

Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3 Randomized Study Comparing JNJ-79635322 versus Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma after 1 to 3 Prior Lines of Therapy, Including an Anti-CD38 Antibody and Lenalidomide

TRIllogy-5

Short Title

A Phase 3 Randomized Study Comparing JNJ-79635322 versus Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma

**Protocol 79635322MMY3002; Phase 3
Version: Amendment 1**

JNJ-79635322

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 1	19 February 2026
Original Protocol	13 February 2026

Amendment 1 (19 February 2026)

Overall Rationale for the Amendment: To correct errors noted in the original protocol.

The changes made to the clinical protocol 79635322MMY3002 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale	
5.1 Inclusion Criteria	Inclusion criterion 6 table updated for hematology laboratory values.	To correct an error.	
	Hematology		
	Hemoglobin		≥7.5 g/dL, without use of transfusion or growth factors within 7 days prior to laboratory testing
	Platelets <u>ANC</u>		≥0.75×10 ³ /μL (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF prior to the laboratory testing)
	ANC <u>Platelets</u>		≥50×10 ³ /μL, without use of transfusion or growth factors within 7 days prior to laboratory testing
5.2 Exclusion Criteria	Exclusion criteria numbering updated.	To remove duplication of number 10 from the exclusion criteria and to renumber the criteria correctly.	
6.1.3 Required Safety Monitoring	Cross reference updated from Section 10.9 to Section 10.10.	To crosslink to the correct appendix.	
8.2.2 Bone Marrow Examination	Superscript ‘d’ removed from the table.	To align with footnotes beneath the table.	
Throughout the protocol	Minor grammatical, formatting, or typographical errors changes were made.	To address minor errors.	

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
β-hCG	beta-human chorionic gonadotropin
BCMA	B-cell maturation antigen
BiPAP	bilevel positive airway pressure
BMPC	bone marrow plasma cells
BSA	bovine serum albumin
C	cycle
CAR-T	chimeric antigen receptor therapy
CBC	complete blood count
CCO	clinical cut-off
CD	cluster of differentiation
CI	confidence interval
CKD-epi	chronic kidney disease-epidemiology collaboration
CNS	central nervous system
CPAP	continuous positive airway pressure
CR	complete response
CRF	case report form (paper or electronic as appropriate for this study)
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDy	Cycle x Day y
DE	disease evaluation
DKd	daratumumab, carfilzomib, and dexamethasone
DPd	daratumumab, pomalidomide, and dexamethasone
DWI	diffusion-weighted imaging
EC90	concentration associated with the 90% maximal drug effect
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
eloPD	elotuzumab plus pomalidomide and dexamethasone
EMD	extramedullary disease
EORTC IL46	European Organization for Research and Treatment of Cancer Item List 46
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EoT	end of treatment
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
EQ-VAS	EuroQol Visual Analogue Scale
ERE	event re-estimation
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor

GPRC5D	G protein-coupled receptor class C group 5 member D
HA	Health Authority
HAART	highly active antiretroviral therapy
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
ICP	intracranial pressure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	immunofluorescence
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	International Staging System
IV	intravenous(ly)
IVIg	intravenous immunoglobulins
IWRS	interactive web response system
Kd	carfilzomib, dexamethasone
LTE	long-term extension
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MM	multiple myeloma
M-protein	monoclonal paraprotein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MySIIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
NAbs	neutralizing antibody
NCI	National Cancer Institute
NDMM	newly diagnosed multiple myeloma
NGF	next-generation flow cytometry
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PaCO ₂	partial pressure of carbon dioxide in arterial blood
PC	plasma cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival

PFS2	progression-free survival 2
PGI-S	Patient Global Impression Scale
PK	pharmacokinetic(s)
POCBP	participants of childbearing potential
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
PVd	pomalidomide, bortezomib, dexamethasone
QIg	quantitative immunoglobulin
QxH	every x hours
QxM	every x months
QxW	every x weeks
RFS	recurrence-free survival
RP2D	recommended Phase 2 dose
RRMM	relapsed or refractory multiple myeloma
RT-PCR	reverse transcription-polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAC	Safety Assessment Committee
SAE	serious adverse event
SAP	statistical analysis plan
sARR	systemic administration-related reaction
SARS CoV-2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous(ly)
SCr	standardized serum creatinine
sCR	stringent complete response
sFLC	serum free light chain
SIFE	serum immunofixation electrophoresis
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	standard of care
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	serum M-protein quantification by electrophoresis
SPM	secondary primary malignancies
SpO ₂	oxygen saturation
SST	subsequent systemic antimyeloma therapy
STP	soft tissue plasmacytoma
SUD	step-up dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TTNT	time to next line of therapy
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine M-protein quantification by electrophoresis
US	United States
USPI	United States Prescribing Information
VGPR	very good partial response

Definitions of Terms

PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study) [Reports directly from the participant without interpretation by clinician or anyone else]
sARR	Systemic reaction related to study treatment administration regardless of the route of administration

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3 Randomized Study Comparing JNJ-79635322 versus Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma after 1 to 3 Prior Lines of Therapy, Including an Anti-CD38 Antibody and Lenalidomide

IND: 161020

EU TRIAL NUMBER: 2025-523815-12

A Phase 3 Randomized Study Comparing JNJ-79635322 versus Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma.

JNJ-79635322 (BCMAxGPRC5DxCD3) is a novel IgG1 trispecific antibody targeting the T-cell receptor (CD3 portion) with 1 binding arm and 2 plasma cell target antigen binding domains (BCMA and GPRC5D).

ETHICAL CONSIDERATIONS

Treatments with T-cell redirecting agents targeting CD3 and BCMA or GPRC5D have shown good results. Participants randomized to Arm B will receive BCMA teclistamab, as a representative SoC for participants with RRMM. A favorable benefit-risk profile for teclistamab has been demonstrated in patients with RRMM and it is authorized in multiple countries worldwide for patients treated with more than 3 lines of therapy. Teclistamab is currently being studied in participants exposed to 1 to 3 prior lines in the ongoing Phase 3 MajesTEC-9 study. The available data demonstrate a positive benefit-risk profile (superior PFS and OS compared with SoC PVD and Kd) for patients with RRMM exposed to 1 to 3 prior lines, including patients who are refractory to anti-CD38 and lenalidomide. In contrast to teclistamab, JNJ-79635322 provides a differentiated approach where both BCMA and GPRC5D are targeted simultaneously with 1 T-cell engager and is hypothesized to demonstrate an enhanced tumor eradicating effect, which would constitute a significant benefit to patients with RRMM.

The study accounts for potential risks associated with study drug exposure by administration of SUDs of JNJ-79635322 as well as accompanying pre- and postdose medications. Other mitigation measures aim to reduce potential risks in conjunction with robust dose modification guidelines and management strategies for hematologic and non-hematologic AEs, including extensive protocol guidance on the monitoring, prophylaxis, and management of infections. An IDMC will review the safety data during the study.

Taking into account the measures taken to minimize risks to participants of this study, the potential risks identified in association with JNJ-79635322 are justified by the hypothesized benefits that may be afforded to participants with RRMM. Therefore, the overall benefit-risk profile in this population is hypothesized to be favorable.

OBJECTIVES

The primary objective is to compare the efficacy of JNJ-79635322 versus teclistamab, based on dual primary endpoints of CR or better and PFS, in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide. Secondary objectives evaluate additional efficacy and overall safety. HRQoL will also be assessed.

OVERALL DESIGN

Key aspects of the trial design are summarized in the table below.

Study Model:	Parallel group, 2 arms, Phase 3
Control:	Teclistamab
Study Treatment Assignment Method:	Randomization (1:1)
Blinding:	Open-label
Population Type and Age:	Adult ≥ 18 years
Population Diagnosis or Condition:	RRMM and received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide
Site Distribution:	Multicenter
Number of Participants	Approximately 700

The end of study or study completion is considered to be the last visit for the last participant in the study.

An IDMC will be commissioned for this study.

The LTE Phase will begin after the sponsor has notified the site.

TREATMENT GROUPS AND DURATION

Participants randomized to Arm A will receive JNJ-79635322 for a finite duration of 36 months. The treatment will begin with a 5 mg SC SUD of JNJ-79635322 two to 8 days before C1D1 and then a 100 mg SC treatment dose on Day 1 of each 28-day cycle for the first 6 cycles, then 100 mg Q8W after Cycle 6 for a total treatment duration of up to 36 months, or until PD or intolerable toxicity (whichever is earlier).

Participants randomized to Arm B will receive teclistamab until PD or intolerable toxicity. The treatment will begin with SUDs of 0.06 mg/kg SC on C1D1 and 0.3 mg/kg SC on C1D3 before the first treatment dose. The first treatment dose of 1.5 mg/kg SC will be given on C1D5 and will then be administered weekly through Cycle 2, 3 mg/kg SC Q2W during Cycles 3 to 6, and 3 mg/kg SC Q4W for Cycle 7 and beyond. Participants may change to Q4W dosing if confirmed VGPR or better prior to Cycle 7 per investigator discretion.

EVALUATIONS

Efficacy assessments will be based on IMWG response criteria. HRQoL, symptoms, functioning, and tolerability will be captured using PRO measures. Blood samples will be collected to characterize the PK and immunogenicity of JNJ-79635322.

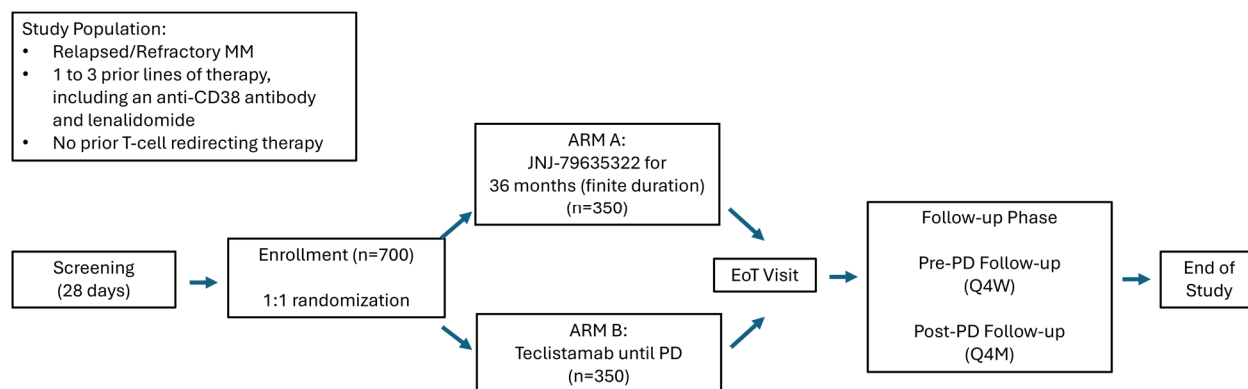
The safety of study treatment will be assessed by AE monitoring, clinical laboratory tests, vital sign measurements, physical examination findings, and ECOG performance status score. The severity of AEs will be assessed using NCI-CTCAE Version 6.0, except for grading of CRS and ICANS, which will be assessed based on ASTCT guidelines. Concomitant medication usage will be recorded.

STATISTICAL METHODS

The primary hypothesis is to demonstrate the superiority of JNJ-79635322 over teclistamab, for at least one of the dual primary endpoints of PFS or CR or better. The sample size of approximately 700 participants is based on an assumption that JNJ-79635322 will reduce the risk of PD or death by 38% (ie, HR=0.62) compared to teclistamab. Based on a log-rank test with one-sided alpha of 0.02, for an HR of 0.62, a total of 198 PFS events are needed to achieve a cumulative power of approximately 90%.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities

1.3.1. Screening

Table 1: Schedule of Activities for Screening

Screening (≤28 days before randomization, unless noted otherwise)	
Study Procedure	Notes
Screening/Administrative	
Eligibility criteria	Reconfirm before the start of study treatment (see Section 5).
ICF, demographics, medical history, myeloma characteristics (including prior therapy and procedures)	
Physical examination (including height and weight), neurologic examination, and ECOG	
Vital signs (including SpO ₂)	
12-lead ECG	
Laboratory Assessments (Local Laboratory)	
CBC with differential, chemistry, and coagulation	Hepatic and hematologic laboratory assessments during the screening period and within 1 day of the start of study treatment (see Section 5 and Section 10.1).
HIV assessment	If known history of HIV, local HIV testing by PCR and CD4 count. Retesting is not required if performed as part of SoC within 3 months prior to randomization. See Section 8.3.5.
HBV and HCV screening	See Section 8.3.5. Retesting is not required if performed as part of SoC within 3 months prior to randomization.
Serum or urine β-hCG	For POCBP.

Table 1: Schedule of Activities for Screening

Screening (≤ 28 days before randomization, unless noted otherwise)	
Study Procedure	Notes
Disease Evaluations (Serum and Urine Testing by Central Laboratory)	
Serum β -2-microglobulin and albumin, Qig	See Section 8.2.1.
SPEP/SIFE and sFLC	See Section 8.2.1.
24-hour urine for UPEP/UIFE	A 24-hour urine collection started as part of SoC the day before the ICF is signed can be used if the sample is sent to the central laboratory after the ICF is signed.
Bone marrow aspirate (or core biopsy)	See Section 8.2.2 Table 18.
Imaging assessment of bone lesions and STPs (para-skeletal and extramedullary)	If performed within 42 days before randomization, it does not have to be repeated. Functional imaging is recommended. See Section 8.2.3.
Ongoing Review	
AEs (including SPM) and concomitant medications (including transfusions and therapeutic procedures)	Continuous from the time of ICF signing.
Randomization	
Randomization through IWRS if eligible (as determined by sponsor)	Eligible participants must be randomized within 3 days of sponsor approval for randomization and must receive the first dose of study medication ≤ 7 days after date of randomization.

1.3.2. Treatment Arm A (JNJ-79635322)

Table 2: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm A (JNJ-79635322)

Phase	Treatment Phase (up to 36 months)		EoT	Follow-up		Notes
Cycle	SUD	C1+ (28 d cycles)		Pre-PD	Post-PD	
Day	2 to 8 d before C1D1	1 (±3 d) ^a		30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	
Safety Assessments ^c						
Physical examination (symptom-directed), ECOG, vital signs (including SpO ₂), weight	X	X	X			See Section 6.1.3 for temperature monitoring instructions in outpatient setting.
Neurologic examination (including ICE tool)	X	When neurologic AE or ICANS is suspected and daily until resolution				See Section 8.3.8.
Clinical Laboratory Assessments (Local Testing) ^c						
CBC with differential and chemistry	X	X	X			Up to 1 day before dosing for C1D1 and up to 3 days before dosing for other cycles. The laboratory values must meet Section 5.1 criteria prior to the first SUD. See Section 10.1.
Coagulation	As clinically indicated during potential CRS/CRS events					
HBV/HCV PCR		At C1D1 (±7 days) and then Q12W (±4 weeks) during Treatment Phase and as clinically indicated		3 and 6 months (±4 weeks) after last dose		Only for participants with history of HBV/HCV infection or HCV antibody positivity. See Section 8.3.5.3.
HIV PCR and CD4 count		At C1D1 (±7 days) and then Q12W (±4 weeks) during Treatment Phase and as clinically indicated		3 and 6 months (±4 weeks) after last dose		Only for participants with history of HIV antibody positivity. See Section 8.3.6.
Serum or urine β-hCG (POCBP)	X	X	X			≤1 day before dose. See Sections 8.3.7 and 8.5.
Study Treatment Administration (JNJ-79635322)						
Pre/post-treatment medications	X	C1D1				See Section 6.1.1 (Table 7) and Section 6.1.2 (Table 9).
JNJ-79635322	X	C1-6: Q4W, then Q8W after C6 (even cycles: C8, C10, C12, etc.) up to 36 months				See Table 5. See Section 6.1 for dosing details.

Table 2: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm A (JNJ-79635322)

Phase	Treatment Phase (up to 36 months)		EoT	Follow-up		Notes
Cycle	SUD	C1+ (28 d cycles)		Pre-PD	Post-PD	
Day	2 to 8 d before C1D1	1 (±3 d) ^a		30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	
Efficacy Assessments (Serum and Urine Testing Q4W [±7 days] by Central Laboratory) ^c						
QIg ^d	X	X (except C1D1)		X		See Section 8.2.1.
SPEP/SIFE and sFLC ^d	X	X (except C1D1)		X		SIFE at every DE and UIFE on every collected 24-hour urine sample at DE for participants with sFLC only measurable disease and only at time of suspected CR or sCR for participants with measurable disease in serum or urine M-spike. See Section 8.2.1.
24H urine for UPEP/UIFE ^d	X	X (except C1D1)		X		
Bone marrow aspirate	For DE, MRD, and molecular markers. Refer to Table 18 for collection time points.					See Section 8.2.2.
Imaging assessment of bone lesions and STPs	For participants without baseline STP: • Within ±3 months of a confirmed CR/sCR (to determine MRD status by imaging). • To document or confirm PD on bone lesions (new or worsening) or STPs (new).					See Section 8.2.3.
	For participants with baseline STPs: • 3 months (±14 days) after the start of therapy. • Repeat imaging Q3M to Q6M from previous imaging scan until CR is confirmed. • Thereafter, as clinically indicated to document or confirm PD on bone lesions (new or worsening) or STP (new or worsening).					

