Janssen Research & Development

Statistical Analysis Plan
Amendment 2

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

Protocol 54179060MCL3004; Phase 2/3 Seamless Design

JNJ-54179060 (ibrutinib)

Status:	Approved
Date:	15 December 2023
Prepared by:	Janssen Research & Development, LLC
Document No.:	EDMS-RIM-651402, 3.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

STATISTICAL ANALYSIS PLAN AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment 2	15 December 2023
Amendment 1	28 September 2023
Original SAP	21 July 2022

Amendment 2 (15 December 2023)

Overall Rationale for the Amendment: Added ibrutinib 560 mg QD monotherapy analysis population, corresponding treatment phase and its safety analysis. See details listed below.

Section Number and Name	Description of Change	Brief Rationale
4. Populations (Analysis Sets) for Analysis	Added Ibrutinib 560 mg QD Monotherapy Population	Analysis for participants switched to monotherapy
5.1 General Considerations	Added Ibrutinib 560 mg QD Monotherapy Phase	Monotherapy treatment phase
5.2 Participant Dispositions	Added participants who completed the study and removed the word "prematurely" from study termination	Participants who died or sponsor terminated study are considered completion of study. Others are considered study termination.
5.3 Safety Analyses	Added ibrutinib 560 mg QD monotherapy population	Safety analysis to be done separately after switching to monotherapy
5.3.1 Extent of Exposure	Added extent of exposure for ibrutinib 560 mg QD monotherapy group	To separate treatment phase
5.3.2 Adverse Events	Added the same rules for defining treatment emergent adverse events for ibrutinib 560 mg QD monotherapy phase and distinguished the boundary timeframe between the last of the randomized treatment and ibrutinib 560 mg QD monotherapy phase. Deleted the sentence of only including serious treatment emergent adverse events (TEAE, TEAEs leading to treatment discontinuation, and Grade ≥ 3 TEAEs. Removed the wording "death" from listing for serious TEAEs	Safety analysis to be done separately after switching to monotherapy Follow original protocol to report all AEs. Redundant: "TEAE with outcome of death" already listed
5.3.2.1 Adverse Events of Interest and Other Safety Observations	Added appropriate wording for additional other safety observations	Considering clinical relevancy
5.3.2.2 Death	Added the same rules for defining death count for ibrutinib 560 mg QD monotherapy phase and distinguished the boundary timeframe between the last of the randomized treatment and ibrutinib 560 mg QD monotherapy phase.	Death is count separately after switching to ibrutinib 560 mg QD monotherapy
5.3.3.1 Clinical Laboratory Tests	Removed creation of shift table.	Lab data is few for shift table.

Amendment 1 (28 September 2023)

Overall Rationale for the Amendment: As a result of the decision for early study discontinuation, the overall reason for the amendment is to be consistent with Protocol Amendment 1.

Section Number and Name	Description of Change	Brief Rationale
Updates made as a result of early study discontinuation		
Throughout SAP	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.
1.1. Objectives	Primary objective revised and text added: **As a result of the early study discontinuation, the primary objective of SAP Amendment 1 is to follow Protocol Amendment 1. 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** Phase 2 primary objective deleted; Phase 3 Primary and Secondary objectives deleted	As a result of the early study discontinuation
1.2 Study Design	Study design deleted. Text added: **"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. 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."**	
2. Statistical Hypotheses	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	
3. Sample Size Determination	Text updated: "**Due to the early discontinuation of the study, this is not applicable**." Phase 2 and 3 sample size determination sections deleted	
4. Populations for Analysis	Removed "/control" from "Pharmacokinetic-	No data is going to be

