermore, it is hypothesized that by combining ibrutinib with rituximab, MCL cells associated with the ibrutinib redistribution lymphocytosis could be targeted, leading to more potent antitumor activity and thus positively impacting efficacy. Combination studies of ibrutinib 560 mg orally QD with rituximab 375 mg/m^2 IV demonstrated a positive impact on efficacy while no new safety issues were noted with this combination (Section 2.2.7). However, ibrutinib and rituximab as anti-CD20 therapy have overlapping unfavorable effects. Amongst these, the most common (≥10%) ADRs of any grade reported in patients treated with either ibrutinib or rituximab include upper respiratory tract infection/bronchitis, neutropenia, thrombocytopenia, nausea, rash, fever/pyrexia, and headache. In addition, common safety warnings and precautions for ibrutinib and rituximab include infections (including hepatitis B reactivation and progressive multifocal leukencephalopathy (PML), cardiac disorders (including arrythmia and cardiac failure), and cytopenias (IMBRUVICA® SmPC 2022; RUXIENCE® SmPC 2022).

The proposed dose for lenalidomide is 20 mg orally once daily on Days 1 through 21 of a 28-day cycle until disease progression or unacceptable toxicity is based on a Phase 1/2 study in 52 subjects with r/r MCL (see Section 2.2.8.2). In this study the maximum tolerated dose of lenalidomide was identified as 20 mg when combined with rituximab 375 mg/m^2 IV. This combination was effective, with an ORR of 57%, a median duration of response of 18.8 months, and was associated with less severe toxicities than 25 mg lenalidomide plus rituximab and, therefore, allowing longer drug exposure (Wang 2012).

The proposed dose for bortezomib is 1.3 mg/m^2 IV or SC on Days 1, 4, 8, and 11 of a 21-day cycle until disease progression or unacceptable toxicity which is the dose used for the treatment of adult patients with MCL as detailed in the product label (VELCADE USPI® 2021; VELCADE® SmPC 2021). The proposed dose for rituximab is 375 mg/m^2 IV which is the recommended dose for the treatment of NHL and chronic lymphocytic leukemia (CLL) as detailed in the product label (RUXIENCE® USPI 2021; RUXIENCE® SmPC 2022).

4.4. End of Study Definition

The clinical database will close and no further data will be collected in the eCRFs as soon as possible but no later than when the last study participant has completed the first 6 cycles of study treatment. Only data collected in the eCRF during the data collection period will be included in the final Clinical Study Report.

The sponsor will ensure that participants benefiting from study treatment will be able to continue receiving study treatment after the end of eCRF data collection and clinical database closure until study treatment is commercially available, or available from another source, or study completion, whichever occurs earlier. Refer to Section 10.13 (Appendix 13) for further guidance on data collection and reporting procedures for participants who continue study treatment after the end of eCRF data collection.

The study is considered completed when all participants still receiving study treatment have transitioned to commercial or alternative access to study treatment, have stopped receiving study treatment, or upon a decision by the sponsor to terminate the study, whichever occurs earlier.

5. STUDY POPULATION

Screening for eligible participants will be performed up to 30 days before randomization. Refer to Section 5.5, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants of this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent.

2. Have pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR) (see Section 8.1.2).

   A report from the local laboratory is acceptable; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to randomization.

   If the report from the local laboratory is not available prior to randomization, or the central laboratory is not able to confirm MCL diagnosis based on the local laboratory report, a newly obtained tissue sample or most recent dated FFPE archival tissue sample is required to confirm MCL diagnosis prior to enrollment. The tumor tissue block or slides must be sent to the central pathology laboratory for confirmation of MCL diagnosis prior to randomization. If central laboratory is not able to confirm diagnosis from the archived tissue sample, a fresh tissue sample is required.

   If Cyclin D1 and t(11;14) are negative, but the central laboratory confirms MCL, participants can still enroll into the study.

3. At least 1 prior treatment regimen for MCL excluding BTKi.

4. Documented disease progression or relapse following the last anti-MCL treatment.

5. At least 1 measurable site of disease on cross-sectional imaging that is ≥2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per computed tomography (CT).

6. Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1 (see Section 10.5 [Appendix 5]).

7. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to first dose, with the exception of pegylated granulocyte-colony stimulating factor (G-CSF) (pegfilgrastim) and darbopoeitin which requires at least 14 days prior to the first dose), defined as:
   a. Absolute neutrophil count (ANC) ≥ 1000/mm^3
   b. Platelets ≥50,000/mm^3
   c. Hemoglobin ≥8.0 g/dL

8. Adequate hepatic and renal function defined as:
   a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN)

b. Total bilirubin ≤1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin (in which case direct bilirubin ≤1.5 x ULN is required)
c. Estimated creatinine clearance (Cockroft-Gault [Cockroft 1976]) ≥30 mL/min (see Section 10.12 [Appendix 12]).

9. Prothrombin time <1.5 x ULN/international normalized ratio (INR) <1.5 and activated partial thromboplastin time (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR must be ≤3.0.

10. Participants must not be diagnosed or treated for malignancy other than MCL. Allowed recent second or prior malignancies are as follows:

- Any malignancy that was not progressing nor requiring treatment change in the last 12 months.
- Malignancies treated within the last 12 months and considered at very low risk for recurrence:

  Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low grade, <3 cm, no carcinoma in situ [CIS]).

  Skin cancer (non-melanoma or melanoma).

  Non-invasive cervical cancer.

  Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, localized breast cancer and receiving antihormonal agents.

  Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (Radical Prostatectomy/Radiation Therapy/focal treatment).

11. A female of childbearing potential must have a negative highly sensitive serum pregnancy test at screening and must agree to further serum or urine pregnancy tests during the study.

12. A female must be:

a. Not of childbearing potential, or
b. Of childbearing potential and
   1) Practicing true abstinence; or
   2) Practicing ≥1 highly effective method of contraception (see Section 10.4 [Appendix 10.4] for further information). A female using oral contraceptives must use an additional contraceptive method. See Section 6.7.2.4 for details regarding concomitant use of estrogen containing products and lenalidomide.

NOTE: Participant must agree to continue the above throughout study treatment and for 4 weeks following ibrutinib or lenalidomide treatment, 3 months following bortezomib treatment, and 12 months following rituximab treatment.

NOTE: If a female becomes of childbearing potential after start of the study the female must comply with point (2) as described above.

13. A female must agree not to donate eggs (ova, oocytes) or freeze for future use, for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment.

14. A female must not be pregnant, or planning to become pregnant, while receiving study treatment or 4 weeks following lenalidomide treatment and must not breastfeed during study treatment or 12 months following rituximab treatment.

15. A male must wear a condom (with or without spermicidal foam/ gel/ film/ cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 3 months after receiving the last dose of study treatment. If a female partner is of childbearing potential, she must also be practicing a highly effective method of contraception.

    NOTE: If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/suppository), but his female partner is not required to use contraception.

16. A male must agree not father a child or donate sperm for the purpose of reproduction during the study and for a minimum of 3 months after receiving the last dose of study treatment.

17. Must sign an informed consent form (ICF) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

18. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Prior therapy with ibrutinib or other BTK inhibitor.

2. Major surgery within 4 weeks of randomization.

3. Participants with any contraindications to one of the study treatments including hypersensitivity to the active substance or to any of the excipients of ibrutinib, rituximab, lenalidomide, bortezomib or its excipients (refer to the ibrutinib Investigator's Brochure or product labels).

4. Concurrent enrollment in another therapeutic investigational study.

5. Known central nervous system lymphoma.

6. Prior treatment with both lenalidomide and bortezomib. Prior treatment with only 1 of these therapies is allowed, but the investigator must select the other therapy as the potential comparator regimen at randomization.

7. Anticancer therapy including chemotherapy, radiotherapy, small molecule, monoclonal antibody and investigational agents ≤21 days (or at least 5 drug half-lives, whichever is shorter) prior to first administration of study treatment.

8. History of stroke or intracranial hemorrhage within 6 months prior to randomization.

9. Ongoing treatment with agents known to be strong CYP3A inhibitors.

10. Active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia, or uncontrolled hypertension or Class II, III or IV congestive heart failure as defined by the New York Heart Association Functional Classification (see Section 10.7 [Appendix 7]); or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 1 year prior to randomization (if >1 year, a cardiology consultation documenting cardiac clearance is required to be eligible) or hypertension, despite treatment with 3 or more anti-hypertensive medications, with screening systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.

11. Currently active, clinically significant Child-Pugh Class B or C hepatic impairment according to Child-Pugh classification. Refer to (Section 10.8 [Appendix 8]) for Child-Pugh classification.

12. Vaccinated with live, attenuated or replicating viral vector vaccines within 4 weeks of randomization.

13. Any uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the participant's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk (including uncontrolled diabetes mellitus or HbA1C >7).

14. Known history of Human Immunodeficiency Virus (HIV).

15. Active hepatitis B or C virus infection according to local laboratory range, on all available tests for the past 6 months or other clinically active liver disease.

    Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen [HBsAg]. Participants with resolved infection (ie, participants who are HBsAg negative with antibodies to total hepatitis B core antigen [anti-HBc] with or without the presence of hepatitis B surface antibody [anti-HBs]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic

marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR (see Appendix 11 [Section 10.11, Hepatitis B Virus Screening]).

Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV antibody.

Positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained.

Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

Active or chronic persistent hepatitis E virus (HEV) infection: participants seropositive for Hepatitis E (anti-Hep E IgG positive) must be screened (serum or stool) using real-time polymerase chain reaction (RT-PCR) measurement of HEV RNA levels. Those who are RT-PCR positive will be excluded.

16.. Known bleeding disorders.

17. Inability or difficulty swallowing capsules/tablets, malabsorption syndrome, or any disease or medical condition significantly affecting gastrointestinal (GI) function.

18. Prior stem cell transplant that requires ongoing immunosuppressive therapy or clinical graft versus host disease.

19. Only applicable if investigator selects bortezomib as the potential comparator prior to randomization. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version (NCI-CTCAE) Version 5.0.