Table 2: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm A (JNJ-79635322)

Phase	Treatment Phase (up to 36 months)		EoT	Follow-up		Notes
Cycle	SUD	C1+ (28 d cycles)		Pre-PD	Post-PD	
Day	2 to 8 d before C1D1	1 (±3 d) ^a		30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	
Patient-reported Outcomes ^c , MRU, and Symptomatic Worsening Assessment						
MySIm-Q, EORTC QLQ-C30, EQ-5D-5L, PGI-S, EORTC IL46	X	PROs should be collected as follows: - On Day 1 of C1 to C6 - Then on D1 of every other cycle starting on C8D1 up to C24D1 - Then on D1 of every 4 cycles after C24 (C28D1, C32D1, etc.); even for participants who completed treatment) - At EoT			PROs completed in the order shown in SoA. While participants are receiving study drug, PROs should be administered on Day 1 of each dosing cycle or within 7 days prior to Day 1. In the event of PD or treatment discontinuation, PROs should still be continued to be completed per schedule. See Section 8.2.4.	
MRU	Continuously from the first day of study treatment until PD or 30 days after last dose of study treatment or start of subsequent therapy, whichever is later.					
Symptomatic worsening of MM	First occurrence of a significant worsening or onset of MM-associated symptoms will be documented from randomization until end of study.				See Section 8.2.5.	
Pharmacokinetics ^c and Immunogenicity Assessments						
Serum samples (up to 8 hours pre-dose)	X	C2, C4, C6, C8. Q6 cycles after C8 (C14, C20, etc.)	X	8 weeks after EoT	See Section 8.6 and Section 8.10.	
Ongoing Participant Review						
AEs and concomitant medications	Continuous from signing of the ICF until 30 days after last dose (if unrelated to study treatment) or until start of subsequent therapy (if earlier). Continue to report any AEs/SAEs related to study treatment until the end of study.				Concomitant medications includes transfusions and therapeutic procedures. See Section 8.4.	
SPMs	Continuous until end of study.					
SST and survival					X	

^a Window does not apply for C1D1.^b In the Pre-PD Follow-up Phase, DEs should continue at Q4W intervals from the previous efficacy assessment until C12 if participant has achieved CR, then Q8W until PD occurs. If the participant has not achieved CR at C12, then DEs must continue Q4W until CR is achieved, followed by Q8W thereafter. In the Post-PD Follow-up Phase, required assessments should be performed at Q4M intervals from the date of confirmed PD.^c Assessments scheduled on dosing days should be done predosing (unless specified otherwise).^d In the event of treatment/cycle delays, during the Q8W dosing phase of JNJ-79635322, or after treatment discontinuation and before PD, DEs should continue to occur Q4W (± 7 days) from the last DE.

1.3.3. Treatment Arm B (Teclistamab)

Table 3: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm B (Teclistamab)

Phase	Treatment Phase (28-day cycle)											Follow-up Phase		Notes
Cycle	Cycle 1					Cycle 2		Cycle 3-6 ^a		Cycle 7+	EoT	Pre-PD	Post-PD	
Day	1	3 (+2d)	5 (+4d)	12 (+4d)	19 (+4d)	1 (±3d)	8, 15, 22 (±2d)	1 (±3d)	15 (±3d)	1 (±3d)	30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	Q4M (±14 d) ^b	
Safety Assessments ^c														
Physical examination (symptom-directed), ECOG, vital signs (including SpO ₂), weight	X	X	X			X		X		X	X			See Section 6.1.3 for temperature monitoring instructions in outpatient setting.
Neurologic examination (including ICE tool)	X	When neurologic AE or ICANS is suspected and daily until resolution												See Section 8.3.8.
Clinical Laboratory Assessments (Local Testing) ^c														
CBC with differential	X	X	X			X		X		X	X			May be performed within 3 days before dosing. See Section 8.3.4 and Section 10.1.
Chemistry	X	X	X			X		X		X				
Coagulation	As clinically indicated during potential CRS/CRS events													
HBV/HCV PCR	X							C4D1 and D1 of every 12 weeks (±4 weeks) thereafter and as clinically indicated			3 and 6 months (±4 weeks) after last dose		If history of HBV/HCV infection or HCV antibody positivity. See Section 8.3.5.3.	
HIV PCR and CD4 count	X							C4D1 and D1 of every 12 weeks (±4 weeks) thereafter and as clinically indicated			3 and 6 months (±4 weeks) after last dose		If history of HIV antibody positivity. See Section 8.3.6.	
Serum or urine β-hCG (POCBP)	X					X		X		X	X			≤1 day before dose. See Sections 8.3.7 and 8.5.

Table 3: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm B (Teclistamab)

Phase	Treatment Phase (28-day cycle)											Follow-up Phase		Notes
Cycle	Cycle 1					Cycle 2		Cycle 3-6 ^a		Cycle 7+	EoT	Pre-PD	Post-PD	
Day	1	3 (+2d)	5 (+4d)	12 (+4d)	19 (+4d)	1 (±3d)	8, 15, 22 (±2d)	1 (±3d)	15 (±3d)	1 (±3d)	30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	Q4M (±14 d) ^b	
Study Treatment Administration (Teclistamab)														
Pretreatment medications	X	X	X											Up to approximately 3 hours prior to teclistamab. See Section 6.1.1 (Table 8).
Teclistamab Step-up Dose	X	X												There must be ≥2 days between SUDs. First treatment dose must be administered ≥2 days after SUD 2. SUDs and treatment doses must be delayed until CRS and/or ICANS associated with prior doses have fully resolved. See Section 6.1 for dosing details.
Teclistamab Treatment Dose			X	X	X	X	X	X	X	X				There must be ≥5 days between weekly treatment doses (1.5 mg/kg) and ≥12 days between Q2W treatment doses (3 mg/kg). See Section 6.1 for dosing details
Efficacy Assessments (Serum and Urine Testing Q4W [±7 days] by Central Laboratory) ^c														
QIg	X					X		X		X		X		See Section 8.2.1.
SPEP/SIFE and sFLC	X					X		X		X		X		SIFE at every DE and UIFE on every collected 24-hour urine sample for DE for participants with sFLC only measurable disease and only at time of suspected CR or sCR for participants with measurable disease in serum or urine M-spike. See Section 8.2.1.
24-hour urine for UPEP/UIFE	X					X		X		X		X		See Section 8.2.2.
Bone marrow aspirate	For DE, MRD, and molecular markers. Refer to Table 18 for collection time points.													See Section 8.2.2.

Table 3: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm B (Teclistamab)

Phase	Treatment Phase (28-day cycle)											Follow-up Phase		Notes
Cycle	Cycle 1					Cycle 2		Cycle 3-6 ^a		Cycle 7+	EoT	Pre-PD	Post-PD	
Day	1	3 (+2d)	5 (+4d)	12 (+4d)	19 (+4d)	1 (±3d)	8, 15, 22 (±2d)	1 (±3d)	15 (±3d)	1 (±3d)	30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	Q4M (±14 d) ^b	
Imaging assessment of bone lesions and STPs	For participants without baseline STPs: - Within ±3 months of a confirmed CR/sCR (to determine MRD status by imaging). - To document or confirm PD on bone lesions (new or worsening) or plasmacytomas (new).													See Section 8.2.3
	For participants with baseline STPs: 3 months (±14 days) after the start of therapy. - Repeat imaging Q3M to Q6M from previous imaging scan until CR is confirmed. - Thereafter, as clinically indicated to document or confirm PD on bone lesions (new or worsening) or plasmacytomas (new or worsening).													
Patient Reported Outcomes (PRO) ^c , MRU, and Symptomatic Worsening Assessment														
MySIIm-Q, EORTC QLQ-C30, EQ-5D-5L, PGI-S, EORTC IL46	PROs should be collected as follows - First SUD (C1D1) and first treatment dose (C1D5) - On Day 1 of Cycles 2 to 6 - Then on Day 1 of every other cycle starting on C8D1 up to C24D1 - On Day 1 of every 4 cycles after C24 (C28D1, C32D1, etc); even for participants who completed treatment - At EoT													PROs completed in the order shown in the SoA. While participants are receiving study drug, PROs should be administered on Day 1 of each dosing cycle or within 7 days prior to Day 1. In the event of PD or discontinuation, PROs should still be completed per schedule. See Section 8.2.4 .
MRU	Continuously from the first day of study treatment until PD or 30 days after last dose of study treatment or start of subsequent therapy, whichever is later.													
Symptomatic worsening of MM	First occurrence of a significant worsening or onset of MM-associated symptoms will be documented from randomization until end of study.													See Section 8.2.5 .

Table 3: Schedule of Activities for Treatment Phase, End of Treatment, and Follow-up Phase - Arm B (Teclistamab)

Phase	Treatment Phase (28-day cycle)											Follow-up Phase		Notes
Cycle	Cycle 1					Cycle 2		Cycle 3-6 ^a		Cycle 7+	EoT	Pre-PD	Post-PD	
Day	1	3 (+2d)	5 (+4d)	12 (+4d)	19 (+4d)	1 (±3d)	8, 15, 22 (±2d)	1 (±3d)	15 (±3d)	1 (±3d)	30 d (+7 d) after last dose or before SST	Q4W (±7 d) ^b	Q4M (±14 d) ^b	
Ongoing Participant Review														
AEs and concomitant medications	Continuous from signing of the ICF until 30 days after last dose (if unrelated to study treatment) or until the start of subsequent therapy (if earlier). Continue to report any AEs/SAEs related to study treatment until the end of study.												Concomitant medications includes transfusions and therapeutic procedures. See Section 6.9 and Section 8.4.	
SPMs	Continuous until end of study.													
SST and survival													X	

^a Participants may change to Q4W dosing when in confirmed VGPR or better prior to C7 per investigator discretion. The D15 visit is not required in this case.

^b In the Pre-PD Follow-up Phase, DEs should continue at Q4W intervals from the previous efficacy assessment until C12 if participant has achieved CR, then Q8W until PD occurs. If the participant has not achieved CR at C12, then DEs must continue Q4W until CR is achieved, followed by Q8W thereafter. In the Post-PD Follow-up Phase, required assessments should be performed at Q4M intervals from the date of confirmed PD.

^c Assessments scheduled on dosing days should be done predosing (unless specified otherwise).

2. INTRODUCTION

JNJ-79635322 (BCMAxGPRC5DxCD3) is a novel IgG1 trispecific antibody targeting the T-cell receptor (CD3 portion) with 1 binding arm and 2 plasma cell target antigen binding domains (BCMA and GPRC5D). The mechanism of action of JNJ-79635322 is to act as a bridge between cancer cells and cytotoxic T lymphocytes, resulting in T-cell activation and lysis of cancer cells. This study will evaluate JNJ-79635322 in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide.

For the most comprehensive nonclinical and clinical information regarding JNJ-79635322 and teclistamab, refer to the latest version of the IBs.

The term “study treatment” used throughout the protocol refers to JNJ-79635322 and teclistamab, as defined in Section 6.1.

The term “sponsor” used throughout this document refers to the entities listed on the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

Therapeutic options for MM have substantially improved over time and include a variety of combinations using IMiDs, proteasome inhibitors, and anti-CD38 monoclonal antibodies with or without stem cell transplant as the mainstay of treatment for both NDMM and RRMM. Although new methods for redirecting and re-engineering T cells have revolutionized the treatment paradigm by harnessing the vast potential of the immune system in patients with MM, the disease inevitably relapses and remains incurable. With each subsequent relapse, treatment options become more limited due to drug exposure from previous regimens. While attrition rates have improved over time with better therapies, up to 20% of patients may not receive a third line of therapy due to toxicities, death, or PD, highlighting the need to move effective therapies into earlier lines of treatment ([Rodriguez-Lobato 2025](#)). Thus, there is an unmet need for novel safe and efficacious therapies for patients with RRMM that can be provided in early relapse, particularly for patients who have been previously exposed to the currently available treatment options.

It is hypothesized that the use of JNJ-79635322, through concurrent T-cell-mediated cytotoxicity to both BCMA and GPRC5D positive myeloma cells, will offer a significant benefit to patients with RRMM by achieving deep and durable responses ([de Larrea 2020](#)). It is also hypothesized that T cell engagement through CD3 and dual targeting might lead to decreased on-target off-tumor side effects by improving the tumor selectivity ([van de Donk 2023](#); [Ellerman 2019](#)).

2.2. Background

Clinical Study 79635322MMY1001

The safety and preliminary efficacy of JNJ-79635322 in participants with RRMM are evaluated in the ongoing Phase 1 study 79635322MMY1001. Treatment doses of 50 mg Q4W, 100 mg Q4W, 200 mg Q4W induction, followed by 100 mg Q4W, and 300 mg Q4W were explored. The monotherapy JNJ-79635322 RP2D consists of a single SUD of 5 mg SC followed by the treatment

dose of 100 mg SC Q4W. An exposure-response relationship was observed in the rates of oral, skin, and nail AEs; however, the increase in calculated AE rates going from 50 mg exposure to 100 mg exposure were minimal, and 100 mg Q4W was overall well-tolerated and manageable and was selected as the RP2D. The most frequently reported Grade 3 or 4 AEs ($\geq 20\%$) were lymphopenia (15 participants [41.7%]) and neutropenia (11 participants [30.6%]). All grade CRS was reported in 19 participants (52.8%; 15 participants [41.7%] with Grade 1 and 4 participants [11.1%] with Grade 2; none had Grade 3 or 4). No participants had ICANS. The most frequently reported SAEs (≥ 2 participants) were pneumonia (4 participants [11.1%]) and CRS (3 participants [8.3%]). Data from this study, as of 28 September 2025, showed ORR in 31 participants was 86%, with 27 participants (75%) with CR or better. Among participants treated with JNJ-79635322 at RP2D naïve to BCMA- or GPRC5D-directed therapies ($n=27$), ORR was 100%, with 88.9% demonstrating CR or better, and MRD-negativity (10^{-5}) was 100% in evaluable patients (Krishnan 2025).

For the most comprehensive nonclinical and clinical information regarding JNJ-79635322, refer to the latest version of the IB for JNJ-79635322.

2.3. Benefit-risk Assessment

2.3.1. Risks for Study Participation

The potential risks and mitigation strategies are based on the target expression data, known mechanism of action (ie, T-cell activation and tumor cell lysis), route of administration, and the clinical data from Study 79635322MMY1001, evaluating bispecific T-cell redirecting antibodies talquetamab (targeting CD3 and GPRC5D) and teclistamab (targeting CD3 and BCMA).

The design of Study 79635322MMY3002 accounts for potential risks associated with study drug exposure (ie, CRS/ICANS, sARRs, and injection-site reactions), as described in the table below, by administration of SUDs of JNJ-79635322, as well as accompanying pre- and postdose medications. Other mitigation measures (see Section 6.1.3 and Section 6.6.3) aim to reduce potential risks in conjunction with robust dose modification guidelines and management strategies for hematologic and non-hematologic AEs, including extensive protocol guidance on the monitoring, prophylaxis, and management of infections. An IDMC will review the safety data during the study.

More detailed information about the known and potential benefits and risks of JNJ-79635322 and teclistamab can be found in the respective IBs.

The potential risks for study participation and their mitigation strategies are provided in Table 4 and further described in Section 6.6.3.

Table 4: Potential Risks of Clinical Significance

Potential Risks of Clinical Significance	Mitigation Strategy
CRS	Closely monitor for early signs and symptoms of CRS. SUD and SC administration are employed to reduce severity of CRS. Required pretreatment medications are provided in Section 6.1.1. Follow guidance in Section 6.6.3.1, including Table 13, and Section 10.5 for grading and management of CRS, and follow instructions for dose modification/delay (Section 6.6) or treatment discontinuation (Section 7.1).
ICANS	Early recognition of neurotoxicity is critical to management. Participants should have close follow-up in the clinic and be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible CNS abnormalities, such as new onset of headache or mental status changes. Suspected ICANS will be evaluated using the ICE tool (see Table 19), with ICANS grading and recommended management per ASTCT (see Section 6.6.3.2). Neurologic/psychiatric AEs that do not meet criteria for ICANS will be graded per NCI-CTCAE Version 6.0 and managed per institutional guidelines (Section 6.6.3.2).
Infections	Frequently monitor for the presence of infections, with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment and institutional guidelines. Perform screening for HBV and HCV, monitor as clinically indicated, and initiate treatment or supportive care as appropriate (Section 6.6.3.3).
Hypogammaglobulinemia	Monitor Ig levels on or after treatment and treat as indicated in Section 6.6.3.4, including administration of Ig replacement and monitoring for infection.
Immune-mediated toxicity	Monitor closely for possible development of immune-mediated AE(s), including but not limited to pneumonitis, colitis, hypophysitis, and hypothyroidism, and treat per institutional guidelines (Section 6.6.3.5).
Oral toxicity	Oral side effects may occur and may include dry mouth, altered taste, loss of taste, weight loss, and difficulty swallowing. Supportive care may include saliva-stimulating agents, corticosteroid mouth wash, or consultation with a nutritionist (Section 6.6.3.6).
Skin and nail toxicity	Rashes on the body that are distinct from injection-site reactions should be recognized. Monitoring of rash progression is critical and early intervention may be necessary (see Section 6.6.3.7). For nail toxicity, good hygienic practices should be followed. Participants should be advised to keep fingers and toes cleaned and nails trimmed (avoid aggressive trimming), and to wear comfortable shoes with extra room around the toes. The presence of infection will be monitored (eg, periungual edema, erythema, tenderness, and/or discharge) with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment (see Section 6.6.3.8).
sARRs	Participants will be monitored for signs and symptoms of sARRs. Required pretreatment medications are provided in Section 6.1.1. Follow guidance in Section 6.6.3.9, including Table 17, for management of sARRs, and follow instructions for dose modification/delay (Section 6.6) or treatment discontinuation (Section 7.1). Agents for the treatment of serious allergic reactions (including anaphylaxis) should be available for immediate use in the event of a reaction.