Section Number and Name	Description of Change	Brief Rationale
	Evaluable Population" definition Phase 2 populations: removed dose selection analysis setting Phase 3 population deleted	collected for control arm post-treatment As a result of the early study discontinuation
5.1 General Considerations	Post-treatment Follow-up Phase deleted	As a result of the early study discontinuation
5.3-5.6 Primary, Secondary, and Tertiary Endpoint(s) Analysis, Multiplicity Adjustment	Due to the early discontinuation of the study, an IDMC to monitor safety data, and to review efficacy data at interim analysis, is no longer required. Sections deleted	Updated as a result of the early study discontinuation and Objective of Protocol Amendment 1
5.3.2 Adverse Events	Text updated: Only **SAEs, Grade ≥3 AEs, and AEs leading to treatment discontinuation**, regardless of seriousness, severity, or presumed relationship to study treatment, will be recorded using medical terminology in the source document and the eCRF	To clarify safety evaluations and safety data collection effective at the moment of implementation of Protocol Amendment 1
5.3.3.4.2 Concomitant Medications 6.5 Appendix 5 Prior and Concomitant Medications	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, will be provided** Concomitant medications of special interest and Subgroup analysis by CYP3A deleted.	
5.4.1 Pharmacokinetics	Text added: **At the moment of implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected (ibrutinib treatment arm only) may be** analyzed for ibrutinib plasma concentration and 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 at the moment of implementation of protocol Amendment 1**	Only blood samples already received before implementation of Protocol Amendment 1 can be used for PK analysis
6.3 Appendix 3 Demographics and Baseline Characteristics	Baseline TP53 and Ki67 deleted.	Potential inconsistent data only collected by investigator

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1. INTRODUCTION

1.1. Objectives

As a result of the early study discontinuation, the primary objective of Statistical Analysis Plan 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.

1.2. Study Design

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. 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.

2. STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be conducted due to early study discontinuation and the primary purpose of Protocol Amendment 1 is continued access of study treatment.

3. SAMPLE SIZE DETERMINATION

Due to the early discontinuation of the study, this is not applicable.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The analysis sets for Phase 2 part are defined below.

- **Intent-to-Treat (ITT) population**: defined as all participants randomized into the Phase 2 part and who will be classified according to the assigned study treatment dosage and control group, regardless of the actual treatment received.
  - Participants in study treatment arm (Arm A1, A2, A3) and the control arm will be used for descriptive analyses, analyses of disposition, demographic, and baseline disease characteristics.
- **Safety Population**: all randomized participants who receive at least one dose of any ibrutinib dosage level or control drug. This population will be used for all safety analyses and analyses of exposure. All participants will be analyzed according to the treatment which they actually received before switching to ibrutinib 560 mg QD monotherapy if occurs. Safety data after switching to ibrutinib 560 mg QD monotherapy will be summarized separately.
- **Ibrutinib 560 mg QD Monotherapy Population:** Participants randomized to the 420 mg QD or 140 mg BID study treatment arms or control arm and later on switched to ibrutinib 560 mg QD monotherapy. Safety data after switching to ibrutinib 560 mg QD monotherapy will be summarized under ibrutinib 560 mg QD monotherapy population.
- **Pharmacokinetic-Evaluable Population**: all randomized participants who have received at least one dose of any ibrutinib dosage level and have at least one pharmacokinetic sample

obtained post-treatment. The pharmacokinetic-evaluable population will be used to summarize pharmacokinetic parameters and metrics of exposure.

5. STATISTICAL ANALYSES

5.1. General Considerations

Phase 2: Visit window will be based on phases and cycles:

- **Screening Phase:** prior to the first dose of study treatment.
- **Treatment Phase:** Between the date of the first dose of study treatment and the date of the last dose of study treatment before switching to ibrutinib 560 mg QD monotherapy, if occurs. As noted above, the term "study treatment" refers to all of the drugs used in the combination treatment.
- **End-of-treatment Phase:** Between the date of the last dose of all study treatment +1 and the date of the last dose of all study treatment (prior to switching to ibrutinib 560 mg QD monotherapy, if occurs) + 30 days. The assessments performed during the 'End of Treatment Visit' will be included in this phase.
- **Ibrutinib 560 mg QD Monotherapy Phase:** Between the date of switching to ibrutinib 560 mg QD monotherapy and the date of the last dose of ibrutinib 560 mg QD monotherapy treatment.

Unless specified otherwise, the baseline value is defined as the last non-missing value collected on or before the administration of the first dose of study medication. For participants who have been randomized but not treated, randomization date will be used as the reference date for baseline value calculation.

Cycle-based descriptive analysis may be performed for safety parameters during the treatment up to date of last dose + 30 days or end of treatment visit, whichever comes later. For the analysis of lab measurement by cycle, mean values within each cycle will be used. For the analysis of lab grade by cycle, worst grade within each cycle will be used.

Assessments will be presented chronologically by cycle day or study day as described below. Unless specified otherwise, date of first dose of study drug (randomization date for participants who have been randomized but not treated) will be used as the reference date for study day calculation.