5.3. Restrictions During Study Participation

Potential participants must be willing and able to adhere to the following restrictions during the study to be eligible for participation:

1. A female participant of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria). Contraception must begin 4 weeks before initiating study treatment, and continue during the Treatment Phase, during dose interruptions and continuing for at least 4 weeks following ibrutinib or lenalidomide treatment; 3 months following bortezomib treatment; and 12 months following rituximab treatment. In addition, females must not donate ova during the study, or for 6 months after the last dose of study treatment.
2. For participants randomized to lenalidomide, two negative pregnancy tests must be obtained prior to initiating study treatment. The first test should be performed at screening and the second test within 24 hours prior to the first dose of study treatment. Weekly (±2 days) pregnancy tests are required during the first month, then monthly (-2 days) thereafter in females with regular menstrual cycles or every 2 weeks (±2 days) in females with irregular menstrual cycles. Additional pregnancy tests may be required, as specified in the local lenalidomide Risk Evaluation and Mitigation Strategy (REMS) (where lenalidomide is supplied locally) or the Lenalidomide Global PPP (where lenalidomide is supplied centrally and no local lenalidomide REMS program exists).
3. A man who has not had a vasectomy and who is sexually active with a pregnant female or a female of childbearing potential must agree to use a barrier method of birth control eg, condom with spermicidal foam/gel/film/cream/suppository during the study and for at least 3 months after the study. All men must not donate sperm during the study, during dose interruptions, or for at least 3 months after the last dose of study treatment. The exception to this restriction is that if the participant's female partner is surgically sterile, a second method of birth control is not required.
4. Because of the embryo-fetal risk of lenalidomide all participants must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the Lenalidomide Global PPP (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).
5. Participants must not donate blood during treatment, during dose interruptions and for at least 7 days following discontinuation of lenalidomide.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Refer to Section 5.5, Screen Failures, which describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2: Regulatory, Ethical, and Study Oversight Considerations (Appendix 2).

5.4. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.7, Concomitant Therapy for details regarding prohibited and therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Carry a "wallet study card" with pertinent information about the study for the duration of study participation.

5.4.1. Meals and Dietary Restrictions for Participants Receiving Ibrutinib

Participants should avoid consuming food and beverages containing grapefruit, Seville oranges (including marmalade containing Seville oranges), blood oranges, pomelos, tangelos, and star fruit as these contain certain ingredients that inhibit CYP3A4/5 enzymes. Supplements such as fish oil and vitamin E preparations should be avoided.

Participants should refrain from taking the study drug on the morning of study visits designated for PK sampling until seen at the site. See Section 6.1 (Table 4) for dosing instructions before and during PK sampling visits.

5.5. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Retesting of abnormal screening values that led to exclusion are allowed during the screening phase (to reassess eligibility). The last result obtained prior to the first dose of study drug will be used to determine eligibility. The measurements collected at the time closest to, but prior to, the start of study drug administration will be defined as the baseline values for safety assessment and treatment decisions.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Study participants in Treatment Arm A1, A2 or A3 will receive ibrutinib orally (560 mg QD, or 420 QD, or 140 mg BID, respectively, 28-day cycle) until disease progression or unacceptable toxicity. Participants in Treatment Arm B will receive either lenalidomide (20 mg [or 10 mg if CrCl is 30 to <60 mL/min] orally once daily on Days 1 through 21 of a 28-day cycle) or bortezomib (1.3 mg/m^2 IV or SC on Days 1, 4, 8, and 11 of a 21-day cycle) until disease progression or unacceptable toxicity. Participants in all treatment arms will have the choice to also receive rituximab (375 mg/m^2 IV) on Day 1 of Cycles 1 to 6 (28-day cycle in combination with ibrutinib or lenalidomide, and 21-day cycle in combination with bortezomib). For participants on ibrutinib + rituximab, it is recommended that ibrutinib is administered prior to rituximab on Day 1 of Cycles 1 to 6.

Dosing instructions for ibrutinib, rituximab, lenalidomide, and bortezomib are detailed in Table 4. Refer to the Site Investigational Product and Procedures Manual (SIPPM) for details regarding the drug products and information describing study drug administration, and storage. It is strongly recommended that premedication guidelines are followed per study drug package insert(s). Study drug administration must be captured in the source documents and the case report form (CRF). Refer to the respective Investigator's Brochure or product labels for a list of excipients. Study-site personnel will instruct participants on how to store study drugs for at home use as indicated for this protocol. Sufficient study drugs required until the next visit will be dispensed. The study treatments in this study are designated as follows:

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Products</td><td>Ibrutinib, Rituximab, Lenalidomide, Bortezomib
Authorization status in the EU:<table><tr><td>Authorized</td><td>Ibrutinib
Rituximab
Lenalidomide
Bortezomib</td></tr></table></td></tr>
</table>

Table 4: Description of Ibrutinib, Rituximab, Lenalidomide, and Bortezomib, and Study Treatment Administration Instructions

Arm Name	Arm A1, A2 and A3	Arm B
Treatment Name	Ibrutinib + Rituximab	Lenalidomide + Rituximab **OR** Bortezomib + Rituximab
Dose Formulation	Ibrutinib – capsules Rituximab – IV	Lenalidomide – capsules Bortezomib – IV or SC Rituximab – IV
Unit Dose Strength(s)	Ibrutinib – 560 mg QD (4×140 mg) Ibrutinib – 420 mg QD (3×140 mg) Ibrutinib – 140 mg BID Rituximab – 375 mg/m^2	Lenalidomide – 20 mg Bortezomib – 1.3 mg/m^2 Rituximab – 375 mg/m^2
Dosage Level(s) and Frequency	Ibrutinib –until disease progression or unacceptable toxicity Rituximab – 375 mg/m^2 IV on Day 1 of Cycles 1 to 6	Lenalidomide – 20 mg (orally once daily on Days 1 through 21 of a 28-day cycle) until disease progression or unacceptable toxicity Bortezomib – 1.3 mg/m^2 IV or SC on Days 1, 4, 8, & 11 of a 21-day cycle) until disease progression or unacceptable toxicity Rituximab – 375 mg/m^2 IV on Day 1 of Cycles 1 to 6
Route of Administration	Oral - ibrutinib IV infusion - rituximab	Oral - lenalidomide IV injection – bortezomib IV infusion - rituximab SC – bortezomib
Dosing instructions	The ibrutinib capsules are to be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed. Ibrutinib can be taken with or without food. The participant should refrain from taking the study drug on the morning of study visits designated for PK sampling. It is recommended that ibrutinib is administered prior to rituximab on Day 1 of Cycles 1 to 6. If a dose of study drug is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The participant should not take extra capsules to make up the missed dose	The lenalidomide capsules are to be taken at about the same time each day, either with or without food. The capsules should be swallowed whole and should not be opened, broken, or chewed When bortezomib is given IV, administer at a concentration of 1 mg/mL, or given SC, administer at a concentration of 2.5 mg/mL When bortezomib is given IV, administer as a 3 to 5 second bolus IV injection

BID twice daily; CYP cytochrome P450; IV intravenous; PK pharmacokinetic; QD once daily; SC subcutaneous

For a definition of study treatment overdose, refer to Section 6.6, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study drugs must be stored at controlled temperatures according to the label. Refer to the SIPPM for additional guidance on study drug preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the participant, and the return of study drug from the participant (if applicable), must be documented on the drug accountability form. Participants or their legally acceptable representative, where applicable, must be instructed to return all original containers, whether empty or containing study drug. The study treatment administered to the participant must be documented on the treatment accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study drug containers.

Study drugs must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drugs should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug(s) will be supplied only to participants enrolled in the study. Returned study drug(s) must not be dispensed again, even to the same participant. Study drug(s) may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study drugs are provided in the SIPPM. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection and database closure.

6.3. Measures to Minimize Bias: Randomization and Blinding

Procedures for Randomization

Prior to randomization, physician will designate the comparator treatment to be used if participant is randomized to Treatment Arm B.

Phase 2 Part: Participants will be randomly assigned to 1:1:1:1 to Treatment Arm A1 (ibrutinib 560mg QD + rituximab), A2 (ibrutinib 420 mg QD + rituximab), A3 (ibrutinib 140 mg BID + rituximab) or Treatment Arm B (physician's choice of lenalidomide + rituximab or bortezomib + rituximab) based on a computer-generated randomization schedule prepared before

the study by or under the supervision of the sponsor.

Randomization will be stratified by sMIPI score (low/intermediate vs high), prior lines of therapy (1 prior line with POD24 [POD within 24 months of diagnosis] vs 1 prior line with POD>24 [POD >24 months after diagnosis] vs >1 prior line), and geographical region (US/EU vs ROW).

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

As this is an open-label study, blinding procedures are not applicable.

6.4. Study Treatment Compliance

The study drugs are to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required delegation documents. Study drugs may not be used for any purpose other than that outlined in this protocol, including other human studies, patients not in any study, animal investigations, or in vitro testing.

Rituximab will be administered as an IV infusion and bortezomib will be administered as an IV injection or SC by qualified study-site personnel. The details of each administration will be recorded in the CRF; date, start and stop time of the infusions, dose, and volume infused. The site pharmacist will maintain a log of all rituximab/bortezomib vials prepared for infusion and/or SC administration. Drug supplies for each participant will be inventoried and accounted for throughout the study.

Ibrutinib and lenalidomide will be self-administered orally by the participants. The investigator or the site pharmacist will maintain a log of all ibrutinib and lenalidomide dispensed and returned. Drug supplies for each participant will be inventoried and accounted for throughout the study. Site personnel are to instruct the participant to bring any unused ibrutinib or lenalidomide to the site at the beginning of each treatment cycle to check dosing compliance. Instructions for proper self-administration and ibrutinib and lenalidomide storage conditions will be provided. Precautions associated with the use of ibrutinib and lenalidomide and prohibited concomitant medications will be reviewed. Site staff will provide additional instruction to reeducate any participant who is not compliant with the ibrutinib and lenalidomide schedule.

Upon termination of the study, or at the request of the sponsor or its designee, the pharmacist must return the study drug to the sponsor or its designee, after all drug supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the sponsor and the site. Instructions regarding accountability for study drug are provided in the SIPPM. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

6.5. Dose Modification

Any dose/dosage adjustment must be overseen by medically qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present), and recorded in the 'Dosage Administration' page of the CRF.

Always follow local labels if dose modification guidelines are more restrictive than the recommended guidelines presented in this protocol.

6.5.1. Ibrutinib

Ibrutinib interruption and/or dose reduction may be required for toxicities related to ibrutinib. Ibrutinib may be held for a maximum of 28 consecutive days. For any hold beyond 28 days, contact medical monitor prior to restarting. The actions described in Table 5 and Table 6 should be taken for the following potentially drug-related toxicities:

- Grade 2 cardiac failure (Table 7 and Table 8).
- ANC <500 cells/µL for more than 7 days. See Section 6.7.1 for instructions regarding the use of growth factor support.
- Platelets <50,000 cells/µL in the presence of clinically significant bleeding.
- Platelets <25,000 cells/µL.
- Grade 3 or greater non-hematological toxicity.

Adverse events that do not meet the criteria above but are persistent and considered by the investigator to be potentially manageable by dose modification, may also be managed per the instructions in Table 5 and Table 6 for non-cardiac events, and Table 7 and Table 8 for cardiac events.