Table 4: Potential Risks of Clinical Significance

Potential Risks of Clinical Significance	Mitigation Strategy
Injection-site reactions	Monitor for local reactions surrounding the administration site and manage per institutional guidelines (see Section 6.6.3.10).
TLS	Frequently monitor chemistry parameters and monitor for early recognition of signs and symptoms. Initiate preventive measures in high-risk participants (see Section 6.6.3.11) prior to treatment, and promptly initiate supportive care for participants who develop acute TLS during treatment per institutional guidelines.
Cytopenias	Closely monitor hematological parameters. Blood and platelet transfusions and G-CSF for neutropenia should be provided according to institutional guidelines. During CRS, G-CSF and GM-CSF should be limited when possible (see Section 6.6.3.12).

2.3.2. Benefits of Study Participation

Treatments with T-cell redirecting agents targeting CD3 and BCMA or GPRC5D have shown good results. Participants randomized to Arm B will receive BCMA teclistamab, as a representative SoC for participants with RRMM. A favorable benefit-risk profile for teclistamab has been demonstrated in patients with RRMM and it is authorized in multiple countries worldwide for patients treated with more than 3 lines of therapy. Teclistamab is currently being studied in participants exposed to 1 to 3 prior lines in the ongoing Phase 3 MajesTEC-9 study. The available data demonstrate a positive benefit-risk profile (superior PFS and OS compared with SoC PVD and Kd) for patients with RRMM exposed to 1 to 3 prior lines, including patients who are refractory to anti-CD38 and lenalidomide ([Johnson & Johnson TECVAYLI® Press Release 2026](#)). These data will be submitted to global HAS to seek regulatory approvals, meaning teclistamab is potentially a future SoC in the early relapse setting. Further details and efficacy data from MajesTEC-9 are included in Section 2.3.2 and Section 4.2. In contrast to teclistamab, JNJ-79635322 provides a differentiated approach where both BCMA and GPRC5D are targeted simultaneously with 1 T-cell engager and is hypothesized to demonstrate an enhanced tumor eradicating effect, which would constitute a significant benefit to patients with RRMM. Additionally, Study 79635322MMY3002 will provide participants with non-anti-CD38-containing regimens in both study arms, making the study an attractive option for the majority of patients who will expectedly be anti-CD38 exposed and/or refractory, reflective of the current clinical landscape.

2.3.3. Benefit-risk Assessment for Study Participation

Taking into account the measures taken to minimize risks to participants of this study, the potential risks identified in association with JNJ-79635322 are justified by the hypothesized benefits that may be afforded to participants with RRMM. Therefore, the overall benefit-risk profile in this population is hypothesized to be favorable.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the efficacy of JNJ-79635322 with teclistamab	Dual primary endpoints: CR or better, PFS
Secondary	
To further compare the efficacy of JNJ-79635322 with teclistamab	• ORR • VGPR or better • Duration of response • MRD-negative CR • MRD-negative CR at 1 year • MRD-negative CR at 5 years • PFS2 • OS • TTNT
To characterize the overall safety of JNJ-79635322 as compared to teclistamab	TEAE incidence and severity, laboratory results, and other safety parameters
To assess participants' symptoms, functioning and HRQoL through various PRO tools	• Change from baseline in HRQoL, symptoms and functioning using the MySIm-Q, EORTC QLQ-C30 and EQ-5D-5L scores • Time to worsening in HRQoL, symptoms and functioning using the MySIm-Q, EORTC QLQ-C30 and EQ-5D-5L scores • Percent of participants with meaningful improvement in HRQoL symptoms and functioning using the MySIm-Q, EORTC QLQ-C30 and EQ-5D-5L scores
To assess participants' tolerability through PRO tools	Proportion of participants who report side effects burden on the EORTC IL46
Exploratory	
To characterize the PK of JNJ-79635322	
To assess the immunogenicity of JNJ-79635322	
To evaluate the relationship between PK, pharmacodynamic activity, AEs, and clinical response in participants treated with JNJ-79635322	
To evaluate MRD-negative CR at 3 years	
To evaluate 2-year sustained MRD-negative CR	
To explore the relationship between MRD negativity with duration and depth of response in participants treated with JNJ-79635322	
To investigate biomarkers of response and/or resistance in participants treated with JNJ-79635322	
To explore time to symptomatic worsening of MM in both treatment arms	
To collect MRU	

ESTIMANDS

See Section 9.3.2.1.2 and Section 9.3.2.2.2.

HYPOTHESIS

The primary hypothesis is that JNJ-79635322 may significantly improve at least one of the dual primary endpoints compared with teclistamab therapy in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, Phase 3, active-comparator, multicenter, interventional, open-label study in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide. Approximately 700 participants will be randomly assigned in a 1:1 ratio in 2 arms. At randomization, eligible participants will be stratified by ISS staging at screening (I vs. II/III), number of prior lines of therapy (1 vs. ≥ 2) and EMD status at baseline (yes vs. no).

The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days before randomization. The Treatment Phase will extend from start of treatment (including SUD) until study treatment completion or discontinuation. The EoT visit will occur 30 days (+7 days) after last dose or before the start of SST, whichever comes first. The Follow-up Phase will begin once a participant completes or discontinues treatment (refer to Section 4.4.1 and Section 7.1). Participants who complete or discontinue treatment for reasons other than PD will continue to perform DEs according to the SoA (Section 1.3.2 [Table 2] and Section 1.3.3 [Table 3]) in the Pre-PD follow-up schedule. After PD, disease evaluations will be discontinued, and the Post-PD schedule will be followed. The Follow-up Phase will continue until death, withdrawal of consent, lost to follow-up, or end of the study, whichever occurs first. The LTE Phase will begin after the sponsor has notified the site (see Section 10.9).

Participants randomized to the experimental arm (Arm A) will receive treatment with JNJ-79635322 for a fixed duration of 36 months if they have no sign of PD or intolerable toxicity. Participants randomized to the comparator arm (Arm B) will receive teclistamab until PD or intolerable toxicity. See Section 6.1 for details on dosing and schedule for both arms.

Disease status will be evaluated for response and PD according to the most recent IMWG consensus guidelines (Section 10.11).

Efficacy, safety, and other measurements will be assessed as indicated in the SoA (Section 1.3).

An IDMC will be commissioned for this study. Safety data will be reviewed periodically, and efficacy data will be reviewed at prespecified interim analysis timepoints by the IDMC. The IDMC may recommend increasing the planned number of events for the PFS and OS analyses according to the prespecified ERE rule. See Section 9 for more details about the interim and final analysis.

A diagram of the study design is provided in Section 1.2.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods and Treatment Groups

Randomization will be used to minimize bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Randomization will be stratified as described in Section 6.3.

JNJ-79635322 Treatment (Arm A)

After administration of a single SUD of 5 mg SC, JNJ-79635322 will be administered at a target treatment dose of 100 mg SC per scheduled administration for a finite duration of 36 months. The monotherapy treatment dose was established in the Phase 1 Study 79635322MMY1001, which demonstrated this dose as highly efficacious with an acceptable safety profile, and the RP2D regimen was determined based on interim safety, efficacy, PK, and biomarker data (see Section 2.2).

The current dosing of SUD of 5 mg, followed by 100 mg Q4W, and then 100 mg Q8W after Cycle 6 was selected as the RP2D based on the following considerations:

(1) a favorable efficacy profile exists at the RP2D compared with 50 mg Q4W, with 100 mg Q4W being the lowest maximally efficacious dose with plateau in efficacy at this and higher doses. Among participants treated with 100 mg Q4W naïve to BCMA- or GPRC5D-directed therapies (n=27), ORR was 100%, with 92.6% VGPR or better, and 59.3% CR or better. Among participants treated with 50 mg Q4W naïve to BCMA- or GPRC5D-directed therapies (n=21), ORR was 66.7%, VGPR or better 57.1%, and CR or better 38.1%. A trend for a more durable response was also observed in all participants treated with 100 mg Q4W versus 50 mg Q4W, with 9-month event-free rates of 96.7% (n=30) and 70.6% (n=16), respectively. Additionally, as of the CCO of 28 September 2025, 100% of participants in CR with available bone marrow for MRD assessment at RP2D were MRD-negative at both 10^{-5} threshold (10/10) and 10^{-6} threshold (7/7) using next-generation sequencing.

(2) the clinical safety profile observed with JNJ-79635322 at 100 mg Q4W is favorable and manageable (see Section 2.2) and appears similar to those in lower (50 mg Q4W) dosing levels.

(3) exposure-response analyses demonstrating that doses below the RP2D did not provide sufficient exposure to elicit deep and durable responses and lower drug exposure was not associated with additional safety benefit across the majority of clinically significant TEAEs (Grade 3+ neutropenia, Grade 3+ TEAEs, Grade 3+ infection, and Grade 1+ weight loss). The population PK model estimated that 83.1% participants treated with 100 mg Q4W will achieve target exposure of mean EC90; moreover, the population PK analysis showed that systemic exposure to JNJ-79635322 at RP2D was consistent across participants with RRMM regardless of numbers of prior therapy, supporting similar exposure expectations in participants with earlier lines of therapy;

(4) more optimal pharmacodynamic changes in T-cell recovery, T-cell activation, and cytokine induction were observed at the 100 mg Q4W dose level compared with the 50 mg Q4W or lower dose levels; and;

(5) with 100 mg Q4W induction, the majority of participants achieved deep response (eg, $\geq$ VGPR) after 6 months of treatment (median time to VGPR was 3 months [range: 1.0, 9.5]). As of 28 September 2025, of the 15 participants who transitioned from Q4W to Q8W all maintained response (with a median follow-up of 6 months post-switch). PK modeling supports Q8W maintenance dosing, with steady-state half-life (~17 days) and trough concentration above minimum EC90, ensuring sustained pharmacologic activity. Once participants achieve deep response and lower tumor burden, continued treatment with 100 mg Q8W is hypothesized to maintain and deepen responses.

Rationale for Finite Treatment

Supporting evidence for fixed-duration bispecific therapy is emerging across the RRMM landscape. A multi-institutional retrospective cohort study evaluated the outcome of participants treated with either BCMA or GPRC5D (or multispecific; targeting both) bispecific antibodies either through enrollment in early phase studies or as SoC. This study described the outcome of 78 participants after cessation of bispecific antibody due to reasons other than PD or death. Of the 78 participants, the median bispecific antibody treatment duration was 7 months, 80% of whom were in CR at discontinuation. At a median follow-up of 16 months from bispecific antibody discontinuation, the RFS at 2 years was 67% (95% CI, 55%, 80%). The 2-year RFS for patients 1 to 3 prior lines of therapy was 79% (Vega 2025).

In RRMM, the FcRH5xCD3 bispecific antibody cevostamab has been studied as a fixed-duration therapy for ~1 year (Chakraborty 2024). Among 16 participants in the Phase 1 study that completed therapy, 13 [81.3%] remained in remission, with 8 sustaining their response $\geq$ 6 months and 3 sustaining response $\geq$ 12 months after treatment completion (Chakraborty 2024). In that study, 3 participants had progressed thus far (1 from PR and 2 from VGPR) at 1.3, 7.8, and 12.9 months from treatment initiation, respectively.

In addition to cevostamab, the GPRC5D bispecific antibody forimtamig is also being studied in a fixed-duration regimen for 1 year in RRMM (NCT04557150). Another Phase 2 single-arm study (LimiTEC, NCT05932680) is testing limited duration of therapy after 6 to 9 months of single-agent teclistamab among participants who achieve $\geq$ VGPR, with the primary endpoint being failure-free survival at 6 months after discontinuation. MonumenTAL-6 (NCT06208150) is actively evaluating similar fixed-duration strategies, after approximately 2 years of teclistamab therapy.

Given the observed efficacy of JNJ-79635322 along with examples of fixed-duration therapies in other bispecifics as noted, a fixed 36-month duration of therapy for JNJ-79635322 will potentially offer durable response in RRMM patients and allow for a long treatment free interval and enhanced HRQoL. A finite duration of therapy provides an opportunity to mitigate toxicity while maintaining efficacy and may offer an advantage versus existing bispecific therapies which are typically administered chronically until PD.

Teclistamab Comparator Control (Arm B)

Teclistamab, a BCMAxCD3-targeting bispecific antibody will be used as the comparator for this study. The positive efficacy profile for teclistamab was established from the Phase 1/2 study (MajesTEC-1) in patients with RRMM with 3 or more prior lines of therapy, reporting an ORR 65% with 39.4% CR or better among 165 participants who received teclistamab, 77.6% of whom were triple class exposed. MajesTEC-1 utilized a weekly SC dosing schedule of teclistamab (1.5 mg/kg) following 2 SUDs (0.06 and 0.3 mg/kg respectively). Common AEs included CRS in 72% of participants (0.6% Grade 3), infections in 76.4% (44.8% Grade 3-4), and neurotoxic events in 14.5%, including ICANS which was observed in 3% of participants (all Grade 1-2) ([Moreau 2022](#)).

Based on the above-mentioned data, teclistamab is authorized in the EU and multiple countries worldwide for patients with RRMM previously treated with at least 3 prior lines of therapy.

While initial registrations for teclistamab are for later lines of treatment, preliminary ORR and PFS data suggest that teclistamab monotherapy may be more efficacious earlier during treatment of myeloma and its use in earlier lines of therapy may further improve outcomes. Two of the most commonly used therapies for newly diagnosed patients are anti-CD38 antibodies and lenalidomide, and many patients will be refractory to these treatments as early as first relapse. Patients who are refractory to an anti-CD38 antibody and to lenalidomide have limited effective treatment options. Other treatment regimens such as DPd, PVd, Dkd, and EloPD have been considered, but these overall represent insufficient comparator options and are not as highly favored by investigators, which could result in recruitment challenges and are expected to be replaced by modern regimens using bispecific antibodies such as teclistamab. Furthermore, regimens such as DPd and DKd contain an anti-CD38 antibody (daratumumab) which would be suboptimal to use at relapse for a patient who has received this modality at frontline and are refractory to this treatment. Data from MajesTEC-9 have shown improved efficacy compared to aforementioned historical regimens and have expanded available treatment options, particularly for patients with prior anti-CD38 exposure.

Teclistamab, with its BCMAxCD3-targeting mechanism of action, has the potential to fulfill an unmet medical need in this setting for patients with RRMM from second line of treatment, particularly for patients who have already received established SoC therapies such as lenalidomide and an anti-CD38 antibody, making it a strong choice of comparator control for the Study 79635322MMY3002 study. Notably, teclistamab is currently being studied in the ongoing randomized Phase 3 MajesTEC-9 study, and data are now available which demonstrate a positive benefit-risk profile for RRMM patients who have received 1 to 3 prior lines of therapy.

The results at the first prespecified interim analysis showed an HR for PFS of 0.29 (95% CI: 0.23, 0.38) for the teclistamab versus control, indicating a statistically significant and clinically meaningful 71% reduction in the risk of progression or death for participants randomized to teclistamab (p-value < 0.0001) and a 40% reduction in the risk of death (HR=0.60 [95% CI: 0.43, 0.83]). The safety profile was clinically manageable using established protocols and consistent with its known profile, with no new safety concerns identified.

Based on these data, the dose and schedule of teclistamab in Study 79635322MMY3002 will therefore be the same as used in the MajesTEC-9 study and will be administered until PD.

Study Population

As discussed above, bispecific antibody (BCMAxCD3; teclistamab) has already been approved for treatment of RRMM in late relapse (≥ 3 prior lines) and new data has emerged to support use of teclistamab in the early relapse setting (1 to 3 prior lines). Evaluating novel treatments like JNJ-79635322 in early relapse is essential to establish whether deeper response and improved PFS are achieved earlier during treatment, particularly in the setting of increased anti-CD38 antibody exposure.