Day 1 = reference date.

Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.

Cycle Day = assessment date - date of the first dose for the cycle + 1.

5.1.1. Pooling Algorithm for Centers

The data from all investigative sites will be pooled for all analyses.

5.1.2. Imputation of Missing Date

Missing date of initial diagnosis, date of death and start and end dates of AE, prior, concomitant, and subsequent therapies will be imputed according to the following rules:

- General rules
  - If date is completely missing or year is missing, no imputation will be made.
  - If only year is present but month and day are missing, then June 30th will be used.
  - If only day is missing but year and month are available, then the 15th of the month will be used
- Start and end dates rules
  - Start date should be imputed to be before end date;
  - If end date is not missing (i.e., not imputed) and is before the imputed start date, then end date will be used and imputed start date won't be used;
  - If end month and year are not missing and are before the imputed start month and year, then end month and year will be used and imputed start month and year won't be used;
  - If imputed end date is before start date, then start date will be used and imputed end date won't be used.

However, the above imputation will be modified by the following rules sequentially:

- For death: if the imputed date is before the last date that the participant is known to be alive, the latter date + 1 day will be used.
- If any imputed date is after date of death, then date of death will be used.
- For initial diagnosis and prior therapies: if imputed date is on or after the randomization date, then randomization date - 1 will be used.
- For subsequent therapies: if imputed date is before date of treatment discontinuation, then the latter will be used.
- For AE and concomitant medications: *The imputed start date* will be adjusted sequentially using the following steps:
  - If it is in the same month and year but before the first dose date, then the first dose date will be used, or if it is in the same month and year but after the last dose date + 30 days, then the last dose date + 30 days will be used.
  - If it is in the same month and year but after the 1st subsequent systemic therapy start date, then the latter will be used.

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Participants randomized
- Participants who received study treatment
- Participants who completed the study
- Participants who discontinued study treatment
- Reasons for discontinuation of study treatment
- Participants who terminated the study
- Reasons for termination of study

Listings of participants will be provided for the following categories:

- Participants who discontinued study treatment
- Participants who completed or terminated the study

5.3. Safety Analyses

Unless otherwise specified, all safety analyses will be conducted on the safety analysis set based on actual treatment received. However, safety data after switching to ibrutinib 560 mg QD monotherapy will be summarized based on ibrutinib 560 mg QD monotherapy population separately.

The baseline value for safety analysis is defined as the value collected at the time closest to and prior to the start of study medication.

For all continuous safety variables, descriptive statistics by treatment group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment group using frequency counts and percentages.

Frequencies of ECOG scores at baseline will be reported.

5.3.1. Extent of Exposure

Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for total number of cycles, treatment duration, and dosing information for both study drugs.

The number and percentage of participants with dose reduction and dose interruption will be summarized. Dose reduction and dose interruption due to adverse events will be summarized for both treatment groups and ibrutinib 560 mg QD monotherapy group. In addition, dose reduction and dose interruption due to concomitant use of CYP3A4/5 inhibitor will be summarized for ibrutinib treatment.

5.3.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent Adverse Events (TEAEs) will be summarized and are defined as 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 subsequent anticancer therapy, whichever is earlier, or the 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.

If the event occurs on the day of the initial administration of study treatment, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, or time of administration is missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date, or later than 30 days after last study drug administration. If any event is considered drug-related regardless of the start date of the event; or the event that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator, then this event will be assumed to be treatment-emergent. The same rules apply to adverse events that occurred during ibrutinib 560mg QD monotherapy phase. For participants who switch to ibrutinib 560 mg QD monotherapy, treatment-emergent adverse events that occur on or after the first day of ibrutinib monotherapy will be included in summaries for the monotherapy phase except for events considered related to rituximab or lenalidomide, which will be included in summaries for the randomized treatment phase.

TEAEs will be summarized by SOC and PTs. Unless otherwise specified, at each level (e.g., system organ class and/or preferred term) of participant summarization in reporting the incidence of the AE, a participant is counted once if one or more events were recorded. For summarizing new onset events, all event records of the same preferred term from the same participant are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date the same as or 1 day after the end date of the previous record and any features of the adverse event (i.e., toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as one event. A Grade 5 event will be linked to previous event of the same preferred term if the onset date of the Grade 5 record is the same or one day after the end date of previous record. Tables will be sorted by descending frequency in incidence (from the highest to lowest incidence). For each TEAE the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized.