Table 5: Recommended Dose Modifications for Non-cardiac Events for Participants who Started Ibrutinib at 560 mg QD or 420 mg QD

Occurrence	Action
First[a]	Hold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Hold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Third	Hold study drug until recovery to Grade ≤1 or baseline; may restart at 2 dose levels lower from the original dose level
Fourth	Discontinue study drug

[a.] When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg

Table 6: Recommended Dose Modifications for Non-cardiac Events for Participants who Started Ibrutinib at 140 mg BID

Occurrence	Action
First[a]	Hold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second[a]	Hold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Third	Hold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower from the original dose level (ie, 140 mg QD)
Fourth	Discontinue study drug

[a.] When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation.

Table 7: Recommended Dose Modifications for Events of Cardiac Failure or Cardiac Arrhythmias for Participants who Started Ibrutinib at 560 mg QD or 420 mg QD

Event	Toxicity Occurrence	Dose Modification After Recovery
Grade 2 cardiac failure	First	Hold study drug until recover to Grade ≤1 or baseline, may restart at 1 dose level lower from the original dose level
	Second	Hold study drug until recover to Grade ≤1 or baseline, may restart at 2 dose levels lower from the original dose level
	Third	Discontinue ibrutinib
Grade 3 cardiac arrhythmias	First	Hold study drug until recovery to Grade ≤1 or baseline, may restart 1 dose level lower from the original dose level[a]
	Second	Discontinue ibrutinib
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue ibrutinib

[a.] Evaluate the benefit-risk before resuming treatment.

Table 8: Recommended Dose Modifications for Events of Cardiac Failure or Cardiac Arrhythmias for Participants who Started Ibrutinib at 140 mg BID

Event	Toxicity Occurrence	Dose Modification After Recovery
Grade 2 cardiac failure	First	Hold study drug until recover to Grade ≤1 or baseline, may restart at 1 dose level lower (140 mg QD)
	Second	Discontinue ibrutinib
Grade 3 cardiac arrhythmias	First	Hold study drug until recover to Grade ≤1 or baseline, may restart 1 dose level lower (140 mg QD)[a]
	Second	Discontinue ibrutinib
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue ibrutinib

[a.] Evaluate the benefit-risk before resuming treatment.

Hepatic impairment

Ibrutinib is metabolized in the liver, and therefore, subjects with chronic hepatic impairment (Child-Pugh class A, B, or C) should have the dose of ibrutinib modified as indicated below. Refer to Section 10.8 (Appendix 8) for Child-Pugh classification.

For participants with mild liver impairment (Child-Pugh class A), the recommended dose of ibrutinib is 140 mg QD (Arm A1 and A2) or 70 mg QD (Arm A3). Patients with Child-Pugh class B or C at screening are not eligible to participate in this study. For participants who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose of ibrutinib is 70 mg QD for Arm A1 and A2. Participants in Arm A3 who develop moderate liver impairment (Child-Pugh class B) while on study should interrupt treatment until recovery to Child-Pugh class A or better and may restart with 70 mg QD. It is not recommended to administer ibrutinib to participants with severe hepatic impairment (Child-Pugh class C). Therefore, for participants who develop severe hepatic impairment (Child-Pugh Class C), ibrutinib must be held until resolved to moderate impairment (Child-Pugh Class B) or better. Monitor participants for signs of ibrutinib toxicity and follow dose modification guidance as needed.

For dose modifications of ibrutinib related to concomitant medication use, see Section 6.7.2. For dose modifications of ibrutinib during the perioperative period for surgeries or invasive procedures, see Section 6.7.4. Doses of rituximab, lenalidomide, and bortezomib should be reduced or held in accordance with the dose modification guidelines in their respective product labels as described below.

6.5.2. Rituximab

There will be no dose reductions for rituximab. Rituximab should be held for any Grade 4 toxicity or for any rituximab-related, unmanageable Grade 3 AEs. Rituximab should be held until the AE returns to baseline or resolves completely. Detailed dosing and medical management instructions for infusion reactions and cytokine release syndrome are provided in the product label (RUXIENCE® USPI 2021; RUXIENCE® SmPC 2022).

6.5.3. Lenalidomide

Treatment is continued, modified or discontinued based upon clinical and laboratory findings (see lenalidomide product label [Lenalidomide Accord SmPC 2022; or refer to local label if locally sourced]).

Hematologic toxicities

Dose modification guidelines as summarized in Table 9 are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia considered to be related to lenalidomide.

Table 9: Lenalidomide Dose Modifications for Hematologic Toxicities

Platelet Counts **Thrombocytopenia During Treatment in MCL**	
When Platelets	**Recommended Course**
<50,000/µL	Interrupt lenalidomide and follow complete blood counts weekly
≥50,000/µL	Resume lenalidomide at 5 mg less than the previous dose. If previous dose was 5 mg, reduce dose to 2.5 mg daily or 5 mg every other day[a] Do not dose below 2.5 mg daily or 5 mg every other day[a]
Absolute Neutrophil count (ANC) **Neutropenia during treatment in MCL**	
When Neutrophils	**Recommended Course**
<1000/µL for at least 7 days OR <1,000/µL with an associated temperature at least 38.5 degrees Celsius OR <500/µL	Interrupt lenalidomide treatment and follow complete blood counts weekly
≥1,000/µL	Resume lenalidomide at 5 mg less than the previous dose If previous dose was 5 mg, reduce dose to 2.5 mg daily or 5 mg every other day[a] Do not dose below 2.5 mg daily or 5 mg every other day[a]

ANC absolute neutrophil counts; MCL mantle cell lymphoma

[a] If using locally sourced lenalidomide, refer to local label for lowest dose level allowed.

Renal impairment

Adjustments to the dose of lenalidomide is recommended to provide appropriate drug exposure in participants with moderate or severe renal impairment, because lenalidomide is primarily excreted unchanged by the kidney. Lenalidomide dose adjustment should be instituted for participants with a CrCl <60 mL/min. The recommended doses for participants with MCL and renal impairment are shown in Table 10. To be enrolled in the study, participants must have CrCl ≥30 mL/min. If during treatment a participant's renal status changes, the dose should be adjusted. In the event of a dose adjustment, lenalidomide doses may be re-escalated at the investigator's discretion.

Table 10: Recommended Lenalidomide Dosage for Participants with Renal Impairment

Moderate renal impairment-CrCl 30 to <60 mL/min	Lenalidomide should be given at a dose of 10 mg daily
Severe renal impairment-CrCl <30 mL/min (not requiring dialysis)	Lenalidomide should be given at a dose of 15 mg every 48 hours
End-stage renal disease- CrCl <30 mL/min (requiring dialysis)	Lenalidomide should be given at a dose of 5 mg daily. Administer dose after dialysis

CrCl creatinine clearance

Tumor lysis syndrome

Lenalidomide may be continued (maintain dose) in patients with laboratory tumor lysis syndrome (TLS) or Grade 1 clinical TLS, or at the physician's discretion, reduce dose by 1 level and continue

lenalidomide. Vigorous IV hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy may be needed to reduce hyperuricemia. Hospitalization of the participant will be at physician's discretion.

In participants with Grade 2 to 4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinically indicated. Vigorous IV hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalization will be at physician's discretion. When the TLS resolves to Grade 0, restart lenalidomide at next lower dose per physician's discretion.

Tumor flare reaction

At the physician's discretion, lenalidomide may be continued in patients with Grade 1 or 2 tumor flare reaction (TFR) without interruption or modification. At the physician's discretion, therapy with non-steroidal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In participants with Grade 3 or 4 TFR, withhold treatment with lenalidomide and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤Grade 1, restart lenalidomide treatment at the same dose level for the rest of the cycle. Participants may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

Skin rash

Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms is suspected, and should not be resumed following discontinuation from these reactions.

Other toxicities

For other Grade 3 or 4 toxicities judged to be related to lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade ≤2.

For full safety information for lenalidomide, refer to the product label (Lenalidomide Accord SmPC 2022 [or local label if locally sourced]).

6.5.4. Bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib. Bortezomib treatment should be withheld at the onset of any Grade 3 nonhematological or Grade 4 hematological toxicities excluding neuropathy as described in the product label (VELCADE USPI 2021; VELCADE® SmPC 2021). Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose) (Table 11). If the toxicity is not resolved, or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Table 11: Bortezomib Dose Modifications

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Bortezomib 1.3 mg/m^2	Bortezomib 1.0 mg/m^2	Bortezomib 0.7 mg/m^2	Discontinue bortezomib

Neuropathic pain and/or peripheral neuropathy

Starting bortezomib SC may be considered for participants with pre-existing or at high risk of peripheral neuropathy. Participants with pre-existing severe neuropathy should be treated with bortezomib only after careful risk-benefit assessment. Participants experiencing new or worsening peripheral neuropathy during bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for participants who experience bortezomib-related neuropathic pain and/or peripheral neuropathy see Table 12.

Table 12: Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory of Motor Neuropathy

Severity of Neuropathy	Posology Modification
Grade 1 (asymptomatic: loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms: limiting instrumental ADL[a]	Reduce bortezomib to 1.0 mg/m^2 OR Change bortezomib treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[b]	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue bortezomib

ADL Activities of Daily Living

a. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.

b. Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

Hematologic toxicities

Dose modification guidelines for hematologic toxicities are shown in Table 13.

Table 13: Bortezomib Dose Modifications for Hematologic Toxicities

Toxicity	Posology Modification or Delay
Hematological toxicity	
≥Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count <10,000/µL	Bortezomib therapy should be withheld for up to 2 weeks until the participant has an ANC ≥750 cells/µL and a platelet count ≥25,000 cells/µL • If , after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued • If toxicity resolves, ie, participant has an ANC ≥750 cells/µL and a platelet count ≥25,000 cells/µL, bortezomib may be reinitiated at a dose reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2
If platelet counts <25,000 cells/µL, or ANC <750 cells/µL on a bortezomib dosing day (other than Day 1 of each cycle	Bortezomib therapy should be withheld
Grade ≥3 non-hematological toxicities considered to be related to bortezomib	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, bortezomib may be reinitiated at a dose reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 12

ANC absolute neutrophil count

Hepatic impairment

Participants with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Participants with moderate or severe hepatic impairment should be started on bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered. The recommended modification guidelines for participants with hepatic impairment is shown in Table 14.