This study will include patients with RRMM with 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide. IMiDs (eg, lenalidomide) are one of the most commonly used treatments in MM and the inclusion of patients who are anti-CD38 exposed accounts for the evolving landscape of increasing anti-CD38 exposure in frontline treatments.

Primary Efficacy Endpoints

This study has dual primary endpoints of CR or better and PFS.

The IMWG criteria for MM consider PFS an essential time-to-event endpoint ([Durie 2006](#); [Rajkumar 2011](#)). PFS is also widely accepted as a surrogate endpoint for OS in relapsing MM and recognized to represent direct clinical benefit by the FDA (FDA 2018, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics; European Medicines Agency/Committee for Medicinal Products for Human Use [2023, Guideline on the clinical evaluation of anticancer medicinal products – revision 6]). The use of PFS as the primary efficacy endpoint has been considered acceptable in registration studies for MM that have led to full approvals for many agents.

Durable and objective response rate has been accepted by regulatory authorities as reasonably likely to indicate clinical benefit. CR allows for quantification of the depth of response to treatment beyond ORR. CR is also a recognized prognostic indicator for MM; patients who attain CR have improved long-term outcomes ([FDA Guidance 2026](#)) and CR has been assessed in many MM studies. Response in Study 79635322MMY3002 will be assessed according to the most recent IMWG consensus guidelines.

FDA guidance supports the use of CR as an endpoint for accelerated approval in MM, with adequate follow-up to establish that the durability of CR is meaningful ([FDA Guidance 2026](#)). The analysis of CR or better will be supported by PFS and OS data.

Rationale for Pharmacokinetics, Pharmacodynamics and Exploratory Biomarker Evaluations

PK and ADA samples are collected to further assess the impacts of intrinsic and extrinsic factors, including bodyweight, race, age, and disease burden on drug exposure in this target population. The potential impact of ADA and NAb on PK, safety, and efficacy may also be assessed.

Biomarker studies are designed to identify differences in antitumor activity between study treatments by evaluating the effect of study treatments on MRD negativity and its relationship with clinical responses, and identifying participant subgroups that respond differently to treatments through examination of immune or molecular mechanisms of response and resistance and relationships between treatment intervention, PK, safety, and efficacy responses.

Sample collection and testing will comply with local regulations. Biomarker collection and analysis may be discontinued if deemed no longer necessary by the sponsor.

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 this information and provide their consent voluntarily will be enrolled. If applicable, the legally designated representative must sign the ICF. Written consent 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 patient preferences.

The results of this study will provide useful information for further development of JNJ-79635322. Although anti-BCMA and anti-GPRC5D therapies are approved with established safety and efficacy, all the risks and benefits associated with the administration of JNJ-79635322 and teclistamab are not fully known.

It is possible that the participant's disease will not respond to treatment with JNJ-79635322. Furthermore, side effects not anticipated based on data from nonclinical studies or not observed in earlier clinical experience with JNJ-79635322 may occur as well as side effects from the safety

and efficacy assessments in the SoA (Section 1.3). Based on the nonclinical evaluation and clinical experience with JNJ-79635322, a positive benefit-risk profile is hypothesized (see Section 2.3). To ensure the well-being of participants treated in this study, safety and clinical benefit will be closely monitored by the site and by the sponsor via an IDMC.

4.3. Justification for Dose

The justification for dose of study treatment is included in Section 4.2: Rationale for Study Design.

4.4. End of Study Definition

The end of study is the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

4.4.1. Participant Study Completion Definition

A participant will be considered to have completed the study if the participant died while on study or was still on study (ie, did not meet the criteria for withdrawal from study, has not been lost to follow-up, has not withdrawn consent for study participation) at the time of the end of study. Participants who discontinue treatment are not considered to have completed the study and should continue all protocol defined assessments (pre-PD or post-PD) as defined in the protocol until the end of study. All reasonable efforts should be made to maintain the participants who discontinued treatment on study to ensure accurate assessment of all protocol-specified endpoints.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in 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:

Age

1. At the time of informed consent, be ≥ 18 years of age or at least the legal age of majority in the jurisdiction in which the study is taking place.

Type of Participant and Disease Characteristics

2. Documented diagnosis of MM as defined by the criteria below:
 - a. MM diagnosis according to the IMWG diagnostic criteria ([Rajkumar 2014](#))
 - b. Measurable disease at screening as assessed by central laboratory, defined by any of the following:
 - i. Serum M-protein level ≥ 0.5 g/dL; or
 - ii. Serum Ig FLC ≥ 10 mg/dL and abnormal serum Ig kappa lambda FLC ratio; or
 - iii. Urine M-protein level ≥ 200 mg/24 hours

NOTE: In exceptional circumstances and after discussion with, and written approval by, the sponsor, local laboratory results may be used to determine initial eligibility, but only if the local results are clearly ($\geq 25\%$) above the thresholds for measurability. In such cases, central laboratory results should still be obtained from samples collected prior to the start of study treatment to establish baseline values and confirm the results from the local laboratory.

3. Received 1 to 3 prior lines of antineoplastic therapy, including an anti-CD38 antibody and lenalidomide. The participant must have undergone at least 2 consecutive cycles of an anti-CD38 antibody at the approved dosing schedule (or a minimum of 6 doses if the anti-CD38 antibody was only part of a maintenance regimen) in any prior line and 2 consecutive cycles of lenalidomide in any prior line, unless PD was the best response to the line of therapy.
Refer to Section 10.7 for the definition of a line of therapy.
4. Relapsed or refractory disease as defined below:
 - i. Relapsed disease is defined as an initial response to prior treatment, followed by confirmed PD by IMWG response criteria >60 days after cessation of treatment.
 - ii. Refractory disease is defined as failure to achieve a response or confirmed PD by IMWG response criteria during previous treatment or ≤ 60 days after cessation of treatment.
5. Have an ECOG performance status of 0 to 2 at screening and immediately before the first dose of study medication (Oken 1982).
6. Criterion modified per Amendment 1.
 - 6.1. Have clinical laboratory values meeting the following criteria during the screening and within 1 day of the start of administration of study treatment.

Hematology	
Hemoglobin	≥ 7.5 g/dL, without use of transfusion or growth factors within 7 days prior to laboratory testing
ANC	$\geq 0.75 \times 10^3/\mu\text{L}$ (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF prior to the laboratory testing)
Platelets	$\geq 50 \times 10^3/\mu\text{L}$, without use of transfusion or growth factors within 7 days prior to laboratory testing
Chemistry	
AST and ALT	$< 2.5 \times \text{ULN}$
Total bilirubin	$< 1.5 \times \text{ULN}$
Bilirubin in case of known congenital nonhemolytic hyperbilirubinemias such as Gilbert's Syndrome	Isolated total bilirubin $\geq 1.5 \times \text{ULN}$ with direct bilirubin $< 1.5 \times \text{ULN}$
eGFR, calculated with the CKD-epi creatinine formula using adjusted BSA (Section 10.12)	> 30 mL/min

Sex and Contraceptive/Barrier Requirements

7. Participants must agree, while on study treatment and for 6 months after the last dose of study treatment, to:

- Not breastfeed or be pregnant.
- Not donate gametes (ie, eggs or sperm) or freeze for future use for the purposes of assisted reproduction.
- Wear an external condom.
- If of childbearing potential:
 - Have a negative highly sensitive (eg, β -hCG) pregnancy test at screening and within 24 hours before the first dose of study treatment and agree to further pregnancy tests.
 - Practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used.
- If a participant's partner is of childbearing potential:
 - The partner must practice a highly effective method of contraception unless the participant is vasectomized.

See Section 10.3 for details.

Informed Consent

8. Must provide informed consent as described in Section 10.2.3.
9. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol (see Section 5.3).

5.2. Exclusion Criteria

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

Medical Conditions

1. Serious underlying medical conditions, such as:
 - i. Evidence of active systemic viral, fungal or bacterial infection requiring systemic antiviral, antifungal, or antimicrobial therapy.
 - ii. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of treatment. EXCEPTION: Participants with vitiligo, Type 1 diabetes, or prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.
 - iii. Overt clinical evidence of dementia or altered mental status.
2. Major surgery, (eg, requiring general anesthesia) or significant traumatic injury within 2 weeks prior to first dose, or not fully recovered from prior surgery, or has major surgery planned during the time the participant is expected to participate in the study. Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.
3. Suspected or known allergies, hypersensitivity, intolerance, or other contraindications to the use of JNJ-79635322 or teclistamab, or their excipients (refer to the IBs).
4. Any of the following within 6 months prior to first dose of study treatment: Seizure, severe or unstable angina, myocardial infarction, major thromboembolic events (eg,

pulmonary embolism, cerebrovascular accident [including transient ischemic attack and stroke]), clinically significant ventricular arrhythmias or heart failure New York Heart Association functional classification Class III to IV (see Section 10.13) . Uncomplicated deep vein thrombosis is not considered exclusionary.

Prior Malignancies

5. Presence of any of the following:

- i. Any ongoing myelodysplastic syndrome or B-cell malignancy (other than MM).
- ii. Any history of malignancy, other than MM, that is considered at high risk of recurrence requiring systemic therapy.
- iii. Any active malignancy (ie, progressing or requiring treatment change in the last 24 months) other than MM.

The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:

- i. Non-muscle invasive bladder cancer (solitary Ta-papillary urothelial neoplasm of low malignant potential or low-grade, <3 cm, no carcinoma in situ).
 - ii. Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone.
 - iii. Non-invasive cervical cancer.
 - iv. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer (anti-hormonal therapy is permitted).
 - v. Localized prostate cancer (M0, N0) with a Gleason Score ≤ 7 , treated locally only (radical prostatectomy/radiotherapy/focal treatment).
 - vi. Other malignancy that is considered cured with minimal risk of recurrence in consultation with the sponsor.
6. PC leukemia at the time of screening ($\geq 5\%$ circulating PCs in peripheral blood smear), Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or systemic amyloid light chain amyloidosis (Rajkumar 2014; participants with myeloma who have incidental amyloid deposits on biopsy of an impacted organ, without clinical manifestations of amyloidosis, are not excluded and may participate in the study).

Brain and Central Nervous System Metastases

7. Known active or prior CNS involvement or exhibits clinical signs of meningeal involvement of MM. If either is suspected, negative whole brain MRI and lumbar cytology are required.

HIV Status

8. Participants who are HIV-positive and meet any of the following:
- i. Detectable viral load (ie, >50 copies/mL) at screening.
 - ii. CD4+ count <300 cells/mm³ at screening.
 - iii. AIDS-defining opportunistic infection within 6 months of screening.

- iv. Receive treatment other than continued HAART. A change in HAART due to resistance/progression must occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

Note: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

Viral Hepatitis Assessments

9. Active hepatitis of infectious origin.
 - i. Seropositive for hepatitis B: defined by a positive test for HBsAg. Participants with resolved infection (ie, participants who are HBsAg negative with positive antibodies to total HBe antigen [anti-HBe]) must be screened using RT-PCR measurement of 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 Section 10.6).
 - ii. Known hepatitis C infection or positive serologic testing for HCV (anti-HCV) antibody.
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 at screening or within 3 months prior to first dose of study treatment.
 - iii. Other clinically active liver disease of infectious origin.

Prior/Concomitant Therapy or Clinical Study Experience

10. Concurrent use of any other anticancer treatment (including non-palliative radiotherapy) or investigational agent.
For participants who received an allogeneic stem cell transplant, the transplant must be dated at least 6 months before first dose of study drug. Participants who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks before the start of study treatment administration without signs of graft-versus-host disease.
Toxicity related to prior anticancer treatment must have resolved to Grade 1 or better (except alopecia, skin fibrosis or discoloration, dry mouth, hearing loss, endocrinopathy managed with replacement therapy, peripheral neuropathy, which must be Grade 2 or better).
11. Received prior or concurrent exposure to T-cell redirecting therapy (eg, CAR-T, bispecific antibodies), directed at BCMA or GPRC5D.
12. Received a cumulative dose of corticosteroids equivalent to ≥ 160 mg of dexamethasone within 14 days prior to first dose of study drug.
13. Received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study drug or within 90 days after the last dose of study drug. Non-live and non-replication-competent vaccines approved or authorized for emergency use by local HAs are allowed.

Other Exclusions

14. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

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, even after the participant has been randomized, but before the first dose of study treatment is given, such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria is noted in Section 10.2.

5.3. 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. Carry a "wallet study card" for the duration of study participation.
The participant must be provided with a "wallet study card" which must contain (a) study number, site number, and participant's study ID number, (b) statement, in the local language(s), that the participant is participating in this clinical study, (c) investigator's name and 24-hour contact telephone number, (d) local sponsor's name and 24-hour contact telephone number (for medical personnel only).
2. Agree to self-monitor for signs and symptoms of CRS (such as fever) and to seek immediate medical treatment.
3. Any blood donation is not allowed until ≥ 90 days after the last dose of study treatment.
4. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).
5. Refer to Section 6.9.3 for details regarding prohibited and restricted therapy during the study.

5.4. Screen Failures

Individuals who do not meet all inclusion and exclusion criteria for participation in this study (and are thus a screen failure) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are determined to be eligible for rescreening must sign a new ICF and will be assigned new participant numbers.

This exceptional and limited retesting of abnormal screening values (that led to exclusion), is allowed on only 1 occasion using an unscheduled visit during the screening period (to reassess eligibility). The total duration of the screening period should remain within 28 days in such cases.

Mandatory Participant Identification and Enrollment Log Form

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.

Participant Screening Log Form

The investigator agrees to complete a participant screening log tracking participants from prescreening (as applicable) to randomization, to record reasons why screened participants were not enrolled, and to identify those patients that did not meet the eligibility criteria, to permit better understanding of participant population and enrollment at the site by the sponsor. This study will use an RTMS system (eg, IWRS). The investigator will generate screening logs directly from IWRS.

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Table 5: Designation of Treatments

Designation	Product			
Investigational Medicinal Product(s)	JNJ-79635322; teclistamab			
	Authorization status in the EU/EEA:			
	<table> <tr> <td>Authorized</td><td>Teclistamab Used not in accordance with marketing authorization</td></tr> <tr> <td>Unauthorized</td><td>JNJ-79635322</td></tr> </table>	Authorized	Teclistamab Used not in accordance with marketing authorization	Unauthorized
Authorized	Teclistamab Used not in accordance with marketing authorization			
Unauthorized	JNJ-79635322			
Non-investigational Medicinal Product(s)/Auxiliary Medicinal Product(s)	None			

Dose schedule and pretreatment/post-treatment medications, as well as additional information about administration of the study treatments, are presented in the SoAs (Section 1.3) and Section 6.1.1 and Section 6.1.2. A description of the study treatments is provided in Table 6.

Study treatment administration must be captured in the source documents and the eCRF.

JNJ-79635322 and teclistamab will be manufactured and provided under the responsibility of the sponsor. Refer to the IBs for a list of excipients.

Table 6: Description of Treatments

Arm/Treatment Name	Arm A (JNJ-79635322)	Arm B (Teclistamab)
Type	Drug	Drug
Dose Formulation	Solution for injection	Vial
Unit Dose Strength(s)	5 mg or 100 mg	10 mg/mL (30 mg/vial) and 90 mg/mL (150 mg/vial)

Table 6: Description of Treatments

Arm/Treatment Name	Arm A (JNJ-79635322)	Arm B (Teclistamab)
Dose Level(s)	SUD: 5 mg (once) Treatment dose ^a : 100 mg Q4W × 6 doses (C1 to C6) and Q8W dosing starting after C6 (even cycles: C8, C10, C12, etc.) for a total treatment duration of up to 36 months, or until PD or intolerable toxicity (whichever is earlier).	2 SUDs ^b of 0.06 mg/kg and 0.3 mg/kg, respectively followed by treatment doses: 1.5 mg/kg weekly starting on C1D5 through Cycle 2, 3 mg/kg every 2 weeks Cycles 3-6, and 3 mg/kg every 4 weeks for Cycle 7+ ^{c, d}
Route of Administration	SC injection	SC injection
Use	Experimental	Active Comparator
Investigational Medicinal Product	Yes	Yes
Non-investigational Medicinal Product/Auxiliary Medicinal Product	No	No
Sourcing	Provided centrally by sponsor	Provided centrally by sponsor

^a First treatment dose may be given between 2 to 4 days after the SUD and up to 8 days after the SUD to allow for AE resolution. A minimum of 48 hours needs to be kept between the SUD and the treatment dose.

^b SUD1 to be administered on C1D1. Thereafter, there must be ≥2 days between SUDs. SUDs must be delayed until CRS and/or ICANS associated with prior doses have fully resolved.

^c First treatment dose must be administered ≥2 days after SUD2. Thereafter, there must be ≥5 days between weekly treatment doses (1.5 mg/kg) and ≥12 days between Q2W treatment doses (3 mg/kg). Treatment doses must be delayed until CRS and/or ICANS associated with prior dose have fully resolved.

^d Participants may change to Q4W dosing when in confirmed VGPR or better prior to Cycle 7 per investigator discretion.