In addition to the summary tables, listings will be provided for participants who:

- Had Serious TEAEs
- Had TEAE with outcome of death
- Had TEAE of Grade≥3
- Had TEAEs leading to treatment discontinuation

5.3.2.1. Adverse Events of Interest and Other Safety Observations

There is no AEs of Interest (AEIs) for this study.

Other Safety Observations

Other malignancies are defined as new malignant tumors including solid tumors, skin malignancies and hematologic malignancies and are to be reported by investigators for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS. Summary tables for other malignancies occurring during the entire study and during the treatment-emergent reporting period by PT will be provided, categorized by 3 groups: non-melanoma skin cancer, melanoma skin cancer, and non-skin cancer.

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query (SMQ) excluding laboratory terms and be tabulated. Major hemorrhage is a subset of hemorrhagic events which are grade ≥ 3 or serious or belong to central nervous system (CNS) hemorrhage/hematoma.

Additional other safety observations will be summarized by treatment group if considered clinically relevant based on review of the data after the final database lock.

5.3.2.2. Death

Deaths will be displayed by actual treatment received. For the ibrutinib 560 mg QD monotherapy phase, if death occurred on or after first day of monotherapy, it will be included in monotherapy only unless death due to AE that is related to rituximab or lenalidomide, which will be included in summaries for the randomized treatment phase. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death

A listing of participants who died will be provided.

5.3.3. Additional Safety Assessments

5.3.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Laboratory data of hematology and serum chemistry up to 30 days after the last dose or the start of subsequent anticancer therapy, whichever is earlier, will be reported in SI units. Applicable laboratory results will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Note, toxicity grading for creatinine increase will be based on the NCI CTCAE v5.0 criteria but limited only to the part based on the upper limit of normal (ULN); the other part that is based on the change from baseline will not be used for toxicity grading. Toxicity grading for all other laboratory parameters will be based on the NCI CTCAE v5.0 criteria as is. Generic normal ranges will be applied whenever reference ranges are not available. The following laboratory tests will be analyzed:

- Hematology: hemoglobin, WBC, ANC, absolute lymphocyte counts (ALC), and platelets
- Chemistry: sodium, creatinine, CrCL, AST, alanine aminotransferase (ALT), alkaline phosphatase (AST), LDH, total bilirubin, albumin, potassium, calcium, phosphate, uric acid

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each time point of assessment as well as for the changes from baseline to the last value. Worst toxicity for hematology and clinical chemistry during treatment will also be summarized.

5.3.3.1.1. Creatinine Clearance

CrCL is calculated using the Cockcroft-Gault formula:

$$CrCl_{(est)} = \frac{(140 - age[yr])(lean\ body\ wt[kg])}{(72)(serum\ creatinine[mg/dL])} \times 0.85 (if\ female)$$

for males, the factor is 1 instead of 0.85.

A shift summary from baseline to worst on-treatment toxicity grade for CrCL will be provided.

5.3.3.2. Vital Signs

Continuous vital sign parameters including blood pressure, heart rate, temperature, height, weight, and body surface area will be summarized and/or listed.

5.3.3.3. Electrocardiogram

Not applicable.

5.3.3.4. Other Safety Parameters

5.3.3.4.1. ECOG

Frequencies of ECOG scores at baseline will be reported.

5.3.3.4.2. Concomitant Medications

Use of concomitant therapies other than antineoplastic agents or other systemic therapies for MCL between treatment start and the end of the study will be provided by ATC class and drug generic term. Multiple medication usage by a participant will be counted only once for that therapeutic class. Concomitant medications are defined as medications that were taken at any time on treatment (i.e., from the date of the first dose of study treatment through 30 days after the last dose of study treatment).

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, will be provided.

5.4. Other Analyses

5.4.1. Pharmacokinetics

At the moment of implementation of Protocol Amendment 1, venous blood samples for ibrutinib analysis already collected (ibrutinib treatment arm only) may be analyzed for ibrutinib plasma concentration and 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 at the moment of implementation of protocol Amendment 1.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) may be used to summarize ibrutinib plasma concentrations at each sampling time point. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time.

Ibrutinib plasma concentrations below the LLOQ will be imputed as zero in the summary statistics.

All participants and samples excluded from the analysis will be clearly documented.