Table 14: Recommended Starting Dose Modification for Bortezomib in Participants with Hepatic Impairment

Grade of Hepatic Impairment[a]	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	≤1 x ULN	More than ULN	None
	More than 1 x to 1.5 x ULN	Any	None
Moderate	More than 1.5 x to 3 x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation of 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on participant tolerability
Severe	More than 3 x ULN	Any	

AST aspartate aminotransferase; NCI National Cancer Institute; SGOT serum glutamic oxaloacetic transaminase; ULN upper limit of normal

[a] Based on NCI Organ Dysfunction Working Group classifications for categorizing hepatic impairment (mild, moderate, severe).

For full safety information for bortezomib refer to the product label (VELCADE USPI 2021; VELCADE® SmPC 2021).

6.6. Treatment of Overdose

There is no specific experience in the management of ibrutinib overdose in participants. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1,680 mg of ibrutinib.

There is no specific experience in the management of lenalidomide overdose in participants. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg, and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritis, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.

There is no known specific antidote for bortezomib overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia.

Limited experience with doses higher than the approved dose of IV rituximab formulation is available from clinical trials in humans. The highest IV dose of rituximab tested in humans to date is 5,000 mg (2,250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.

The sponsor does not recommend a specific intervention for an overdose. In the event of an overdose, the investigator or treating physician should provide supportive care and:

- Contact the sponsor's medical monitor immediately.

- Evaluate the participant to determine, in consultation with the sponsor medical monitor, whether study drug(s) should be interrupted, or the dose reduced.
- Closely monitor the participant for AEs, SAEs, and laboratory abnormalities until study treatment(s) can no longer be detected systemically (at least 7 days).
- Obtain a plasma sample for PK analysis if requested by the sponsor's medical monitor (determined on a case-by-case basis).
- Document the prescribed dose, the quantity of the excess dose as well as the duration of the overdosing in the CRF. Refer to Section 10.3.4, Special Reporting Situations [Appendix 3]).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on the clinical evaluation of the participant.

6.7. Concomitant Therapy

Pre-study therapies up to 30 days before first dose of study treatment must be recorded at screening. Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study treatment to 30 days after the last dose of study treatment or until the start of subsequent anti-lymphoma therapy, whichever is first. All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

As of implementation of Protocol Amendment 1, only concomitant therapy related to SAE, or ≥Grade 3, up to 30 days after the last dose of study treatment or until the start of subsequent anti-lymphoma therapy, whichever occurs first, needs to be recorded.

For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, only SAEs and pregnancy information will be documented in the participant file/source notes and reported to the sponsor's Global Medical Safety database only until the end of the study (see Section 4.4) and as described in Section 10.13 (Appendix 13).

6.7.1. Permitted Concomitant Medications

The participant should receive full supportive care during study participation (including fluids and electrolyte replacement, and antibiotics when appropriate). Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines or per the institution's guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy. Use of anti-microbial prophylaxis (eg, *pneumocyctis jirovecii* pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent), and vaccines, per the institution's guidelines is strongly recommended, especially in participants who are at increased risk for opportunistic infections. It is strongly recommended that anti-viral prophylaxis recommendations are followed per rituximab and bortezomib product labels.

Localized, hormonal, or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies may be considered with approval from the medical monitor. Short courses (<14 days) of corticosteroids for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, and infusion -related reactions) or treatment for autoimmune cytopenias are permitted at doses not exceeding 100 mg/day of prednisone or equivalent. Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for >14 days is prohibited unless reviewed and approved by the sponsor's medical monitor. Corticosteroids are permitted as premedication for administration of rituximab or for the management of hypersensitivity as per institutional policy.

6.7.2. Medications to be Used with Caution

6.7.2.1. CYP3A Inhibitors/Inducers

Concomitant use With Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and strong CYP3A inhibitors should be avoided. The recommended ibrutinib dose modifications for coadministration with CYP3A inhibitors is provided below (Table 15). Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction. Always follow local labels if dose modification guidelines are more restrictive than the recommended guidelines presented in this protocol.

If antivirals for the treatment of COVID-19 that are strong CYP3A inhibitors (eg. Paxlovid) are indicated, ibrutinib should be interrupted for the duration of the treatment (see Section 10.10 [Appendix 10] and Table 15).

Table 15: Recommended Ibrutinib Dose Modifications for Co-administration with CYP3A Inhibitors

Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]
• Mild CYP3A inhibitors	No dose adjustment required
• Moderate CYP3A inhibitors	280 mg QD is for participants who started on 560 mg QD or 420 mg QD; 140 mg QD for participants who started on 140 mg BID
• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg QD for participants who started on 560 mg QD or 420 mg QD 70 mg QD where available for participants who started on 140 mg BID or interrupt ibrutinib for the duration of the inhibitor use
• Other strong CYP3A inhibitors • Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg QD for the duration of the inhibitor use

BID twice daily; CYP cytochrome P450; IV intravenous, QD once daily

[a] Monitor for adverse reactions to ibrutinib and interrupt or modify dose as recommended (see Section 6.5.1).

[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed release tablets 300 mg once daily).

Concomitant use With Bortezomib

- Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib which may decrease bortezomib efficacy. Avoid coadministration with strong CYP3A4 inducers.
- Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib which may increase the risk of bortezomib toxicities. Participants should be monitored for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

Concomitant use With Lenalidomide

- Lenalidomide undergoes limited metabolism and does not inhibit or induce CYP3A4 isoenzymes.

Examples of inhibitors, inducers, and substrates can be found at:

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

and

http://medicine.iupui.edu/clinpharm/ddis/main-table/

6.7.2.2. Antiplatelet Agents and Anticoagulants

Concomitant use With ibrutinib

- The concomitant use of warfarin or a vitamin K antagonist with ibrutinib should be avoided. Supplements such as fish oil and vitamin E preparations should be avoided. Participants requiring the initiation of anticoagulation therapy during the course of the study should have treatment with ibrutinib held, the sponsor's medical monitor should be contacted, and ibrutinib should not be restarted until the patient is clinically stable and the re-initiation of ibrutinib is approved by the sponsor's medical monitor. Participants should be observed closely for signs and symptoms of bleeding.

6.7.2.3. Drugs That may Have their Plasma Concentration Altered by Ibrutinib

- In vitro studies indicated that ibrutinib is a mild P-glycoprotein (P-gp) inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There are no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.

6.7.2.4. Drugs That may Increase the Risk for Thrombosis

Concomitant use With Lenalidomide

- Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after taking a benefit-risk assessment in participants receiving lenalidomide.

6.7.3. Prohibited Concomitant Medications

- Any non-study protocol-related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy other than the outlined in the study regimen.
- Administration of live attenuated and replication-competent viral vector vaccines are prohibited and must only be administered ≥30 days after the last dose of ibrutinib (see Section 10.10 [Appendix 10]). Recommendations for COVID-19 vaccination are included in Section 10.10 (Appendix 10).
- Corticosteroids for the treatment of the underlying malignancy are prohibited. See Section 6.7.1 for further details on concomitant use of ibrutinib and corticosteroids.
- Participants may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), blood oranges, pomelos, tangelos, and star fruit within the 3-day period prior to the first ibrutinib and bortezomib administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.7.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

The following guidance should be applied during the perioperative period for participants who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the participant is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study intervention
- The participant experiences overt disease progression or relapse
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

If a participant discontinues study treatment before the onset of disease progression, end of treatment and post-treatment assessments should be obtained and follow-up of scheduled assessments should be continued. Refer to Section 8.2.1 for instructions regarding the post-treatment efficacy assessments and Section 8.2.2.1 for instructions on the progressive disease form. The reason(s) a participant discontinues treatment will be recorded on the eCRF. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Loss to follow-up
- Withdrawal of consent
- The sponsor discontinues the study (see Section 10.2.12 [Appendix 2])

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion), as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 10.2.4: Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls,

emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts, and any contact with the appropriate family members, if applicable, should be documented in the participant's medical records.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Study Procedures

8.1.1. Overview

For the Phase 2 part of the study, there are 2 phases: a Screening Phase, and a Treatment Phase. The frequency and timing of assessments and procedures to be performed during the study are outlined in the Schedule of Activities (Table 1) and further discussed within this section. Assessments/procedures should be completed on the day indicated; if this is not possible because of a weekend, holiday, or emergency, the assessment/procedure should be completed within 48 hours of the scheduled day. During treatment, the clinical laboratory samples can be taken on the day of or day prior to dosing, provided the results are available before any study treatment is administered.

Repeat or unscheduled samples may be taken for safety reasons. Serum or urine pregnancy tests should be performed for females of childbearing potential, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during their participation in the study. For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, Section 10.13 (Appendix 13) describes the study procedures to be followed.

8.1.2. Screening Phase

The Screening Phase will be up to 30 days prior to randomization. All participants (or their legally acceptable representative) must sign an ICF prior to the conduct of any study-related procedures. During this phase, eligibility criteria will be reviewed by the investigator and a complete clinical evaluation will be performed as specified in the Schedule of Activities. Screening procedures will be performed up to 30 days before randomization.

Eligibility criteria will be reviewed and a complete clinical and disease history evaluation will be performed. Laboratory tests noted in the inclusion criteria must be performed within 14 days prior to randomization and the results within the limits specified in the inclusion criteria.

Testing may be repeated for this purpose. The last result obtained prior to start of study treatment will be used to determine eligibility. Assessments performed as part of the participant's routine clinical evaluation and not specifically for this study can be used after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within 30 days prior to randomization.

8.1.3. Open-label Treatment Phase

The Treatment Phase will extend from randomization until study treatment discontinuation. Participants should start study drug treatment within 72 hours after randomization. The last measurements taken before randomization will be defined as the baseline values. These values should be consistent with the values in the inclusion and exclusion criteria in order for the participant to receive treatment. The sponsor recommends disease evaluations be performed per standard of care. Response assessments will be performed preferably using Lugano Criteria (Cheson 2014). Participants with confirmed progressive disease will discontinue study treatment. Safety data collection will be limited to SAEs, Grade ≥3 AEs, and AEs leading to treatment discontinuation; and concomitant medications related to SAEs and Grade ≥3 AEs, and will be recorded in the eCRF. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

8.2. Efficacy

8.2.1. Efficacy Assessments

Eligible participants must have at least 1 measurable site of disease by radiological assessment (Cheson 2014). Efficacy evaluations will be conducted as specified in the Schedule of Activities (Table 1) and may include the following: CT scans, MRI, PET using [18F]-FDG, bone marrow aspirate and biopsy, endoscopy, physical examination, per standard of care.

To determine whether continued study treatment is warranted, investigators should monitor and assess participants for response to treatment or disease progression per standard of care preferably using the Lugano Criteria (Cheson 2014). Disease status and date of disease progression should be documented. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

8.2.2. Efficacy Criteria

8.2.2.1. Assessment of Disease Response and Progressive Disease

Assessment of disease response and progressive disease will be based on Lugano criteria (Cheson 2014). For all participants with disease progression by the investigator, the investigator should notify the sponsor medical monitor promptly when becoming aware of the progression including after database closure.