6.1.1. Required Pretreatment Medications

For participants randomized to Arm A and receiving JNJ-79635322, pretreatment medications must be administered as shown in [Table 7](#). In addition, for participants with high disease burden, a prophylactic administration of allopurinol is recommended during the phase of SUD and first treatment dose, as well as the provision of analgesic or corticosteroid medications for cancer-related pain, especially during initial dosing.

Table 7: Pretreatment Medications for JNJ-79635322

Class	Medication and Dose	Administration	Schedule Day(s)
Glucocorticoid	Dexamethasone 16 mg or equivalent	IV or orally, up to approximately 3 hours before JNJ-79635322	SUD and first treatment dose of JNJ-79635322 After Grade ≥2 CRS/sARR ^a
Antihistamine	Diphenhydramine 25 to 50 mg or equivalent	IV or orally, up to approximately 3 hours before JNJ-79635322	SUD and first treatment dose of JNJ-79635322 After Grade ≥2 CRS/sARR ^a
Antipyretic	Acetaminophen 650 to 1000 mg or equivalent	IV or orally, up to approximately 3 hours before JNJ-79635322	SUD and first treatment dose of JNJ-79635322 After Grade ≥2 CRS/sARR ^a
Other Recommended Pretreatment Medication:			

Table 7: Pretreatment Medications for JNJ-79635322

Class	Medication and Dose	Administration	Schedule Day(s)
Anticytokine	Tocilizumab ^b 8 mg/kg	IV, 3 hours ($\pm$ 1 hour) before JNJ-79635322 SUD (not to exceed 800 mg)	SUD of JNJ-79635322

^a A participant who experiences Grade $\geq$ 2 CRS/sARR related to JNJ-79635322 must receive pretreatment medications for at least the 2 subsequent doses of JNJ-79635322. Administration of pretreatment medication beyond this should be per investigator's discretion. Dexamethasone should not be administered as a pretreatment medication after C1D1, except for participants who experience Grade $\geq$ 2 CRS or sARRs.

^b The interval between consecutive doses should be at least 8 hours if more than the initial pretreatment dose is necessary.

For participants randomized to Arm B and receiving teclistamab, pretreatment medications must be administered as shown in [Table 8](#).

Table 8: Pretreatment Medications for Teclistamab

Teclistamab			
Class	Medication and Dose	Administration	Schedule Day(s)
Glucocorticoid	Dexamethasone 16 mg or equivalent	IV or orally, up to approximately 3 hours before teclistamab	SUDs and first treatment dose ^a
Antihistamine	Diphenhydramine 50 mg or equivalent	IV or orally, up to approximately 3 hours before teclistamab	SUDs and first treatment dose ^a
Antipyretic	Acetaminophen 650 to 1000 mg or equivalent	IV or orally, up to approximately 3 hours before teclistamab	SUDs and first treatment dose ^a

^a Administration of pretreatment medications may be required prior to subsequent doses of teclistamab 1) in participants who repeat doses within the SUD schedule following a dose delay, 2) in participants who experienced CRS following the prior dose of teclistamab. In case of repeat SUDs after first full treatment dose, pretreatment medications should be administered prior to the SUDs and the first full dose.

6.1.2. Post-treatment Medications

Post-treatment medications are required for participants randomized to Arm A, after receiving JNJ-79635322 and must be administered as shown in [Table 9](#). Participants will be asked to record their post-treatment medications in a diary.

Table 9: Required Post-treatment Medications for JNJ-79635322

Class	Medication and Dose	Administration	Schedule Day(s)
Glucocorticoid	Dexamethasone 8 mg or equivalent ^a	IV or orally, given 24 hours ($\pm$ 4 hours) and 48 hours ($\pm$ 4 hours) after JNJ-79635322.	SUD and first treatment dose of JNJ-79635322 ^b
Antipyretic	Acetaminophen 500 to 1000 mg or equivalent	IV or orally, every 8-10 hours after JNJ-79635322 SUD for 48 hours or until pretreatment medication for the next treatment dose, whichever is earlier.	SUD of JNJ-79635322 ^b

Table 9: Required Post-treatment Medications for JNJ-79635322

Class	Medication and Dose	Administration	Schedule Day(s)
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^a If a post-treatment dexamethasone dose post-SUD is scheduled on the same day when premedication with dexamethasone for the first treatment dose is required, then only the premedication dose should be given.

^b In case of repeat step-up dosing, post-treatment medications should be administered per investigator discretion.

6.1.3. Required Safety Monitoring

Arm A (JNJ-79635322) and Arm B (Teclistamab)

Hospitalization is not required for administration of JNJ-79635322 or teclistamab. At investigator discretion and the participant's willingness, the participant may be admitted for inpatient monitoring SUDs and the first treatment dose of JNJ-79635322 or teclistamab and/or may receive the SUDs and first treatment dose of JNJ-79635322 or teclistamab as an outpatient; see Section 10.10 for guidance to be considered for outpatient dosing through the first treatment dose. If JNJ-79635322 or teclistamab is provided as outpatient, if Grade 1 CRS-related AEs occur or any suspected symptoms of ICANS, participants should be observed and the need for hospital admission should be evaluated.

All participants, regardless of treatment arm, should remain in close proximity (within 30 minutes travel time) to the site and in the company of a competent adult for a minimum of 2 days after each SUD and first treatment dose of JNJ-79635322 or teclistamab. During this period, participants will be asked to check their temperature at least twice daily at an interval of ≥ 8 hours apart and record in a participant diary. They will be instructed to report any fever ($\geq 38^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) to the investigator (see additional details in Section 10.10) and return to the treatment facility or hospital for evaluation immediately. During this safety monitoring period, the participant must notify the investigator of development of fever or any other suspected CRS/ICANS symptoms. Notably, if the participant experiences any signs or symptoms of CRS, ICANS, or other clinically significant event(s) following either of the SUDs or the first treatment dose, the participant should be immediately evaluated.

Admission to the hospital is required at any time in the event of any presenting signs and symptoms of Grade ≥ 2 CRS, persistent Grade 1 CRS lasting more than 8 hours, any ICANS, or other clinically significant event(s) in association with SUDs and first treatment dose. Participants should be promptly treated upon presentation to the hospital. The participant should be discharged from the hospital per local SoC in managing AEs with the following recommended criteria:

- Absence of fever, defined as a temperature $< 100.4^{\circ}\text{F}$ (38°C) for ≥ 8 hours.
- Absence of any suspected study treatment-related ICANS (any grade).

6.2. Preparation/Handling/Storage/Accountability

Study treatment must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants in the study.

The study treatment administered to the participant must be documented on the treatment accountability form.

Refer to the study materials, such as Investigational Product Preparation Instructions, instructions for use, or, if applicable, to the Package Insert, for all guidance on study treatment preparation, handling, storage and disposal.

The investigator is responsible for ensuring that all study treatment received at the site is inventoried, accounted for throughout the study, stored and disposed of according to the sponsor's instructions, in accordance with the protocol, study manuals and as indicated on the container label.

6.3. Assignment to Study Treatment

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be stratified by ISS staging at screening (I vs. II/III), number of prior lines of therapy (1 vs. ≥ 2) and EMD status at baseline (yes vs. no).

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

6.4. Blinding, Masking

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

6.5. Study Treatment Compliance

Study treatment will be administered as an SC injection by qualified study site personnel and the details of each administration will be recorded in the eCRF (including date, start time, and volume of the injection). Deviation(s) from the prescribed dose regimen should be recorded in the eCRF.

6.6. Dose Modification

Before each dose, the participant will be evaluated for possible toxicities, and clinically significant changes in laboratory results or general physical status that may have occurred. Dose delay is the primary method for managing toxicities related to JNJ-79635322 or teclistamab (Section 6.6.3). Dose reductions are not allowed to manage toxicities related to these treatments.

Any dose adjustment must be overseen by medically qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present). In case a dose delay is necessary, the study treatment will be administered following the below guidelines in Sections 6.6.1 and 6.6.2.

6.6.1. Dose Delay

The criteria for a dose delay of JNJ-79635322 are:

- Ongoing CRS or ICANS (any grade)
- Grade ≥ 1 ataxia, balance disorder, or cerebellar symptoms including cerebellar ataxia, cerebellar syndrome, dyskinesia, dysmetria, gait disturbance, intentional tremor, nystagmus, or dysarthria
- Grade 3 neutropenia ($<0.5 \times 10^9/L$), otherwise Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia or
- Grade 3 non-hematologic toxicities that are clinically significant and do not meet discontinuation criteria outlined in Section 7, with the following exceptions:
 - Grade 3 nausea and Grade 3 vomiting that responds to antiemetic treatment within 7 days.
 - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days.
 - Grade 3 fatigue and Grade 3 asthenia that was present at baseline or that lasts for <7 days.
 - Grade 3 elevations in lipase or amylase without signs or symptoms of pancreatitis.
 - Grade 3 weight loss without clinical sequelae.
 - Grade 3 pain at known disease site (ie, plasmacytoma or bone lesion, etc.).
 - Other isolated Grade 3 laboratory or vital sign abnormalities without clinical consequence which are self-limiting and respond well to supportive therapy within 24 hours.
 - Other Grade 3 laboratory or vital sign abnormalities occurring as part of CRS (Section 6.6.3.1) or ICANS (Section 6.6.3.2) should follow dose guidelines under the respective sections.
- For any Grade 4 non-hematologic toxicities that do not meet discontinuation criteria outlined in Section 7, the dose should be delayed, and restart should be discussed with the sponsor. For the following Grade 4 non-hematologic toxicity situations, dosing should be discussed with the sponsor:
 - A participant remains asymptomatic, requires no significant intervention, and the investigator feels that the participant may derive clinical benefit from continuing to receive therapy.
 - The reported event(s) are transient Grade 4 laboratory abnormalities related to TLS.

Following a dose delay, any non-hematologic toxicity other than CRS, ICANS or weight loss must resolve to Grade ≤ 1 or to baseline before the next administration of JNJ-79635322. For Grade 3 weight loss with clinical sequelae, the clinical sequelae must have resolved, and restart should be discussed with the sponsor. CRS and ICANS must fully be resolved before the next administration of JNJ-79635322.

The criteria for a dose delay of teclistamab are:

Adverse Event	Severity	Action(s)
CRS/ICANS	Grade 1/Grade 2/Grade 3 (First Occurrence)	Withhold teclistamab until CRS/ICANS resolves
	Grade 3 (Recurrent)/Grade 4	Permanently discontinue teclistamab
Non-ICANS neurological toxicity	Grade 1	Withhold teclistamab until neurologic toxicity symptoms resolve or stabilize
	Grade 2/Grade 3 (First Occurrence)	Withhold teclistamab until neurologic toxicity symptoms improve to Grade 1 or less
	Grade 3 (Recurrent)/Grade 4	Permanently discontinue teclistamab
Hematologic Toxicities	ANC $<0.5 \times 10^9/L$	Withhold teclistamab until ANC is $0.5 \times 10^9/L$ or higher
	Febrile Neutropenia	Withhold teclistamab until ANC is $1 \times 10^9/L$ or higher and fever resolves
	Hemoglobin <7.5 g/dL	Withhold teclistamab until hemoglobin is 7.5 g/dL or higher
	Platelet count $<25 \times 10^9/L$ or platelet count between $25 \times 10^9/L$ and $50 \times 10^9/L$ with bleeding	Withhold teclistamab until platelet count is $25 \times 10^9/L$ or higher and no evidence of bleeding
Infections	All grades	During the step-up dosing schedule, withhold teclistamab in participants with active infection
	Grade 3	Withhold teclistamab until infection improves to Grade 1 or less
	Grade 4	Consider permanent discontinuation of teclistamab If not permanently discontinued, withhold subsequent treatment doses until infection improves to Grade 1 or less
Other non-hematologic adverse reactions	Grade 3	Withhold teclistamab until improvement to Grade 1 or less
	Grade 4	Consider permanent discontinuation of teclistamab If not permanently discontinued, withhold subsequent treatment doses until the adverse reaction improves to Grade 1 or less

6.6.2. Treatment Restart After Dose Delay**Dose Delay for JNJ-79635322**

If a dose of JNJ-79635322 is delayed, the following recommendations for restarting therapy should be followed in [Table 10](#):

Table 10: Guidance for Restarting Therapy With JNJ-79635322 After Dose Delay

Last Dose Administered	Duration of Delay from the Last Dose Administered	Action
SUD (5 mg)	More than 8 days	Must contact the sponsor to discuss next step in treatment before any further dosing.
Any full treatment dose (100 mg)	90 days or less	Continue with the planned treatment dose (100 mg)
	More than 90 days	Must contact the sponsor to discuss continuation of treatment and if SUD is required before any further dosing.

Dose Delay for Teclistamab

Except on Day 1 of a cycle, if a treatment dose of teclistamab does not occur within the prespecified window (Table 10), the dose will be considered as skipped and not made up. SUDs of teclistamab cannot be skipped but may be delayed. Following a skipped treatment dose of teclistamab, administration may resume at the next planned dosing date. There must be ≥ 5 days between doses (Table 11).

Table 11: Teclistamab Dose Skips

Study Drug(s)		Cycles	Dosing Frequency	Skip Dose if Dosing Interrupted:	Resume Dosing
Teclistamab	SUDs	Cycle 1	See Table 3	May not be skipped	
	1.5 mg/kg	Cycle 1	Weekly	>2 days from last day of dosing window	Next planned weekly dosing day
	1.5 mg/kg	Cycle 2	Weekly	>3 days from planned dose date	Next planned weekly dosing day
	3 mg/kg	Cycle 3-6 ^a	Q2W	>7 days from planned dose date	Next planned Q2W dosing day
	3 mg/kg	Cycle 7+	Q4W	Not applicable ^a	Not applicable ^b

^a Participants may change to Q4W dosing when in confirmed VGPR or better prior to Cycle 7 per investigator discretion.

^b Teclistamab is given on Day 1 only in Q4W dosing schedule. Day 1 of a cycle cannot be skipped. If teclistamab cannot be given, delay cycle and adjust Day 1 of subsequent cycles accordingly to maintain a 28-day cycle.

If a dose of teclistamab is delayed, therapy should be restarted based on the recommendations below in Table 12.

Table 12: Recommendations for Teclistamab Dosing After Delays in Treatment

Last Dose Administered Prior to Delay	Duration From the Last Dose Administered	Action ^b
Disease evaluations (serum and urine testing) must be performed Q4W (± 7 days) even if drug is interrupted or a cycle is otherwise delayed (Section 8.2).		
SUD1 (0.06 mg/kg)	7 days or less	Continue teclistamab at SUD2 (0.3 mg/kg) ^a Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.
	More than 7 days	Restart teclistamab at SUD1 (0.06 mg/kg) ^a . Administer SUD2 (0.3 mg/kg) ^a ≥ 2 days later. Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.

Table 12: Recommendations for Teclistamab Dosing After Delays in Treatment

Last Dose Administered Prior to Delay	Duration From the Last Dose Administered	Action ^b
Disease evaluations (serum and urine testing) must be performed Q4W (± 7 days) even if drug is interrupted or a cycle is otherwise delayed (Section 8.2).		
SUD2 (0.3 mg/kg)	7 days or less	Continue teclistamab at 1.5 mg/kg treatment dose ^a .
	8 to 28 days	Repeat SUD2 (0.3 mg/kg) ^a . Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.
	More than 28 days	Restart teclistamab at SUD1 (0.06 mg/kg) ^a . Administer SUD2 (0.3 mg/kg) ^a ≥ 2 days later. Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.
Treatment dose (1.5 mg/kg or 3 mg/kg)	62 days or less	Resume planned treatment per SoA.
	63 to 111 days	Restart teclistamab at SUD2 (0.3 mg/kg) ^a . Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.
	More than 111 days	Restart teclistamab at SUD1 (0.06 mg/kg) ^a . Administer SUD2 (0.3 mg/kg) ^a ≥ 2 days later. Then proceed to 1.5 mg/kg ^a treatment dose ≥ 2 days later.

^a Administer pretreatment medications, prior to teclistamab dose and monitor participants accordingly.

^b After the required 1.5 mg/kg dose, resume planned treatment per SoA. Note: If participant's cycle specifies 3 mg/kg as the next scheduled dose after the required 1.5 mg/kg dose above, please defer this dose to Day 1 of the following cycle.

6.6.3. Management Guidelines of Potential Toxicities

Management guidelines for potential toxicities of study treatment are described in the following sections. Trained study staff at the clinic should be prepared to intervene, and resources necessary for resuscitation must be available at the bedside. Appropriate staffing levels should be maintained when multiple participants will receive study treatment at the same time.

If an sARR or CRS occurs, vital signs and laboratory parameters must be monitored at regular intervals until the toxicity has normalized.

6.6.3.1. Cytokine Release Syndrome

Clinical symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachycardia, hypotension, hypoxia, headache, confusion, tremor, and delirium (Lee 2019). Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation.

All AEs except CRS and ICANS will be graded per NCI-CTCAE Version 6.0. CRS and ICANS will be graded based on the ASTCT guidelines (Lee 2019; see Table 14 and Section 10.5, respectively). Symptoms of CRS and ICANS will be graded according to NCI-CTCAE Version 6.0 and also reported in the eCRF.