If sufficient data are available, then population PK analysis using plasma concentration time data of ibrutinib may be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan, and the results of the analysis will be presented in a separate report.

5.4.2. Immunogenicity

5.4.2.1. Immunogenicity Analysis

Not applicable.

5.4.2.2. Other Immunogenicity Analyses

Not applicable.

5.4.3. Pharmacodynamics

At the moment of 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 at the moment of implementation of protocol Amendment 1.

5.4.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

5.4.5. Biomarkers

Refer to Section 5.4.3 for BTK and/or ITK occupancy.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
CRF	case report form
eCRF	electronic case report form
IDMC	independent Data Monitoring Committee
IQ	interquartile
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
PopPK ER	Population pharmacokinetic and exposure-response
r/r	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQs	standardised MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not applicable.

6.3. Appendix 3 Demographics and Baseline Characteristics

All demographic and baseline characteristics will be summarized for the ITT population using descriptive statistics. Participant enrollment will be summarized by region, site, and country. The following demographics and baseline disease characteristics information will be summarized for ITT participants:

- Demographics: Age (continuous and grouped as ≥50 vs. <50 or ≥65 vs. <65), sex (male or female), race, region, ethnicity
- Baseline disease characteristics: Time from the initial diagnosis to randomization, Serum β2 microglobulin, stage of MCL at study entry (II or III or IV), type of histology, simplified sMIPI score (low risk / intermediate risk vs. high risk), Eastern Cooperative Oncology Group (ECOG) performance status score (0 vs. 1), endoscopy, hepatic impairment, renal function impairment, and histology group (grouped as Blastoid/Pleomorphic vs. Non-Blastoid/Non-Pleomorphic vs Unknown)
- Extent of disease: Number of lesions, extranodal disease, tumor bulk (grouped as <5 cm, ≥5 cm), tumor burden, baseline lymphoma symptoms, bone marrow involvement, and baseline lactic acid dehydrogenase (LDH)
- Hematology: hemoglobin (Hgb), white blood cell count (WBC), absolute neutrophil count (ANC), and platelets
- Chemistry: sodium, potassium, creatinine clearance (CrCL), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactic acid dehydrogenase (LDH), total bilirubin, albumin, calcium, magnesium, phosphate, and uric acid
- Vital signs: height (cm), weight (kg), temperature (C°), systolic blood pressure, diastolic blood pressure, heart rate, body surface area (BSA)
- Coagulation: Prothrombin international normalized ratio (INR), and activated partial thromboplastin time (aPTT)

6.4. Appendix 4 Protocol Deviations

Participants with major protocol deviations will be listed by treatment group. Protocol deviations will be based on clinical review primarily on the following aspects (but not limited to): (1) eligibility criteria, (2) treatment compliance, (3) participant safety (4) efficacy assessment deviation. Protocol deviations will be closely monitored during the execution of the study, and the final set of protocol deviation criteria will be finalized before database lock. The major protocol deviations will be reviewed and/or classified based on clinical review of the protocol deviations.

Major protocol deviations due to COVID-19 will be summarized and listed by treatment group. Listing of minor protocol deviations due to COVID-19 will also be provided. Summary table and listing of study assessment compliance will be presented.

6.5. Appendix 5 Prior and Concomitant Medications

Use of concomitant therapies other than antineoplastic agents or other systemic therapies for MCL between treatment start and the end of the study will be provided by ATC class and drug generic term. Multiple medication usage by a participant will be counted only once for that therapeutic class. Concomitant medications are defined as medications that were taken at any time on treatment (i.e., from the date of the first dose of study treatment through 30 days after the last dose of study treatment).

6.6. Appendix 6 Medical History

Medical history will be summarized by body system class and preferred term.

6.7. Appendix 7 Treatment Compliance

Compliance will be summarized descriptively for each study arm. Compliance to randomized treatment versus actual treatment will be presented in the participant disposition summary table specified in Section 5.2.

Treatment compliance will be assessed using Section 5.3.1.

6.8. Appendix 8 Adverse Events of Interest

Refer to Section 5.3.2.1.

6.9. Appendix 9 Medications of Special Interest

Refer to Section 5.3.3.4.2 for details.

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms;* *>5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *treatment initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *treatment initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; treatment indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic;* *120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs; urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

6.11. Appendix 11 Estimands Examples

Not applicable.

7. REFERENCES

Not applicable.