8.2.2.2. Definition of Measurable and Assessable Disease

Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be clearly measurable in 2 perpendicular dimensions, as determined by imaging evaluation. Eligible participants must have at least 1 measurable site of disease ≥2 cm in the long axis. All other measurable sites of disease must be greater than 1.5 cm in the long axis for lymph nodes and greater than 1.0 cm in the long axis for extranodal lesions.

Up to 6 measurable sites of disease will be followed as target lesions for each participant. Measurable sites of disease should be chosen such that they are from as disparate regions of the body as possible and are representative of the participant's overall disease burden. If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm, at least 1 lymph node mass from each region should always be included.

Sites of disease that are not measurable as defined above will be considered assessable. Assessable disease includes any site of disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. Assessable sites of disease will be followed as non-target lesions. In addition, if more than 6 sites of disease are measurable, these other sites of measurable disease may be included as non-target lesions.

8.2.2.3. Response Categories

The response categories being used to assess efficacy are based on the Lugano Criteria (Cheson 2014) as further described in Table 16.

Table 16: Response Assessments Based on the Lugano Criteria

Response category	Criteria
Complete Response	For an overall response of CR, all the following criteria must be met: • Score of 1, 2, or 3 on the 5-point scale, with or without a residual mass, on the most recent post-baseline PET scan • Any organ enlargement must have regressed to normal • If the bone marrow biopsy or aspirate was positive by morphology or immunohistochemistry at baseline, a repeat bone marrow biopsy must be negative by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry • If an endoscopy was positive by morphology or immunohistochemistry at baseline, a repeat endoscopy must be negative by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry • No new lesions
Partial Response	An overall response of PR requires the following: If a post-baseline PET scan is available at the current or a previous timepoint: • A score of 4 or 5 with reduced uptake compared with baseline, with or without residual masses of any size, on the most recent post-baseline PET scan. Residual uptake in the bone marrow higher than uptake in normal marrow but reduced compared with baseline (including diffuse uptake compatible with reactive changes from chemotherapy) is allowed. • No criteria for progressive disease are met If no post-baseline PET scan is available: • A ≥50% decrease in the sum of the product of the diameters of up to 6 target measurable nodes and extranodal sites – When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value – When no longer visible, 0 x 0 mm – For a node greater than 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation • Nonmeasured lesions are absent/normal or regressed, but no increase • Spleen, if enlarged at baseline, must have regressed by >50% in length beyond

Table 16: Response Assessments Based on the Lugano Criteria	
Response category	**Criteria**
	normal • No new lesions
Stable Disease	An overall response of stable disease is defined as follows: If a post-baseline PET scan is available at the current or a previous timepoint: • A score 4 or 5 with no significant change in FDG uptake from baseline, on the most recent post-baseline PET scan • No criteria for progressive disease are met If no post-baseline PET scan is available: • <50% decrease from baseline in sum of the product of the diameters of up to 6 dominant, measurable nodes and extranodal sites • No criteria for progressive disease are met
Progressive Disease	Progressive disease requires at least 1 of the following: • Progression of 1 or more target nodes or extranodal lesions based on the product of the perpendicular diameters. An individual node/lesion must be abnormal with: – LDi >1.5 cm, and – increased by ≥50% from perpendicular diameters nadir. And – an increase in LDi or SDi from nadir of 0.5 cm for lesions ≤2 cm or 1.0 cm for lesions >2 cm • New or clear progression of preexisting nonmeasured lesions • Regrowth of previously resolved lesions • A new node >1.5 cm in any axis • A new extranodal site >1.0 cm in any axis; if ≤1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • New or recurrent splenomegaly. In the setting of prior splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • Assessable disease of any size unequivocally attributable to lymphoma • New or recurrent bone marrow involvement • PET score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.

Note: For any new nodes or extranodal lesions meeting the size criteria for progressive disease by CT or MRI, a PET or biopsy should be performed when possible, and will not be considered progressive disease if the PET score is ≤3 or if the biopsy is negative for MCL.

8.3. Safety Assessments

All participants who receive treatment will be considered evaluable for toxicity. Safety evaluations should be performed as clinically indicated and can include physical examinations and relevant clinical laboratory tests. Participants should be periodically monitored for atrial fibrillation. ECGs should also be performed at the investigator's discretion, particularly in participants with arrhythmic symptoms (eg, palpitations, lightheadedness, or new onset dyspnea).

Adverse events should be monitored and evaluated by the investigator according to routine practice guidelines. All SAEs occurring during the study must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event. The sponsor will collect SAE data by

the SAE reporting process. SAEs, Safety data collection will be limited to Grade ≥3 AEs, and AEs leading to treatment discontinuation, (irrespective of toxicity grade); and concomitant medications related to SAEs and Grade ≥3 AEs.

For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, only SAEs and pregnancy information will be documented in the participant file/source notes and reported to the sponsor's Global Medical Safety database only until the end of the study (see Section 4.4) and as described in Section 10.13 (Appendix 13). Details on initial pregnancy reporting can be found in Section 8.4.5. The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Schedule of Activities (Table 1).

8.3.1. Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 10.3, Adverse Event Reporting (Appendix 3) and graded according to the NCI CTCAE, Version 5.0.

8.3.2. Clinical Laboratory Tests

All laboratory tests should be performed at the laboratory facilities associated with the investigational site. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any participant at the site. If the participant has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents.

Blood samples to assess the safety of study treatment will be collected. Required laboratory tests must be performed within 48 hours of the scheduled visit. For Day 1, Cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study agent.

A complete blood cell count, including white blood cell count with differential count, platelet count, hemoglobin, and hematocrit should be performed every week for the first 8 weeks of lenalidomide treatment.

The investigator 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. For example, laboratory abnormalities leading to an action regarding any study treatment (dose reduction, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values. Details of the clinical laboratory assessments to be performed

are provided in Section 10.1 (Appendix 1). Repeat or unscheduled blood sampling may be taken for safety reasons or technical issues. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

8.3.3. Vital Signs

Temperature, pulse/heart rate, and blood pressure will be recorded at the timepoints shown in Table 1. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). If an abnormal heart rhythm is suspected, further investigation (ECG and/or Holter monitor) is required per investigator's discretion. Vital signs that are considered to be clinically relevant by the investigator are to be documented as AEs.

8.3.4. Physical Examination

Physical examinations will be performed at the timepoints shown in Table 1. The Screening physical examination will include, at a minimum, participant's weight, height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. A limited symptom-directed physical examination is required at Screening.

8.3.5. Electrocardiograms

Twelve-lead ECGs will be performed for all participants during Screening and at end of treatment. ECGs should also be performed at the investigator's discretion, particularly in participants with arrhythmic symptoms (eg, palpitations, lightheadedness or new onset dyspnea). Abnormalities noted at screening should be included in the medical history.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

8.3.6. ECOG Performance Status

The ECOG performance status scale will be used at Screening to confirm eligibility (Oken 1982). ECOG performance status scale is provided in Section 10.5 (Appendix 5).

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. As of implementation of Protocol Amendment 1, safety data collection will be limited to SAEs, Grade

≥3 AEs, AEs leading to treatment discontinuation; and concomitant medications related to SAEs and Grade ≥3 AEs will be recorded in the eCRF as specified in the protocol (Section 10.3). See Section 6.7 for concomitant medication safety reporting.

Further details on AEs, SAEs, and PQCs can be found in Section 10.3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

All AEs with an onset date after the signing of the ICF and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the CRF.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All SAEs occurring after signature of the ICF up to 30 days after study treatment discontinuation must be reported on AE pages in the CRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified in Section 10.3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting (Appendix 3).

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.4.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. If a participant becomes pregnant during the study, a determination regarding study treatment discontinuation must be made by the investigator in consultation with the sponsor.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required. After the end of eCRF data collection and clinical database closure, pregnancy reporting will continue as described above and in Section 10.13 (Appendix 13).

Lenalidomide

Lenalidomide is a thalidomide analog and is contraindicated for use during pregnancy. Birth defects have been observed in preclinical studies of lenalidomide similar to thalidomide in humans. Because of the embryofetal risk of lenalidomide, investigators should comply, and all participants receiving lenalidomide must adhere to the global lenalidomide pregnancy prevention program or equivalent local lenalidomide pregnancy prevention program applicable in their region. Investigators should comply with the lenalidomide Global PPP or with the respective country/territory-specific Lenalidomide Risk Minimization Program (ie, pregnancy prevention program) as implemented in the post-marketing setting and ensure that all participants adhere to these programs. When no Lenalidomide Risk Minimization Program exists, participants receiving lenalidomide must adhere to the lenalidomide Global PPP. Therefore, strict monitoring for pregnancy must be conducted during Screening and throughout the Treatment Phase, as specified in the Schedule of Activities. If pregnancy occurs, study treatment should be discontinued immediately and the participant should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling. The sponsor will collect information on the outcome of the pregnancy and health of the baby for 1 year after birth or until the outcome of an adverse pregnancy event is known or resolved.

If the centrally supplied generic lenalidomide is approved in a country/territory, the locally approved PPP for the product should be used. If the protocol is more stringent than the local PPP, the pregnancy prevention measures described in the protocol should be followed, but the country/territory-specific regulations implemented for lenalidomide in the post-marketing setting for the product need to be fulfilled. If the centrally supplied lenalidomide is not approved in a country/territory, the global PPP should be used.

8.4.6. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered or reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures than being expected from the underlying disease, the treatment-invoked progression (ie, the treatment-invoked signs/symptoms of such progression) should be reported per the usual reporting requirements.

Death that is attributed by the investigator explicitly to progression of disease should not be considered nor reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures than being expected from the underlying disease, the treatment-invoked death due to progression should be reported per the usual reporting requirements.

Progression of disease and death due to disease progression should be documented on the appropriate CRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure, should be documented on the appropriate CRF forms.

8.5. Pharmacokinetics

Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected (ibrutinib treatment arm only) may be used for further development of the existing population-based PK model. No further blood samples will be collected from participants for PK evaluation upon implementation of protocol Amendment 1.

8.5.1. Evaluations

Plasma samples may be analyzed to determine concentrations of ibrutinib using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor.

8.5.2. Pharmacokinetic Parameters

Population PK analysis of plasma concentration-time data of ibrutinib may be performed using nonlinear mixed-effects modeling (NONMEM), with the aim of providing estimates of PK parameters (eg, oral clearance, apparent clearance [CL/F] and apparent volume of distribution at steady state [V/F]) or metrics of systemic exposure (eg, area under the plasma concentration-time curve within the dosing interval [AUC_{ss}] and C_{trough}). Model-derived plasma concentrations or metrics of exposure parameters (eg, AUC) may be subjected to further analyses to explore PK correlation between exposure and relevant clinical information.