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. However, treatment for CRS should not be delayed. Cultures and imaging should be obtained; the clinical signs and symptoms should determine which tests are appropriate.

Supportive care for CRS (including but not limited to antipyretic agents, IV fluid support, vasopressors, supplemental oxygen) should be administered according to the clinical manifestations of the participants' illness (see [Table 13](#)). For additional management, please refer to institutional and consensus guidelines ([Rodriguez-Otero 2024](#)). Laboratory testing including daily monitoring of chemistry and hematology assessments and coagulation laboratory tests should be performed; pulmonary, renal, and hepatic function must be monitored closely. Ancillary testing such as B-type natriuretic peptide assessment, echocardiograms, and arterial blood gas should be performed if clinically indicated. Rarely, severe CRS can evolve into a presentation consistent with HLH or MAS that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as interferon- γ and IL-6), and low serum levels of fibrinogen ([Neelapu 2018](#)).

Tocilizumab intervention should be considered in response to a presenting symptom of fever per investigator discretion if infection is not suspected or in the presence of persistent (>24 hours) fever. Early administration of tocilizumab should be considered in participants at high risk of severe CRS (eg, high baseline tumor burden or early fever onset). The use of growth factors, particularly G-CSF and GM-CSF, should be avoided during CRS. Other mAbs targeting cytokines (eg, anti-IL-1 and/or anti-tumor necrosis factor alpha) may be used based on institutional guidelines, especially for cases of CRS that do not respond to tocilizumab or if tocilizumab is unavailable. In the rare event that high-grade CRS with clinical findings overlapping with HLH or MAS occurs (including hyperferritinemia) and remains unresponsive to tocilizumab and corticosteroids, additional therapy, including chemotherapy, may be considered in consultation with the sponsor.

Prophylactic medications (after initial event) must be used as described in [Section 6.1.1](#).

Table 13: Recommendations for the Management of CRS

CRS Grade^a	Presenting Symptoms	Tocilizumab^{b, c}	Corticosteroids
Grade 1	Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$	May be considered. ^e	May be considered.
Grade 2	Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with either: Hypotension responsive to fluids and not requiring vasopressors. Or Oxygen requirement of low-flow nasal cannula ^f or blow-by.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab Q8H as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.

Table 13: Recommendations for the Management of CRS

CRS Grade^a	Presenting Symptoms	Tocilizumab^{b, c}	Corticosteroids
Grade 3^g	Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with either: Hypotension requiring one vasopressor with or without vasopressin. Or Oxygen requirement of high-flow nasal cannula ^f , facemask, non-rebreather mask, or Venturi mask.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab Q8H as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (eg, 10 mg IV Q6H). Continue corticosteroids use until the event is Grade ≤ 1 , then taper over 3 days.
Grade 4^g	Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or Oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab Q8H as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above or administer methylprednisolone 1000 mg IV per day for 3 days per investigator discretion. If no improvement or if condition worsens, consider alternate immunosuppressants. ^h

^a Grading is per [Lee 2019](#) (ASTCT guidelines). All other AEs should be graded using NCI-CTCAE Version 6.0.

^b Refer to tocilizumab prescribing information for details (Actemra USPI 2024; RoActemra SmPC 2025 or labeled biosimilars).

^c If tocilizumab is not available prior to the first dose, dosing may only occur if alternative treatments for CRS are available and after discussion with the sponsor.

^d Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or corticosteroids).

^e Tocilizumab may be considered in participants with Grade 1 CRS who are at high risk of progressing to a higher grade CRS (eg, with comorbidities or high tumor burden), for whom a higher grade CRS would be clinically detrimental (eg, elderly), who are clinically progressing toward a higher grade CRS (eg, blood pressures decreasing, oxygen saturation decreasing), who have high-grade fever >24 hours not responding to supportive measures, or per institutional guidelines.

^f Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min.

^g Refer to Section 7.1 for recurrent events of CRS.

^h mAbs targeting cytokines may be considered based on institutional guidelines for unresponsive CRS.

6.6.3.2. Neurotoxicity and ICANS

Based on the mechanism of action, neurotoxicity, including ICANS, may occur. Neurotoxicity often presents as confusion, delirium, and somnolence with other immuno-oncology agents that cause CRS ([Lee 2019](#)). Early recognition of neurotoxicity is critical to management. Therefore, participants should be monitored for neurotoxicity including, but not restricted to, ICANS: speech disorders, convulsions, motor weakness, seizures, cerebral edema, disturbances in consciousness, confusion, disorientation, and coordination and balance disorders. Participants should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible CNS abnormalities, such as new onset of headache or mental status changes. If neurotoxicity or ICANS events are suspected, the

medical monitor must be consulted. A neurology consultation and evaluation should be considered per investigator discretion.

Neurologic/psychiatric AEs that do not meet criteria for ICANS will be graded per NCI-CTCAE Version 6.0 and managed per institutional guidelines. ICANS events will be graded per the ASTCT guidelines summarized in [Table 14](#), which also includes management recommendations ([Lee 2019](#)). ICANS events will be captured as an AESI (Section 8.4.6.3). Guidelines for the management of increased intracranial pressure/cerebral edema are presented in [Table 15](#).

Table 14: ASTCT Grading and Recommended Management of ICANS

ICANS Grade ^a	Presenting Symptoms ^b	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9 ^c or depressed level of consciousness ^d : awakens spontaneously.	Management of CRS as appropriate per Table 13 . Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion. Consider dexamethasone ^e .
		Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score-3-6 ^c or depressed level of consciousness ^d : awakens to voice.	Administer tocilizumab ^f per Table 13 for management of CRS. If no improvement after starting tocilizumab ^f , administer dexamethasone ^e 10 mg IV Q6H if not already taking other corticosteroids. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.	Administer dexamethasone ^e 10 mg IV Q6H. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.
		Consider nonsedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	

Table 14: ASTCT Grading and Recommended Management of ICANS

ICANS Grade^a	Presenting Symptoms^b	Concurrent CRS	No Concurrent CRS
Grade 3^g	ICE score-0-2 ^c or depressed level of consciousness ^d : awakens only to tactile stimulus, or seizures ^d , either: - any clinical seizure, focal or generalized, that resolves rapidly, or - nonconvulsive seizures on electroencephalogram that resolve with intervention, or increased ICP: focal/local edema on neuroimaging ^d .	Administer tocilizumab ^f per Table 13 for management of CRS. In addition, administer dexamethasone ^e 10 mg IV with the first dose of tocilizumab ^f and repeat dose Q6H. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.	Administer dexamethasone ^e 10 mg IV Q6H. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.
		Consider nonsedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 4^g	ICE score-0 ^c or depressed level of consciousness ^d either: - participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or - stupor or coma, or seizures ^d , either: - life-threatening prolonged seizure (>5 min), or - repetitive clinical or electrical seizures without return to baseline in between, or motor findings ^d : - deep focal motor weakness such as hemiparesis or paraparesis, or increased ICP/cerebral edema ^d , with signs/symptoms such as: - diffuse cerebral edema on neuroimaging, or - decerebrate or decorticate posturing, or - cranial nerve VI palsy, or - papilledema, or	Administer tocilizumab ^f per Table 13 for management of CRS. As above or consider administration of methylprednisolone 1000 mg IV per day with first dose of tocilizumab ^f and continue methylprednisolone 1000 mg IV per day for 2 or more days, per investigator discretion.	As above or consider administration of methylprednisolone 1000 mg IV per day for 3 days; if improves, then manage as above.
		Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of increased ICP/cerebral edema, refer to Table 15 for additional management guidelines.	

Table 14: ASTCT Grading and Recommended Management of ICANS

ICANS Grade ^a	Presenting Symptoms ^b	Concurrent CRS	No Concurrent CRS
	Cushing's triad.		

^a Grading per ASTCT guidelines (Lee 2019). All other neurologic AEs should be graded using NCI-CTCAE Version 6.0.

^b Management is determined by the most severe event not attributable to any other cause.

^c If the participant is arousable and able to perform mental status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (ICE tool; see Table 19).

^d Attributable to no other cause.

^e All references to dexamethasone administration are dexamethasone or equivalent.

^f If tocilizumab is not available prior to the first dose, dosing may only occur if alternative treatments for CRS are available and after discussion with the sponsor.

^g Refer to Section 7.1 for recurrent events of neurotoxicity.

NOTE: By convention, Grade 5 ICANS is defined as death due to ICANS in which another cause is not the principal factor leading to this outcome.

NOTE: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a participant with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

Table 15: Guidelines for the Management of Increased Cranial Pressure/Cerebral Edema

- Elevate head of participant's bed to an angle of 30 degrees. - If participant has Ommaya reservoir, drain cerebrospinal fluid to target opening pressure of <20 mm Hg. - Hyperventilation to achieve target PaCO₂ of 28 to 30 mm Hg but maintained for no longer than 24 hours. - Consider neurology and/or neurosurgery consultation. - Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended above. - Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below): - Mannitol: initial dose 0.5 to 1 g/kg; maintenance at 0.25 to 1 g/kg Q6H while monitoring metabolic profile and serum osmolality Q6H; withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40. - Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50 to 75 mL/h while monitoring electrolytes Q4H, and withhold infusion if serum sodium levels reach ≥155 mEq/L. - For participants with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed. - Consider IV anesthetics for burst-suppression pattern on electroencephalography.

ICANS must fully resolve before the next administration of JNJ-79635322.

For Grade ≥1 ataxia, balance disorder, cerebellar symptoms including cerebellar ataxia, cerebellar syndrome, dyskinesia, dysmetria, gait disturbance, intentional tremor, nystagmus, and dysarthria, JNJ-79635322 must be withheld and the study team notified. For these events, treatment with JNJ-79635322 should only be resumed after discussion with medical monitor.

For taste-related events (eg, dysgeusia, hypogeusia), refer to Section 6.6.3.6.

Further therapy with JNJ-79635322 may be considered per Section 6.6 after recovery to baseline or Grade ≤ 1 for participants who experience a first Grade 3 neurotoxicity event.

Participants who experience a recurrent Grade 3 neurotoxicity or any Grade 4 neurotoxicity must permanently discontinue study treatment (see Section 7.1).

6.6.3.3. Infections

Infection is frequently reported in patients with MM due to both disease and treatment-related factors causing hypogammaglobulinemia and immunosuppression (Raje 2022; Terpos 2015). BCMA-directed therapies cause depletion of B cells, resulting in hypogammaglobulinemia, and may increase the risk of infection (Mazahreh 2023). Infection is a known potential risk for participants receiving JNJ-79635322 (see Section 2.3 and the IB).

6.6.3.3.1. Infection Prophylaxis

Prophylactic measures per institutional guidelines are recommended due to the susceptibility of patients with MM to infections (Drayson 2019; Mohyuddin 2020). These include:

- Prophylactic Ig replacement (see Section 6.6.3.4)
- Prophylactic administration of antibiotics and antivirals per institutional guidelines
- *Pneumocystis carinii* or *P. jirovecii* pneumonia prophylaxis
- Prophylaxis for herpes zoster reactivation
 - Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after the start of administration of study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir, famciclovir, or valacyclovir.

In addition to the above, see permitted therapies for management of cytopenias in Section 6.6.3.12.

6.6.3.3.2. Infection Management

See guidance regarding non-hematologic AEs for which dosing should be delayed for JNJ-79635322 in Section 6.6.1.

It is recommended that empirical broad-spectrum antibiotics are commenced while performing diagnostic tests in participants with febrile neutropenia or signs/symptoms of infection per institutional guidelines (Raje 2022).

Targeted antimicrobial agents are recommended depending on clinical, radiological, and microbiological findings (Raje 2022).

For participants with persistent fever with undetermined cause, consider testing for opportunistic infections including new onset or reactivation of viral infections such as herpesviruses (eg, herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus), parvovirus B19, and adenovirus. Diagnostic imaging should be considered as clinically indicated.

See guidance regarding requirements for restarting therapy pertinent to infection in Section 6.6.2.

6.6.3.3.3. HBV/HCV/HIV Reactivation

HBV reactivation is a potential risk of study treatment. Primary antiviral prophylaxis is permitted per institutional guidance. HBV-DNA testing by PCR is mandatory for participants at risk for HBV reactivation (for timing of testing, see Section 1.3 and Section 10.6). For participants who are diagnosed with HBV reactivation (ie, HBV-DNA becomes detectable) while on treatment, suspend treatment and any steroids. Manage participants according to current clinical guidelines and consider consulting a hepatitis disease expert as clinically indicated. Resumption of study treatment with concomitant antiviral prophylaxis per SoC in participants whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV and approved by the sponsor.

For participants who are diagnosed with HCV or HIV reactivation (ie, HCV or HIV-RNA becomes detectable) while on treatment, suspend study treatment and any steroids and institute appropriate treatment. Resumption of study treatment should be discussed with physicians with expertise in managing HCV or HIV and approved by the sponsor.

6.6.3.3.4. Vaccinations

Vaccination (as per institutional guidance for MM) is allowed (including annual influenza, respiratory syncytial virus, *Streptococcus pneumoniae* [pneumococcal vaccine], recombinant herpes zoster, and inactivated SARS CoV-2 vaccines); however, some types of vaccines (eg, live, attenuated) are not permitted (see Section 6.9.3). Vaccination with live, attenuated virus vaccines is not permitted within 4 weeks prior to the first dose of study treatment, during treatment, and within 90 days after the last dose of study treatment. Note that antibody responses to vaccines may be suboptimal during study treatment (Ariza-Heredia 2015) and that the expected adverse reactions to vaccines (eg, fever) and CRS may have a similar presentation.

6.6.3.4. Hypogammaglobulinemia

Hypogammaglobulinemia is an important driver of increased infection risk for MM patients. Bispecific antibodies used for treatment of MM have led to profound and prolonged hypogammaglobulinemia. Additionally, patients may have baseline hypogammaglobulinemia at the time of initiation of therapies (Mohan 2023).

For all participants, the following guidance should be considered:

- Prophylactic Ig replacement should be considered. It could be initiated prior to first dose of study treatment (eg, during screening). Alternatively, initiate replacement therapy as early as possible during treatment regardless of IgG levels and regardless of presence of infections per institutional or regional guidance (Rodriguez-Otero 2024; Lancman 2023).
 - Due to the potential for reactions from Ig replacement therapy, it is recommended to be avoided for a minimum of 48 hours after each SUD and also after the first treatment dose of JNJ-79635322 or teclistamab, as well as during any event of CRS.

- If a participant is not receiving prophylactic Ig replacement, it should start as soon as hypogammaglobulinemia is identified (IgG levels <400 mg/dL) regardless of active or history of infection and replacement should be used to maintain serum IgG levels $\geq$ 400 mg/dL (Rodriguez-Otero 2024; Lancman 2023). If a participant is hypogammaglobulinemic (IgG levels <400 mg/dL) during screening, Ig replacement therapy administration should be considered prior to C1D1 or as soon as feasible.
- Where applicable (IgG heavy-chain disease type), assessments to calculate the true IgG level should be considered by subtracting the monoclonal component IgG from the total IgG as a pragmatic approach to determine the underlying non-paraprotein IgG level (Mohan 2023; Giralt 2023).
- It is recommended to administer Ig (ie, IVIg 0.4 g/kg every 3 to 6 weeks). After reaching a steady state, IgG levels should be measured at least Q3M on treatment and for at least 6 months following last dose of study treatment and as clinically indicated (Hayden 2022; Ludwig 2023).

For additional guidance, refer to National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Multiple Myeloma, version 5.2026.

6.6.3.5. Immune-mediated Toxicity

Continuous, careful monitoring, and timely management of immune-mediated AEs may help to mitigate more severe toxicity. Symptomatic and best supportive care measures for specific potential immune-mediated AEs should be initiated as soon as clinically indicated and should follow the institutional guidelines. These treatments may include corticosteroids or other immune suppressive agents, or both as required for the specific immune-mediated AEs. Bone pain associated with tumor flare may occur during early doses and may be associated with an immune-mediated mechanism. Supportive care including steroid and pain management can help manage bone pain.

6.6.3.6. Oral Toxicity

In clinical studies with JNJ-79635322, oral toxicity has typically manifested as dysgeusia, dry mouth, dysphagia, and weight loss. These events are often low-grade; however, over time, significant weight loss may result. Initial workup may include evaluation for active infections (ie, herpes simplex virus, thrush) with appropriate treatment. Symptomatic management may include mouth rinses (salt water, corticosteroid liquid formulations), nutrition consult, pain management as indicated, and possibly a short course of oral corticosteroids in consultation with the sponsor. Refractory symptoms may require further evaluation by an ear, nose, and throat or gastrointestinal specialist.