8.6. Pharmacodynamic Evaluations

Upon implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected may be used for BTK and/or Interleukin-2-inducible T-cell kinase (ITK) occupancy (free and total) evaluation. No further blood samples will be collected from participants for PD evaluation upon implementation of protocol Amendment 1.

8.7. Biomarkers

8.7.1. Biomarker Assessments

A portion of the formalin-fixed paraffin-embedded (FFPE) tumor block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments (eg, Ki-67, *TP53*, and other genes). A buccal swab should be submitted with tumor samples. Only 1 set of buccal swab is needed.

8.7.2. Formalin-Fixed Paraffin-Embedded Tumor Tissue and Lymph Node Biopsies

FFPE tumor block or slides from the most recent dated tumor tissue biopsy (archival) or a newly obtained biopsy will be collected at study entry and evaluated for biomarker assessment. A portion of the slides will also be used to confirm eligibility prior to enrollment if the report from the local laboratory is not available prior to randomization or the central laboratory is not able to confirm MCL diagnosis based on the local laboratory report. If central laboratory is not able to confirm diagnosis from the archived tissue sample, a fresh tissue sample is required.

Expression and mutation patterns may be investigated within the FFPE tissue to determine whether characterization of the FFPE sample could predict response or resistance to study treatment in r/r MCL. The FFPE tissue may be subjected to immunohistochemistry, gene expression profiling, and DNA analysis or other similar technologies.

8.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual. Archival tumor tissue and fresh biopsies collected in this study will be sent to a central laboratory designated by the sponsor. General requirements for suitable archival tumor tissue sample can also be found in the laboratory manual. Refer to the Schedule of Activities (Table 1) for the timing and frequency of all sample collections.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Study protocol
- Ibrutinib Investigator's Brochure
- Package inserts for lenalidomide, bortezomib, and rituximab
- Lugano Criteria (Cheson 2014)
- Site investigational product and procedures manual
- Laboratory manual and supplies (for samples and image acquisition)
- IWRS instructions and guidance and supplies
- NCI-CTCAE Version 5.0
- Electronic data capture manual and CRF completion guidelines
- Participant information materials
- Sample ICF
- Participant wallet (study) card
- Imaging Manual

9. STATISTICAL CONSIDERATIONS

Due to the early termination of the study, an IDMC to monitor safety data, and to review efficacy data, is no longer required. Data will be summarized, and descriptive statistics will be presented.

9.1. Safety Analyses

All safety analyses will use data for the safety population. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of study drug administration. The safety parameters to be evaluated are the incidence, intensity, and type of AEs, clinically significant changes in the participant's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs that occur after the first dose of study treatment, through the Treatment Phase, and for 30 days following the last dose of study treatment; any AE that is considered study treatment-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered treatment-related by the investigator. Any new or worsening AE occurring at or after the initial administration of study treatment through the day of last dose plus 30 days, or prior to the start of a subsequent anticancer therapy, whichever is earlier, or any follow-up AE (linked to an existing TEAE) with onset date and time beyond 30 days after the last dose of study treatment but prior to the start of subsequent therapy, or any AE that is considered treatment-related regardless of the start date of the event, is considered to be treatment-emergent. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Parameters with predefined NCI-CTCAE Version 5.0 toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Hematology and serum chemistry laboratory data up to 30 days after last dose or the End of Treatment visit date, or until start of a subsequent anticancer therapy, whichever is later, will be reported in International System of Units (SI).

Summary statistics (mean, standard deviation, median and range) will be calculated for the raw data and for changes from baseline at each timepoint of assessment as well as for the changes from baseline to the last value.

Graphical displays of over-time summaries and shift tables will be presented for the following key laboratory parameters: hemoglobin, white blood cell count, neutrophils, platelets, AST, ALT, total bilirubin, creatinine, alkaline phosphatase, and electrolytes (sodium, potassium, calcium, and phosphate). The same analysis may be applied to other laboratory parameters.

Shift tables will summarize by cycle the number of participants with each baseline NCI CTCAE grade and changes to the maximum NCI CTCAE grade in the cycle (up to 30 days after last dose or the End of Treatment visit date, whichever is later).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed by the local laboratory according to the Schedule of Activities (Table 1):

- Hematology

  -hemoglobin
  -white blood cell count
  -platelet count
  -ANC
  -absolute lymphocyte count

- Coagulation Studies

  aPTT (activate partial thromboplastin time)

  international normalized ratio (INR) and/or prothrombin time

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -uric acid
  -total bilirubin
  -albumin
  -phosphate
  -AST
  -ALT
  -lactic acid dehydrogenase
  -alkaline phosphatase
  -calcium

- Screening for Hepatitis B and C will include the following evaluations: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody. Participants who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Participants who test positive for Hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for Hepatitis C after completion of the treatment for hepatitis.

- Where endemic, screening for active or chronic persistent HEV infection is required**.** Participants who test positive for anti-Hep E antibody must have Hepatitis E RNA by PCR performed (serum or stool) and confirmed as negative prior to randomization.

- Pregnancy test (serum beta-human chorionic gonadotropin [β-hCG] or urine): for female participants of childbearing potential only.

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the CRF or laboratory requisition form. Refer to Section 10.13 (Appendix 13) for further guidance on study procedures after the end of eCRF data collection.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree

on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairperson or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators, where required
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.2.2. Informed Consent Process

Each participant (or their legally acceptable representative) must give consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy. Informed consent may be obtained remotely. Refer to the monitoring guidelines (or other equivalent documents).

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants or their legally acceptable representative the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment

of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or their legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

If the participant is unable to read or write, an impartial witness must be present for the entire informed consent process (which includes reading and explaining all written information) and must personally date and sign the ICF after the oral consent of the participant is obtained.

10.2.3. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or their legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable

steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory DNA, pharmacodynamics, biomarker, PK and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.2.4. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib and co-medications in the protocol, if applicable, to understand B cell NHL and MCL, to understand differential intervention responders, and to develop tests/assays related to ibrutinib and co-medications in the protocol, if applicable and B cell NHL and MCL. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.2.5. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenetic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ibrutinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenetic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.2.6. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.2.7. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires [see Section 10.9, Appendix 9, for the FACT-Lym questionnaire]) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

Refer to Section 10.13 (Appendix 13) for further guidance after the end of eCRF data collection.

10.2.8. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents must be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria, that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF. Refer to Section 10.13 (Appendix 13) for further guidance on source documentation after the end of eCRF data collection.

10.2.9. Monitoring

The sponsor will use a combination of monitoring techniques (eg, central, remote, or on-site monitoring) to monitor this study. The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the CRF with the source

documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site. Refer to Section 10.13 (Appendix 13) for further guidance on monitoring of participants who continue study treatment after the end of eCRF data collection.

10.2.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.2.11. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical

development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.2.12. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

Following implementation of Protocol Amendment 1, the eCRF data collection period will end, and the clinical database will be closed as soon as possible but no later than when the last study participant has completed the first 6 cycles of study treatment, or switched to ibrutinib monotherapy 560 mg QD (unless ibrutinib dose was reduced for toxicity reasons). The sponsor will ensure that participants benefiting from treatment will be able to continue receiving study treatment after the end of eCRF data collection. Refer to Section 10.13 (Appendix 13) for further guidance on data collection and reporting procedures for participants who continue study treatment after the end of the eCRF data collection. The study is considered completed when all participants still receiving study treatment have transitioned to commercial or alternative access to study treatment, have stopped receiving study treatment, or upon a decision by the sponsor to terminate the study, whichever occurs earlier.

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Note: The sponsor collects SAEs, AEs, Grade ≥3 AEs, AEs leading to treatment discontinuation, and concomitant medications related to SAEs and Grade ≥3 AEs, starting with the signing of the ICF (refer to All Adverse Events under Section 10.3.5, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording (Appendix 3). For participants who continue to receive study treatment after the end of the eCRF collection and clinical database closure, only SAEs and pregnancy information will be documented in the participant file/source notes and reported to the sponsor's Global Medical Safety database only until the end of the study (see Section 4.4) and as described in Section 10.13 (Appendix 13).

All SAEs, AEs, Grade ≥3 AEs, AEs leading to treatment discontinuation, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

Note: Events that do not qualify as an AE cannot be reported as an SAE, even if the conditions for seriousness are met. In particular, this is the case for events due to disease progression leading to death, hospitalization, etc.

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or may not result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious. This also includes the situation when treatment -invoked signs and symptoms of disease progression are determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an AE will be determined by whether or not it is listed in the IB. For the nonsponsored investigational medicinal products with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the VELCADE USPI or SmPC (VELCADE® USPI 2021; VELCADE® SmPC 2021), (Lenalidomide Accord SmPC 2022 [or local label if locally sourced]) or the RUXIENCE USPI or SmPC (RUXIENCE® USPI 2021; RUXIENCE® SmPC 2022).

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the Investigator. The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.3.3. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 5.0. Any AEs or SAEs not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard definitions as follows:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.*
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL=activities of daily living
Notes: A semi-colon indicates 'or' within the description of the grade.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.3.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention, lenalidomide, bortezomib, or rituximab
- Suspected abuse/misuse of a sponsor study intervention, lenalidomide, bortezomib, or rituximab
- Accidental or occupational exposure to a sponsor study intervention, lenalidomide, bortezomib, or rituximab
- Any failure of expected pharmacologic action (ie, lack of effect if used according to the local label) of a sponsor study treatment (to be reported as a PQC for marketed products
- Unexpected therapeutic or clinical benefit from use of a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors), lenalidomide, bortezomib, or rituximab
- Exposure to a sponsor study treatment, ibrutinib, lenalidomide, bortezomib, or rituximab from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF. Refer to Section 10.13 (Appendix 13) for further guidance after the end of eCRF data collection.

10.3.5. Procedures

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.
- Expected progression of disease, which is part of the natural course of the disease under study, should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures, than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

For reporting of death that is attributed by the investigator explicitly to progression of disease, see Section 8.4.6.

For reporting signs or symptoms of disease progression, see Section 8.4.6.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.3.6. Other Malignancies

In addition to AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment.

10.3.7. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.3.8. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.4. Appendix 4: Contraceptive Guidance and Lenalidomide Global / Local PPP/REMS Programs

Participants must follow contraceptive measures as outlined in Section 5.1 (Inclusion Criteria) and Section 5.3. Pregnancy information will be collected and reported as noted in Section 8.4.5.

Definitions

Female Participant of Childbearing Potential

A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

- Participant of child-bearing potential (even if they have amenorrhea) must:

  Practice true abstinence; or

  Practice ≥1 highly effective method of contraception. Contraception must begin 4 weeks before initiating study treatment, and continue during the Treatment Phase, during dose interruptions and continuing for at least 4 weeks after the last dose of study treatment. Best practice is for the pregnancy test, prescribing and/or dispensing to take place on the same day.

Female Participant Not of Childbearing Potential

Female participants in the following groups are considered NOT to have child-bearing potential and do not need to undergo pregnancy testing or receive contraceptive advice.

- Age ≥50 years and naturally amenorrhoeic for ≥1 year. Please note amenorrhea following cancer therapy does not rule out child-bearing potential.
- Premature ovarian failure confirmed by a specialist gynecologist.
- Previous bilateral salpingo-oophorectomy or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis

Treating physicians are advised to refer their patient for a gynecological opinion if at all unsure as to whether a woman meets the criteria for being of non-childbearing potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered. Best practice is for the pregnancy test, prescribing and dispensing to take place on the same day. If not established on effective contraception, the patient must be referred to an appropriately trained healthcare professional for contraceptive advice in order that contraception can be initiated.

Contraceptive (birth control) use by male or female participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical

studies. Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

In the event of pregnancy whilst on treatment with Lenalidomide

- **Stop treatment immediately**
- Refer patient to an obstetrician experienced in reproductive toxicity for further evaluation and counselling.
- Notify the study sponsor/Medical Monitor within 24 hours of awareness using the appropriate pregnancy notification form. A determination regarding study treatment discontinuation must be made by the investigator in consultation with the sponsor.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. All adverse events (AEs) must be reported to the sponsor. The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Because of the embryo-fetal risk of lenalidomide, all participants receiving lenalidomide must be enrolled in the lenalidomide PPP/REMS applicable in their region. Investigators should comply with the lenalidomide Global PPP or with the respective country/territory-specific Lenalidomide Risk Minimization Program (ie, PPP), as implemented in the post-marketing setting and ensure that all participants adhere to these programs. When no Lenalidomide Risk Minimization Program exists, participants must adhere to the Global lenalidomide PPP.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the vasectomized partner is the sole sexual partner of the female participant of childbearing potential and the absence of sperm in the vasectomized partner has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)*

USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• 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 treatment. 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.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment. c) Male condom and female condom must not be used together (due to risk of failure with friction).

10.5. Appendix 5: ECOG Performance Status Score

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

Source: Oken 1982

10.6. Appendix 6: Calculating the Simplified MIPI for MCL

For each prognostic factor, 0-3 points are given to each subject and points are summed up to a maximum of 11. Subjects with 0-3 points in sum are classified as low risk, subjects with 4-5 points as intermediate risk, and subjects with 6-11 points as high risk. ECOG performance status is weighted with 2 points if subjects were unable to work or bedridden (ECOG 2-4). LDH is weighted according to the ratio to the ULN (Hoster 2008).

Points	Age, year	ECOG	LDH/ULN	WBC, /uL
0	< 50	0-1	< 0.67	< 6700
1	50-59	-	0.67-0.99	6700-9999
2	60-69	2-4	1.0-1.49	10000-14999
3	≥ 70	-	≥ 1.5	≥ 15000

10.7. Appendix 7: New York Heart Association Classification of Functional Capacity

The following table presents the New York Heart Association Classification of Functional Capacity and Objective Assessment:

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Source: American Heart Association 2017.

10.8. Appendix 8: Child-Pugh Score for Participants With Liver Impairment

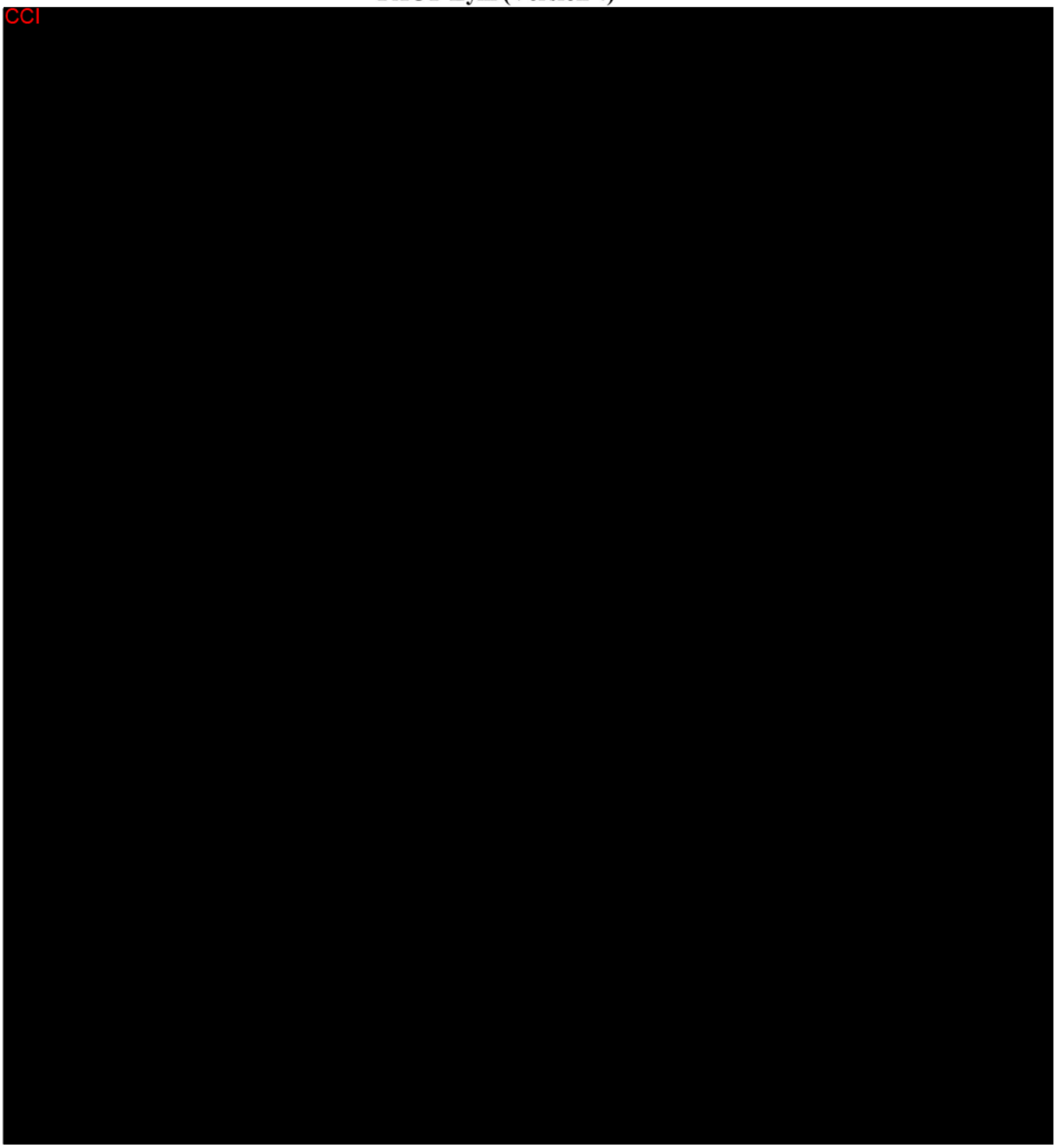
Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Sources:
Child CG, Turcotte JG. Surgery and portal hypertension. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964; 50 64.
Pugh RN, Murray Lyon IM, Dawson L, et al. Transection of the oesophagus for bleeding oesophageal varices. The British Journal of Surgery, 1973; 60:646 649.

10.9. Appendix 9: Sample FACT-Lym (Version 4)

FACT-Lym (Version 4)



English (Universal)
Copyright 1987, 1997

16 November 2007
Page 1 of 3

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

10.10. Appendix 10: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic, scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Testing for COVID-19 should be performed according to local guidance. If a participant has tested positive for COVID-19, the following should be reported in the Electronic Data capture (eDC) tool:

- all cases of COVID-19, regardless of severity or causality (including asymptomatic COVID-19) up to the End of Treatment visit +30 days
- all medications given to prevent (including vaccines) or treat COVID-19 up to the End of Treatment visit + 30 days

If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study treatment, performing. study assessments, and follow-up.

Participant Visits and Assessments

- For participants who are unable to come to the site for Disease Evaluation visits, the visit should be postponed and rescheduled as soon as possible.
- For participants who are unable to come to the site for Cycle visits, contact (eg, telephone, videoconference, or other channels) with the participant should be made in advance, to collect information on the participant's current health status and any new or ongoing AEs and concomitant medications. The remote method that is used for contact with the participant must be allowable per local regulations and fully documented in the participant source record. Home health nursing can be done via site contact with a visiting nurse service independent of the sponsor, if permitted by local regulations. Protocol specified laboratory assessments and physical examinations should be obtained locally, if possible. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. After reviewing all available information, and if the investigator assesses that continued treatment is acceptable, contact the site manager to discuss alternative solutions for the provision of study treatment to participants (see alternatives below). The remote contact with the participant, the local laboratory results, and the sponsor discussion should be documented in the participant source record. Similarly, at a minimum, a comment must be entered in the Comments CRF clearly designating as "COVID19 related" and acknowledging the discussion between the investigator and the sponsor.
- If the participant is not willing or able to go to a local clinic/laboratory, remote contact (eg, telephone, videoconference, or other channels) with the participant is recommended, as well as a thorough review of the participant's medical history, prior labs, and most recent disease evaluation. The remote method chosen must be allowable per local regulations and fully documented in the participant source record. If appropriate, treatment should be interrupted until new laboratory assessments are made. However, if the investigator assesses that continued treatment is acceptable despite the absence of new laboratory tests, contact the site manager to discuss alternative solutions for the provision of study medication to participants (see possible alternatives below). Proper documentation of all discussions and decisions should be made in the participant source record and in the Comments CRF.
- If any change in participant status is identified that may impact the participant's safety, then study treatment should be interrupted until the participant can be assessed. Any changes in study treatment (dose, frequency, interruption) needs to be clearly documented as "COVID-19-related". When conditions improve, travel restrictions are lifted, and the participant is willing and able to come to the clinic, participants should be scheduled for an in-clinic, follow-up visit.
- All deviations from protocol-required assessments should be documented in detail within the participant's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).
- Consenting and re-consenting of participants will be performed as applicable for the measures taken (including also remote consenting by phone or video consultation) and according to local guidance for informed consent applicable during the COVID-19 pandemic

Study Drug Supply

If a participant is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the study monitor and may be considered to ensure continuity of treatment, upon sponsor's approval:

- A caregiver or family member may pick up study drug on behalf of the participant if first discussed and agreed by the participant. The conversation with the participant must be documented in the participant source records. The participant must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain participant privacy. Identification of who will pick up the study drug must be confirmed and documented in the participant source record.
- Investigative site staff may deliver study drug directly to the participant's home. The chain of custody and transit conditions must be clearly documented within the participant source record.
- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the participant and record this in the participant source record for direct-to-patient shipments. It is important to note this process is not allowed by the health authorities in all countries/territories and a specific approval process must be followed with the sponsor before moving forward. If requested by the site, the sponsor will investigate local requirements and confirm health authority requirements for direct-to-patient shipment. If approval is granted by the sponsor, specific procedures including shipment conditions, preferred courier services, and documentation requirements will be communicated by the sponsor to the site.