6.6.3.7. Rash

A variety of rashes can be observed in participants treated on clinical studies, ranging from local injection-site erythema to generalized rashes. It is unknown if these rashes are mediated by target expression. Rashes have been seen in patients treated with JNJ-79635322. Rashes can appear with early doses or be a late manifestation (beyond the first 2 doses) and should be managed per institutional guidelines. It is important for site staff to recognize rashes on the body that are distinct

from injection-site reactions. Monitoring of rash progression is critical and early intervention, including treatment with systemic corticosteroids, may be necessary. Rashes occurring with the first 2 doses should be managed more aggressively with topical corticosteroids and early consideration of a short course of oral corticosteroids to reduce the risk of rash progression (Table 16). Rashes that have not responded to treatment should be evaluated by a dermatologic consult. If a rash occurs, a skin biopsy and photographs (Section 8.3.10) may be obtained for sponsor review.

Table 16: Management of Rash

For guidelines for delaying a dose, refer to Section 6.6.1	
Grade 1-2	Immediately: Symptomatic therapy (eg, antihistamines, topical corticosteroids, oral corticosteroids) Persistence $\leq$ 2 weeks or recurrence: consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics Improvement to $\leq$ Grade 1: taper corticosteroids over at least 4 weeks Worsening to $>$ Grade 2: treat as Grade 3-4
Grade 3-4	Immediately: consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics Improvement to $\leq$ Grade 1: taper corticosteroids over at least 4 weeks
General	Participants on IV corticosteroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

6.6.3.8. Nail Dysfunction

Nail dysfunction, including brittle nails, cracking nails, painful nails, and loss of nails on both hands and feet, has been seen in multiple participants dosed with JNJ-79635322 in clinical studies. For nail toxicity, good hygienic practices should be followed (Section 2.3). Nail changes are often a late manifestation (beyond the first 2 doses) and symptomatic management with nail soaks, topical moisturizers, and topical corticosteroids is recommended. Nail complications that persist should be evaluated by a dermatologic consult.

6.6.3.9. Systemic Administration-related Reactions

sARRs may occur with SC administration. Participants who experience sARRs that manifest as wheezing, flushing, hypoxemia, fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension, or other symptoms should have the symptoms managed according to the recommendations provided in Table 17.

Prophylactic medications (after initial event) must be used as described in Section 6.1.1. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids), as appropriate.

Table 17: Guidelines for the Management of sARRs

NCI-CTCAE Grade	Intervention
Grade 1 or Grade 2 Mild or moderate reaction: Requires therapy or administration interruption but responds promptly to symptomatic treatment	Interrupt study treatment administration (if possible): Start IV fluids; give diphenhydramine 25 mg (or equivalent) IV, paracetamol 650 to 1000 mg (acetaminophen), or both; consider corticosteroids and bronchodilator therapy; monitor participant closely until recovery from symptoms. Symptoms recur: Stop study treatment administration; administer diphenhydramine 25 mg IV and monitor participant until resolution of symptoms. The amount of study treatment administered must be recorded on the eCRF. Treatment re-challenge at next scheduled dose at the discretion of investigator if the participant has no further symptoms in the interval.
Grade 3 or Grade 4^a Severe reaction Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of administration); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: life-threatening pressor or ventilator support indicated	Stop study treatment administration (if possible): Start IV saline infusion. Recommend the following treatment and any other therapies deemed necessary to manage the event: bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 25 mg IV with methylprednisolone 100 mg IV (or equivalent). Investigators should follow institutional guidelines for the treatment of anaphylaxis. Monitor until medically stable, per the investigator's medical judgment. Hospitalization: see Section 6.1.3 for hospitalization requirements. Discontinuation of treatment: See Section 7.1 for details.

^a Refer to Section 7.1.2 for recurrent events of sARR.

6.6.3.10. Injection-site Reactions

SC administration of any medication can be associated with localized injection-site reactions including, but not limited to, induration and erythema. Injection-site reactions should be managed per institutional guidelines.

6.6.3.11. Tumor Lysis Syndrome

Participants should be monitored for evidence of TLS. Management of TLS, including hydration, rasburicase and correction of electrolyte disturbances, such as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia, is highly recommended, as well as consideration for nephrology consultation. It is also recommended that high-risk participants, ie, those with a high tumor burden (a participant with $\geq 60\%$ PC infiltrate on the bone marrow biopsy or aspirate, whichever is higher, or a participant with multiple EMD sites or plasmacytomas), be treated prophylactically in accordance with local standards (eg, hydration; allopurinol 300 mg daily and medication to increase urate excretion).

6.6.3.12. Cytopenias

A study participant's hematological parameters should be closely monitored. Supportive care (eg, blood and thrombocyte transfusions, G-CSF for neutropenia) should be provided according to institutional guidelines. During periods of CRS, G-CSF and GM-CSF should be limited when possible.

6.7. Continued Access to Study Treatment After the End of the Study

At the end of their participation in the study, participants who are still on study treatment as per protocol, will be able to receive continued access until JNJ-79635322 or teclistamab is commercially available and reimbursed for the appropriate therapeutic indication, or available from another source.

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information becomes available during the study or program.

6.8. Treatment of Overdose

No experience with overdose of JNJ-79635322 in clinical studies is available. For any overdose involving JNJ-79635322 or teclistamab, best supportive care measures should be administered according to an institution's SoC and in ongoing consultation with the sponsor.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment must be interrupted.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-79635322 or teclistamab can no longer be detected systemically (at least 30 days after last dose).
- Obtain a serum sample for PK analysis within 8 days from the date of the last dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the details of the overdose in the eCRF (eg, quantity of the excess dose, the number of excess doses, etc).

6.9. Prior and Concomitant Therapy

All prior lines of antimyeloma therapy will be recorded separately and in detail at screening, including information on duration of treatment, best response to the regimen, and date of PD (if applicable).

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed in Section 6.9.3. All medications (including prescriptions or over-the-counter products, and transfusions of blood products) different from the study treatments must be recorded in the appropriate section of the eCRF throughout the study, beginning with the signing of the ICF, until 30 days after the last dose of study treatment(s) or until the start of subsequent systemic antimyeloma treatment, if earlier.

This includes any concomitant therapies and any medications used to treat or support AEs, SAEs, or conditions reported as medical history. After this reporting window, only concomitant therapies to treat AEs that are considered related to the study medication should be reported until the end of study. Recorded information in the eCRF will include a description of the type of the drug, dose schedule, route of administration, dates of use, and its indication.

6.9.1. Supportive Medications

Participants are to receive full supportive care during the study. The following are examples of supportive therapies that may be used during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional guidelines and as deemed necessary by the investigator.
- Bisphosphonates are permitted as part of supportive care. Participants who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. If clinically indicated, participants may initiate bisphosphonate therapy as soon as possible during screening and no later than the end of Cycle 1. After Cycle 1, investigators should not prescribe bisphosphonates to participants who have not received the medication before, unless it has been discussed with the sponsor and there is no sign of PD. Use of bisphosphonates should then continue throughout the Treatment Phase until PD is established. In the case of severe AEs, such as hypercalcemia, bisphosphonates may be administered as clinically indicated, according to institutional guidelines and as deemed necessary by the investigator.
- Growth factor support, erythropoietin-stimulating agents, platelet-stimulating factor, and transfusions are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local standards of care. G-CSF and GM-CSF treatment are to be avoided during CRS.
- Infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice (See Section 6.6.3.3).
- Ig replacement (see Section 6.6.3.4).
- Corticosteroids used as pretreatment or post-treatment medication for the administration of study treatment are permitted, as noted in Table 7, Table 8, and Table 9.
- Vaccinations (see Section 6.6.3.3.4).
- Best supportive care to prevent potential toxicities noted in Section 6.6.3.

6.9.2. Subsequent Antimyeloma Therapy

Participants who discontinue study treatment for reasons other than PD should not start subsequent antimyeloma therapy until PD is observed. If the investigator deems it is in the best interest of a participant to start subsequent antimyeloma therapy in the absence of PD per IWMG criteria, this decision should be discussed with the sponsor for approval prior to the start of the desired therapy.

All efforts should be made to confirm PD per IMWG criteria prior to the start of subsequent antimyeloma therapy.

After confirmation of PD, subsequent therapy is left to the investigator's discretion. All lines of subsequent antimyeloma therapy should be recorded in the eCRF. The start and end date(s) and date(s) of progression and the best response of therapy should be documented in the eCRF, if available.

6.9.3. Prohibited Therapies and Recommended Restrictions

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

- Any chemotherapy, anticancer immunotherapy (other than study treatment), experimental therapy, and radiotherapy (except as noted below).
- Continuation of the study treatment after emergency orthopedic surgery or radiotherapy is allowed only in the absence of PD and after consultation with and approval by the sponsor. If delay of systemic therapy is not appropriate, localized emergent radiotherapy may be provided for pain control or for stabilization of an extensive bone lesion at high risk of causing pathologic fracture or damage to surrounding tissues. The circumstances must be reviewed by the sponsor to determine whether the study treatment may be continued.
- Systemic corticosteroids in excess of 10 mg daily of prednisone (or equivalent) for more than 14 days are prohibited, other than glucocorticoids that are part of the study design (see Section 6.1.1 and Section 6.1.2) and corticosteroids for the management of AEs where no other treatment options are available and in consultation with the sponsor. For medically urgent events (eg, life-threatening cord compression), where discussion with sponsor may delay appropriate medical treatment, corticosteroids may be administered with sponsor notification afterwards.
- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbating potential subclinical myeloma-related kidney disease.
- The use of IV contrast infusions should be avoided to prevent myeloma-related kidney disease. If administration of IV contrast is necessary, then adequate precautions, including hydration, are indicated.
- Routine transfusions should not be given on study treatment administration days.
- The use of transdermal patches at the injection site must be avoided.
- For participants receiving warfarin, investigators should consider switching from warfarin to a different anticoagulant. For participants who cannot switch to a different anticoagulant and who experience CRS, coagulation parameters should be monitored closely during a CRS event and until CRS symptoms resolve.
- Live attenuated vaccines (see Section 6.6.3.3.4).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

If a participant discontinues study treatment for any reason before the end of the Treatment Phase, then the EoT and post-treatment assessments must be obtained and scheduled assessments off study treatment should be continued. Participants will continue in the Pre-PD or Post-PD Follow-up schedule (see SoA in Section 1.3) depending on their PD status at the time of treatment discontinuation. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant.

7.1.1. JNJ-79635322 or Teclistamab Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment.
- Investigator decision (as they believe it is in the best interest of the participant to discontinue study treatment).
- The participant becomes pregnant.
- The participant has recurrent Grade 3 or any Grade 4 CRS (Section 6.6.3.1 and Section 10.5).
- The participant has recurrent Grade 3 or any Grade 4 neurotoxicity (Section 6.6.3.2 and Table 14).
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue all study treatment.
- The participant receives concurrent (non-protocol) systemic antimyeloma treatment (emergency orthopedic surgery or radiotherapy is permitted).
- The participant experiences a second primary malignancy that cannot be treated by surgery alone. Participants who require radiation therapy or hormonal therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the sponsor and review of data, continuation is agreed upon.
- The participant has an intercurrent illness that prevents further administration of study treatment.

7.1.2. Discontinuation of JNJ-79635322

- The participant has recurrent Grade 3 or any Grade 4 sARR (Section 6.6.3.9 and Table 17).

7.1.3. Discontinuation of Teclistamab

- The participant has first occurrence of Grade 3 CRS with duration longer than 48 hours.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent

When a participant withdraws consent as described on the ICF by the participant, further data collection will be limited to what the participant agreed to. In such case, the investigator must discuss the different types for alternative follow-up, should the participant be agreeable to this. Details regarding these alternative contacts must be properly documented in source records including responses by participants.

7.2.1. Withdrawal From the Use of Study Samples

The participant may withdraw consent for use of study samples for compatible scientific research not required by the protocol. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of sample retention are presented in the ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, attempts should be made prior to study entry to obtain contact information from each participant, eg, 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, despite all reasonable efforts documented in the participant's medical records. Reasonable effort includes, where possible, 3 telephone calls, emails or messaging apps, a certified letter to the participant's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit.

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.

Site personnel will attempt to collect the OS status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. The site may engage a third party to search public sources for vital status information. If vital status is determined as deceased, this will be documented. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General/Baseline Procedures

Overview

The SoA summarizes the frequency and timing of all assessments applicable to this study (Section 1.3).

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples. This total blood volume is considered to be acceptable based upon the recommendations by the Dana Farber/Harvard Cancer Center Guidance (DF/HCC 2021), which indicates a maximum of 10.5 mL/kg (52 kg person) or 550 mL, whichever is smaller, over any 8-week period.

Home Health Care and Telemedicine Visits

Home health care and telemedicine visits may be implemented by, or with approval from, the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy and for participants for whom there is no safety concern.

Participants for whom there is no safety concern may have home health care and telemedicine (conducted via phone or video conference) visits.

Study procedures such as PRO collection, ECOG assessment, AE and concomitant medication reporting, review of body systems, and collection of information on the participant's current health status may be performed with home health care and telemedicine visits. Study procedures such as laboratory sample collections for efficacy and safety may be performed with home health care visits (see SoA in Section 1.3). All assessments should be followed with in-person examination, as applicable.

If local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. Source documentation and, if applicable, the appropriate eCRFs should be completed and detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by participant or delegated in-home nursing).

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided.

8.2. Efficacy Assessments

Disease evaluations will be performed as specified in the SoA (Section 1.3). Disease evaluation assessments and sample collections that are scheduled for treatment days should be collected before the study treatment is administered.

Response assessments will be based on the IMWG response criteria. Responses or PD will be evaluated by investigators.

All response assessments and assessment of MRD negativity will be performed based on results from a central laboratory. Local laboratory data can only be used in exceptional circumstances when central laboratory data are not available, and should be discussed with the sponsor on a case-by-case basis.

Disease evaluations will continue until confirmed PD or the start of subsequent antimyeloma therapy, whichever occurred earlier (see section 6.9.2). The study sites are requested to notify the sponsor as soon as possible if a participant is diagnosed with PD (including confirmation by repeat assessment if required per the IMWG criteria) and provide documentation of the PD. The sponsor's medical monitor must review the data provided to confirm that the IMWG criteria for PD have been met. If PD is confirmed by sponsor while the participant is still on study treatment, then the participant will discontinue study treatment, complete the EoT visit, and enter the Post-PD Follow-up Phase.

If PD has not occurred at the time of the EoT visit, disease evaluations must continue at Q4W intervals from the previous efficacy assessment until Cycle 12 if the participant has achieved CR, then Q8W until PD occurs. If the participant has not achieved CR at Cycle 12, then DEs must continue Q4W until CR is achieved, followed by Q8W thereafter. In the Post-PD Follow-up Phase, required assessments should be done at Q4M intervals from the date of confirmed PD.

8.2.1. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be analyzed by a central laboratory. If the study site also obtained results from a local laboratory for the same date, the central laboratory results must be used for the assessment of response.

Blood and 24-hour urine samples will be collected consistent with IMWG recommendations and as specified in the SoA (Section 1.3) until the development of confirmed PD.

8.2.2. Bone Marrow Examination

Bone marrow aspirate will be performed for exploratory biomarkers, including molecular markers, clinical assessments, and MRD (Table 18; Section 1.3).

Table 18: Bone Marrow Testing

Time Point	Notes	Local Testing	Central Testing
Screening	Disease characterization (morphology and PC clonality) and cytogenetics by FISH, and molecular markers. If an evaluation of bone marrow was done as part of SoC within 42 days before enrollment, no need to repeat for morphology and FISH; however, fresh aspirate sample needs to be obtained and sent to central laboratory for molecular markers. IHC^a (requires exact κ/λ ratio from analysis of >100 PCs) or 2- to 4-color (at least) flow cytometry are acceptable methods to evaluate PC clonality.	Evaluate BMPC% Evaluate clonality of BMPCs by flow cytometry or IHC Evaluate cytogenetics by FISH^b	FISH ^b Molecular Markers
At time of suspected CR/sCR	If these time points occur within 1 month of another bone marrow aspiration, a repeat bone marrow aspiration will not be requested. IHC^a (requires κ/λ ratio from analysis of >100 PCs) or 2- to 4-color (at least) flow cytometry are acceptable methods to evaluate PC clonality.	Evaluate BMPC% to confirm CR Evaluate clonality of BMPCs by flow cytometry or IHC in the bone marrow to confirm sCR	
For participants with suspected or confirmed CR or sCR, additional samples will be collected 12 months, 36 months and 60 months post C1D1 (± 30 days).		If sCR criteria are not already met, repeat evaluation of clonal BMPCs (ie, flow cytometry or IHC) with subsequent bone marrow testing	MRD
PD		Evaluate BMPC% Evaluate clonality of BMPCs by flow cytometry or IHC	Molecular Markers ^c

^a IHC includes IF methods (immunostaining with fluorophore-conjugated antibodies and microscopic examination). IF should not be confused with flow cytometry techniques.

^b In case the local laboratory cytogenetics (FISH) results are missing, inconclusive or incomplete, and a prescreening (within 42 days before enrollment) FISH result is also not available, a fresh bone marrow aspirate for central laboratory FISH testing will be collected during screening.

^c Collection of molecular markers at PD will be required for Arm A only.

NOTE: Samples collected outside of the specified window will be retained for potential analysis.