If a participant is able to come to the site for a Cycle visit but anticipates being unable to come to the next Cycle visit, the investigator may dispense study treatment for the current cycle and an additional cycle, after agreement with the sponsor's medical monitor. Prior to continuing treatment with the additional study treatment, the participant should obtain protocol-specified laboratory assessments and physical examinations locally, if possible, and the investigator should conduct a remote contact as described above. After reviewing all available information, if the investigator assesses that continued treatment is acceptable, the participant may continue treatment using the previously supplied additional study treatment. Proper documentation of all discussions and decisions should be made in the participant source record and in the Comments CRF.

For participants who have reason to believe they have been exposed to COVID-19 but do not yet have a confirmed diagnosis and/or are not showing symptoms of infection:

- The investigator should consider the risk/benefit of continuing ibrutinib based on the individual participant's underlying condition and the potential risks associated with COVID-19.

- If the participant becomes symptomatic at any point, refer to guidance below for participants with symptomatic COVID-19 infection.

For participants who have been diagnosed with COVID-19:

- Investigators should instruct participants to notify them or study site staff immediately if they are diagnosed with COVID-19, even if asymptomatic, so that appropriate treatment measures can be determined.
- The investigator should consider the risk/benefit of continuing ibrutinib based on the nature and status of the participant's underlying condition and the potential risks associated with COVID-19.
- As with all infections, the investigator should follow the protocol guidance which is to interrupt therapy for Grade 3 or higher non-hematologic AE (see Section 6.5) and resume once infection has resolved to Grade 1 or baseline (recovery). Given that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a relatively new pathogen, a more cautious approach would be appropriate, with interruption for confirmed cases of SARS-CoV-2-infection of any grade.
- Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for participants diagnosed with COVID-19 infection.
- If available in the region, antivirals (eg, Paxlovid or other available agents) should be considered early after COVID-19 diagnosis. Anti-viral treatment with Paxlovid is highly recommended within the first 5 days after COVID-19 diagnosis. Participants may remain asymptomatic or have minimal symptoms for a period of time prior to deteriorating. Investigators should make participants aware that these drugs may potentially significantly lower their risk of severe COVID-19. Note: for antivirals that are strong CYP3A inhibitors (eg. Paxlovid), ibrutinib should be interrupted for the duration of the treatment (Table 15).

On-site Monitoring Visits

In case on-site monitoring visits are not possible, as per institution policies, the sponsor's site managers may contact the investigator to arrange remote monitoring visits. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

All of the above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to enable continuity of treatment and to ensure that participant assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to participants, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and risk/benefit assessment in determining if a participant can continue study treatment in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider temporarily interrupting study treatment (for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor) or discontinuing study treatment.

Recommendations for COVID-19 Vaccination for Ibrutinib Recipients

It is recommended that participants receive prophylactic COVID-19 vaccination when locally available, at the discretion of investigator judgement or institutional practice, and in compliance with the study protocol and local labels for the vaccine. Below is general guidance for consideration.

All vaccines authorized for use (eg, full or conditional approval, or emergency use authorization [EUA]), are allowable unless they are live, attenuated, or replicating viral vectors. Live attenuated vaccines must be completed ≥4 weeks prior to randomization or initiated ≥30 days after last dose of ibrutinib. There are no specific timing restrictions for inactivated vaccines, which include vaccines which use alternative technology like mRNA or replication-incompetent viral vectors, per protocol**.** Any vaccination, including COVID-19 vaccinations, must be recorded on the Concomitant Medication page of the CRF.

No data are currently available to suggest that COVID-19 vaccines pose specific or additional safety risk beyond other vaccines for MCL patients undergoing treatment. Theoretically, a diminished immune response may occur in immunocompromised patients, and therefore these patients may have reduced vaccine effectiveness.

Several organizations and journals have published recommendations for COVID-19 vaccine administration in cancer patients, including:

- Garassino MC, et al. The ESMO call to action on COVID-19 vaccinations and patients with cancer: Vaccinate. Monitor. Educate. Ann Oncol. 2021;32:579-581:

  https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic
- Desai A, et al. COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nat Rev Clin Oncol. 2021;18:313-319:

  https://www.nature.com/articles/s41571-021-00487-z
- European Society for Blood and Marrow Transplantation:

  https://www.ebmt.org/covid-19-and-bmt
- American Society for Transplantation and Cellular Therapy (ASTCT):

  https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients
- Centers for Disease Control and Prevention (CDC):

  https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
- National Comprehensive Cancer Network (NCCN):

  https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V2.0.pdf

Based on guidance from the organizations listed above, the following measures should be implemented to minimize participants' risk of severe COVID-19 infection:

- Participants should be reminded that the ongoing pandemic is still putting them at risk of contracting COVID-19. Investigators should ask participants to continue to limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention measures such as proper masking, hand hygiene, social distancing, and avoiding travel and public transportation to the largest extent possible.
- Investigators should discuss with participants the importance of COVID-19 vaccines in the prevention of severe illness, hospitalization, and death from COVID-19. For this reason, it is strongly recommended that all participants receive a full COVID-19 vaccination series prior to enrollment with repeated vaccination throughout study conduct per institutional practice or investigator´s discretion. In addition, if not already vaccinated, caregivers, family, and household contacts should be advised to receive COVID-19 vaccination as well.
- Investigators should consider prophylaxis (eg, Evusheld, if available in the region) to reduce participants' risk of severe/fatal COVID.

10.11. Appendix 11: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine participant eligibility (see Section 5.2) for the study:

Active or chronic hepatitis B:

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the subject ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this protocol.

Eligibility Based on Hepatitis B Virus Test Results

	Hepatitis B test result			
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**Hepatitis B DNA**
Exclude	+	*or* +	*or* +	NA
			+	+
Include				NA
		+	+	NA
		+		NA
			+	

Modified from source: https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf. Accessed 11 March 2020.

10.12. Appendix 12: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$\text{CrCl} \quad \frac{(140 - \text{age [in years]}) \times \text{weight (kg)}}{(72 \times \text{serum creatinine [mg/dL]})} \quad (\times 0.85 \text{ for females})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory and Diagnostic Tests, 2004):

- serum creatinine (micromol/L) divided by 88.4 serum creatinine (mg/dL)

Source: Cockcroft and Gault 1976

10.13. Appendix 13: Continuation of Study Treatment After the End of eCRF Data Collection and Clinical Database Closure to the End of the Study

Protocol Amendment 1 will allow those participants who are benefiting from treatment to continue receiving study treatment after the end of eCRF data collection and clinical database closure until ibrutinib is commercially available, available from another source, or until the end of the study (as defined in Section 10.2.12), whichever occurs earlier. Investigators are expected to transition their participants to commercially available study treatment or alternative access to study treatment as these become available.

The following limited schedule is applicable.

Documentation of assessments performed is required only in the participant file/source notes.

Dosage and Administration

Ibrutinib will be administered according to the regimen established in Protocol Amendment 1.

Dispensing of ibrutinib will occur every 6 months. Participants will be supplied with ibrutinib as per local standard practice. For lenalidomide, refer to the product label (Lenalidomide Accord SmPC 2022); follow local labels for dispensing instructions for other study drugs.

Treatment Period

The sponsor will ensure that participants benefiting from study treatment will be able to continue receiving treatment after the end of eCRF data collection and clinical database closure until study treatment is commercially available or available from another source, or study completion, whichever occurs earlier.

Efficacy Evaluations

Investigators should monitor and assess participants for response to treatment or disease progression according to local institutional practice. If investigators determine that a participant is no longer benefiting from study treatment (ie, disease progression has occurred), the participant should discontinue study treatment and study participation. The assessments and outcome should be entered in the participant file/source notes. Notification of progressive disease to the medical monitor should be via email.

Safety Evaluations

Once the eCRF data collection has ended, any test for safety (ie, hematology laboratory assessments, chemistry laboratory assessments, pregnancy tests, assessment of vital signs) should comply with standard local institution practice. These local test results should be entered in the participant file/source notes, and do not need to be reported to the sponsor unless they meet the SAE criteria.

Safety Reporting

Once the eCRF data collection has ended, serious adverse events that occur while the participant is receiving study treatment and within 30 days after the last dose of study treatment or until the start of a subsequent systemic anti-cancer therapy, if earlier will be reported to the sponsor's global

medical safety database only via the same serious adverse event reporting process used over the course of the study (see Section 10.3.5 [Serious Adverse Events]). Serious adverse events should also be documented in the participant file/source notes.

Pregnancy reporting should continue as described in Section 8.4.5. The pregnancy should be documented in the participant file/source notes.

Treatment Compliance

No study treatment will be recorded in diary cards after the end of eCRF data collection.

Biomarker

No biomarker specimens will be collected after clinical database closure.

Case Report Form Completion

No data will be collected in the eCRF after clinical database closure.

Monitoring

Once the clinical database will be closed after all participants completed Cycle 6, the sponsor will no longer perform on-site monitoring visits, unless specifically required, but will perform remote monitoring visits. At these remote visits, the sponsor will monitor the adequate reporting and follow-up of SAEs and pregnancy information and ensure participants not benefiting from study treatment stopped the study treatment. Documentation around drug receipt/dispensing/return will be discussed with the site staff.

Source Documentation

At a minimum, the type and level of detail of source data collected should be consistent with that commonly recorded at the site as a basis for standard medical care. This should include: participant and study identification, study discussion, documentation of the informed consent process including the date, dates of visits, drug receipt/dispensing/return records, study drug administration information

10.14. Appendix 14: Protocol Amendment History

The protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

11. REFERENCES

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development, LLC

Signature: *electronic signature appended at the end of the protocol* Date: 08-June-2023

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	08-Jun-2023 11:50:59 (GMT)	Document Approval