8.2.3. Imaging Assessments for Bone Lesions and Extramedullary Disease

Whole-body imaging must be performed at screening for baseline disease staging. If possible, functional imaging techniques should be used and will be interpreted locally. Baseline staging will be done to describe the presence and extent of lytic bone lesions, as well focal lesions and soft tissue plasmacytomas (both para-skeletal or extramedullary).

The following modalities for functional imaging are allowed:

- Whole-body DWI-MRI
- Whole-body PET/CT with diagnostic CT component

Measurable sites of EMD and para-skeletal plasmacytomas will be documented and measured through bidimensional measurements on MRI or the diagnostic CT component of the PET/CT images. Additionally, Deauville score (PET) or response assessment category scale (DWI-MRI) should be documented for the bone marrow, focal lesions, and para-skeletal or extramedullary plasmacytoma to facilitate the harmonization of the clinical data with evolving imaging-based response criteria. Imaging will also be used to confirm the presence or absence of EMD (yes or no) for stratification.

If functional imaging modalities are not available as SoC, a whole-body low-dose CT scan can be performed if there is no contraindication to the use of IV contrast for the documentation of soft tissue plasmacytomas. In this case the CT scan result will be used to document existence of lytic bone disease as well as location and size (conventionally through bidimensional measurements) of sites of known extramedullary or para-skeletal plasmacytomas.

Subsequent imaging assessments will be performed as specified in the SoA (Section 1.3), with different scheduling requirements for participants with baseline soft tissue plasmacytoma and without baseline soft tissue plasmacytomas.

Caution should be exercised with the interpretation of any imaging results within the first 3 months of treatment to ensure that observations of increased metabolic activity are not considered as signs of PD while these could be indications of eg, a tumor flare after therapy, bone regeneration processes, or other biological activity not related to progression of the MM. The modality used for screening should be maintained for any subsequent imaging procedures and, if indicated, to evaluate for possible PD. If the diagnosis of PD is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. If changes are equivocal, then repeat imaging is needed in 1 to 3 weeks.

Results obtained from functional imaging techniques will also be used to determine the MRD status by imaging per the IMWG criteria.

8.2.4. Patient-reported Outcomes

- The PRO instruments will be provided in the local language in accordance with local guidelines.

- The PRO instruments will be available for regulators and for IRB/IEC submissions and will be provided separately in a companion manual with the instruments that will be submitted with the protocol.
- PRO instruments should be completed in the order presented in the SoA (Section 1.3) by the participant before any clinical tests (other than blood draws), procedures, or other consultations that would influence his or her perceptions of their current health state.
- PROs should be completed before the first SUD, before the first treatment dose (which is on C1D1 for Treatment Arm A and C1D5 for Treatment Arm B), on Day 1 of Cycles 2 to 6 and then on Day 1 of every other cycle starting as of C8D1 up to C24D1; then on Day 1 of every 4 cycles after Cycle 24 (even for participants who completed treatment), and at the EoT visit. Continue until a planned analysis shows statistical significance for the OS endpoint. While participants are receiving study drug, PROs should be administered on Day 1 of each dosing cycle or within 7 days prior to Day 1. For participants who discontinue study treatment, continue PRO assessments as follows, regardless of PD status: Q4W (± 7 days) up to 6 months since first dose, followed by Q8W (± 14 days) through 24 months; followed by Q4M (± 14 days), to align PRO collection with the timepoints associated with dosing specified in the SoA (Section 1.3).

The participant's symptoms, functioning, and general well-being will be captured using PRO instruments:

- MySIm-Q
- EORTC QLQ-C30
- EQ-5D-5L
- PGI-S
- EORTC IL46

If a participant requires assistance completing the PRO instruments, a study coordinator may assist by reading the questions and response options verbatim and should not prompt the participant in selecting their response. At completion, the study coordinator should verify that the questionnaires are completed in full or document the reason for missing information. Only study coordinators that have completed the PRO completion training will be permitted to assist participants in completing the PRO instruments.

PRO and AE data will not be reconciled with one another.

All PRO instruments will be on electronic forms and will continue to be administered even if subsequent antimyeloma therapy is begun. A backup method for PRO data collection will be provided for the participants if they do not return to the site for their scheduled visit or if the visit is conducted by home healthcare or telehealth.

8.2.4.1. MySIm-Q

The MySIm-Q is a disease-specific PRO assessment with established content validity for patients with RRMM and NDMM. It is included to be complementary to the EORTC QLQ-C30. It includes

17 items resulting in a symptom subscale and an impact subscale. The recall period is the “past 7 days” and responses are reported on a 5-point verbal rating scale.

8.2.4.2. EORTC QLQ-C30

The EORTC QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea/vomiting), and 5 single symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea) and a single impact item (financial difficulties). Refer to [Wisløff 1996, 1997](#) for further information.

8.2.4.3. EQ-5D-5L

The EQ-5D-5L is a self-administered, generic health status measure, consisting of a descriptive system and a visual analogue scale (EQ-VAS). The descriptive system covers 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each with 5 levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems) with higher scores indicating worse HRQoL, providing a descriptive health state profile which can be linked to a country/territory-specific value set to provide a single summary index value (sometimes referred to as utility score). The EQ-VAS asks respondents to rate their own health on a scale from 0 to 100, recording the respondent’s overall HRQoL. The EQ-5D-5L has a recall period of ‘today’ and can generally be completed in 2 to 3 minutes ([EQ-5D-5L User Guide 2025](#)).

8.2.4.4. PGI-S

The PGI-S is a 2-item questionnaire that assesses severity of the participant’s symptoms and impacts of their symptoms, respectively, on a 5-point verbal rating scale, at the time of completing the PRO measure. Response on the PGI-S will be used as an anchor to determine meaningful change thresholds and interpretation of results of the MySIm-Q.

8.2.4.5. EORTC IL46

The EORTC IL46 consists of one single question that measures global impression of burden due to treatment-related symptoms. The response options range from “not at all” to “very much” on a 4-point scale.

8.2.5. Symptomatic Worsening of Multiple Myeloma

To assess clinical benefit of JNJ-79635322, the first occurrence of a worsening of one or multiple symptoms of MM, will be collected in the eCRF. This event can occur at any point during the study (either before or after IMWG disease progression) and will be collected from time of enrollment until end of study.

8.3. Safety Assessments

Timing of assessments are specified in the SoA (Section [1.3](#)).

AEs will be reported and followed by the investigator as specified in Section [8.4](#).

Any clinically relevant changes occurring during the study must be recorded in the AE section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until 30 days after last dose or until start of subsequent therapy, if earlier.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

A complete physical examination will be conducted at screening. As part of the physical examination, the investigator will perform a baseline neurological examination to document any pre-existing neurological conditions. Thereafter, all other examinations will be symptom-directed physical examinations to be conducted per the SoA (Section 1.3).

8.3.2. Vital Signs

Temperature, body weight, pulse/heart rate, respiratory rate, blood pressure (systolic and diastolic), and SpO₂ will be assessed as specified in the relevant SoA (Section 1.3). 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 phone). Pulse/heart rate and blood pressure will be assessed with an automated device, if not available, manual techniques are allowed. Body weight will be measured as specified in the SoA (Section 1.3). Any clinically relevant abnormality at baseline must be reported under medical history and any clinically relevant change while on study must be reported as an AE.

8.3.3. Electrocardiograms

12-lead ECGs will be collected according to the SoA (Section 1.3). During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phone). 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.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected according to the SoA (Section 1.3). See Section 10.1 for additional information and testing. The investigator must review the laboratory results, document this review, and record any clinically relevant changes (eg, laboratory abnormalities leading to an action taken regarding study drug, cycle delay or treatment discontinuation) occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Any additional chemistry and hematologic laboratory assessments supporting the start and end dates of an AE should be reported in the eCRF.

8.3.5. Hepatitis Testing

8.3.5.1. Hepatitis B Virus Testing

HBV serology including surface antigen (HBsAg), surface antibody (anti-HBs) and core antibody (anti-HBc or HBcAb) is required at screening per SoA (Section 1.3).

HBV serology is not required at screening if this was performed as part of SoC within 3 months prior to randomization. The HBV screening guide in Section 10.6 will be used to determine participant eligibility for the study.

8.3.5.2. Hepatitis C Virus Testing

HCV serology (anti-HCV antibody) testing is required at screening per SoA (Section 1.3).

HCV antibody testing is not required at screening if this was performed as part of SoC within 3 months prior to randomization. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing.

8.3.5.3. Ongoing Hepatitis B Virus and Hepatitis C Virus Testing

During and following study treatment, participants who have history of HBV infection (eg, anti-HBc-positive irrespective of anti-HBs status, anti-HBs-positive and unknown HBV vaccination history, or known history of prior HBV infection irrespective of hepatitis B serology findings) will be closely monitored for clinical and laboratory signs (including DNA PCR) of reactivation of HBV at C1D1 (± 7 days) and then every 12 weeks (± 4 weeks) during the Treatment Phase and at 3 and 6 months (± 4 weeks) after the last treatment dose, and as clinically indicated. See Section 10.6 for additional information and testing for hepatitis B. Where required by local law, the results of HBV testing may be reported to the local health authorities.

Participants with history of HCV antibody positivity will be monitored for HCV-RNA testing at C1D1 (± 7 days) and then Q12W (± 4 weeks) during the Treatment Phase and at 3 and 6 months (± 4 weeks) after the last treatment dose, and as clinically indicated.

8.3.6. HIV Testing

HIV testing by PCR and CD4 count is required at screening, as specified in the SoA (Section 1.3) for participants with HIV or history of HIV antibody positivity. If HIV testing by PCR and CD4 count was performed as part of SoC within 3 months prior to randomization, repeat testing during screening is not required. The criteria in Section 5 will be used to determine participant eligibility for the study. Participants with a history of HIV antibody positivity who otherwise meet eligibility criteria must undergo HIV-RNA and CD4 count testing at C1D1 (± 7 days) and then Q12W (± 4 weeks) during the Treatment Phase and at 3 and 6 months (± 4 weeks) after the last treatment dose, and as clinically indicated.

8.3.7. Pregnancy Testing

Pregnancy testing will be conducted for POCBP as presented in the relevant SoA (Section 1.3). Additional serum or urine β -hCG tests may be performed, as determined necessary by the

investigator or required by local regulation to establish the absence of pregnancy at any time during the participation in the study.

8.3.8. ICE Neurologic Test

The ICE tool presented below will be used prior to the first SUD to establish baseline neurologic status and during the Treatment Period if a neurologic AE or ICANS is suspected. If ICANS is suspected, additional assessments should be performed to assess severity per the ASTCT grading scale in Section 6.6.3.2.

Table 19: ICE Tool

Category	Points
Orientation: orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle.”)	1 point
Attention: ability to count backward from 100 by 10	1 point

Scoring is as follows (see also Table 14 for additional details regarding ICANS severity grading):

10; no impairment

7 to 9; Grade 1 ICANS

3 to 6; Grade 2 ICANS

0 to 2; Grade 3 ICANS

0 due to participant unarousable and unable to perform ICE assessment; Grade 4 ICANS.

Source: Lee 2019

8.3.9. ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the participant’s ADL (Oken 1982).

8.3.10. Other Safety Evaluations

During the study, if a tissue biopsy is obtained as part of the SoC workup of an AE (eg, rash), the sponsor may request to receive additional material from that biopsy sample.

During the study, photographs or videos may be taken of physical findings associated with AEs (eg, rash, nail findings, neurotoxicities). Photographs and videos will be anonymized with no participant identification. Photographs and videos may be shared with the sponsor and may be included in presentations and publications related to the study.

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 study participants and patients, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures to ensure appropriate safety reporting; and this study is to be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally designated representative).

The sponsor assumes responsibility for appropriate reporting of the safety information, including SUSARs, to the regulatory authorities/IECs/IRBs in each respective country/territory, as applicable.

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

All AEs and special reporting situations, whether serious or non-serious, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures, must be recorded using medical terminology in the source document and on the appropriate pages of the eCRF and appropriate forms. 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 eCRF their opinion concerning the relationship of the AE to study therapy (see Section 8.4.3.). All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained.

All AEs, special reporting situations and SAEs that occur until 30 days after last study treatment dose or until starting new subsequent anticancer therapy, whichever is earlier, must be reported and recorded on the appropriate pages in the CRF or on specific forms.

Beyond the standard AE reporting period described above, AEs that are considered to be possibly, probably, or very likely related to study drug must be reported until the end of the study.

AEs unrelated to study treatment will be collected until 30 days after the last dose of study treatment or until start of SST (if earlier). AEs related to study treatment will be collected until end of study. If a participant is unable to return to the site for the EoT visit, or if the EoT visit occurs before Day 30 after the last dose of study treatment, the participant should be contacted to collect AEs that occur up to 30 days after the last dose of study treatment or until the start of a subsequent anticancer therapy, whichever comes first. The primary reason for treatment discontinuation will be documented in the eCRF.

Participants with non-ICANS neurotoxicity Grade ≥ 2 and Grade 3 or higher AEs or unresolved AEs of any grade that lead to study drug discontinuation will continue to be assessed until recovery to Grade ≤ 1 or baseline, the event is deemed irreversible, the participant discontinues the study, or for a maximum of 6 months, whichever comes first. CRS and ICANS should be followed until full recovery or until there is no further improvement.

Information regarding SAEs (initial and any follow-up) will be transmitted to the sponsor/Contract Research Organization immediately, but no later than 24 hours of their knowledge of the event,

using the appropriate SAE Form with the complete (eg, causality, narrative) information available in the medical records that has been already assessed by a study site physician, and transmitted via eCRF through Janssen Electronic Inbound Safety Reporting.

8.4.2. Definitions and Classifications

8.4.2.1. All Adverse Events

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 treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding from a diagnostic procedure or laboratory assay), symptom, or disease that is new in onset or aggravated in severity or frequency from baseline and temporally associated with the use of such product (as defined by ICH).

The investigator is obligated to take all necessary steps to elucidate the nature and causality of the AE as fully as possible.

8.4.2.2. Serious Adverse Event

A 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
The cause of death of a participant in a study within 30 days of the last dose of study treatment, whether or not the event is expected or associated with the study treatment, is considered an SAE. However, death attributed to progression of disease should not be considered an AE or SAE. For details, see Section [8.4.6.1](#).
- 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, except:
 - Hospitalization attributed to progression of disease; for details, see Section [8.4.6.2](#).
 - Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, convenience for participant).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).
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.
 - Hospitalizations for administration of study drug.
- 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 indicating suicidal ideation or behavior.
- Is a Hy's Law Case (defined by the occurrence of ALT or AST $\geq 3 \times \text{ULN}$, alkaline phosphatase $< 2 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ or international normalized ratio > 1.5 [if measured] with no alternate etiology).
A confirmed Hy's Law as well as a possible Hy's Law Case must be reported as SAE.
- Is Medically Important
Exercise medical judgment to decide on reporting as SAE of other events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

SAE recording and reporting

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

- The event resolves, stabilizes or returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study treatment 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, or participant is lost to follow-up).

8.4.3. Attribution of Causality

The causal relationship between study treatment administration and the AE is assessed by the investigator and documented in the medical records. This assessment must consider factors such as characteristics of participant and event, temporal relationship, pharmacologic plausibility and confounding clinical factors. Data on challenge can help the assessment (did the event improve when the study treatment was withdrawn in the absence of any other intervention and what happened when participant restarted the study treatment). The following must be used for all AEs:

- **Related:** There is a reasonable causal relationship.
- **Not Related:** There is not a reasonable causal relationship.

8.4.4. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 6.0. Any AE or SAE not listed in the NCI-CTCAE Version 6.0 should be evaluated for severity/intensity by using the standard grades as follows:

- | | |
|---------|--|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.* |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.** |

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

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

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

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).

8.4.5. Special Reporting Situations

Safety events of interest pertaining to the study treatment in this study that require expedited reporting and may trigger safety evaluation include, but are not limited to:

- Overdose of study treatment
- Suspected abuse/misuse of study treatment
- Accidental or occupational exposure to study treatment
- Exposure to study treatment from breastfeeding
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Reporting of participant pregnancy or participant partner(s) pregnancy

Participant-specific special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF. Reporting should occur as for other AEs and SAEs (Section 8.4.1).

8.4.6. Procedures

8.4.6.1. Anticipated Events

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in Section 10.8.

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

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Progression of disease and signs and symptoms thereof, that are part of the natural course of the disease under study, should not be considered or reported as a (serious) AE, even if the participant is hospitalized or died due to this progression:

- PD: document on the appropriate eCRF form (eg, Disease Progression form).
- Death due to PD: document on the appropriate eCRF form (eg, Death form).
- A symptomatic worsening of the MM disease that is of clinical significance or onset of new symptoms, such as spinal cord compression, bone pain, hyperviscosity syndrome, renal impairment, etc.: document on the appropriate eCRF form: Symptomatic Worsening of MM form.
- Of note, for the rare case of (accelerated) progression of disease induced by the study treatment: report this accelerated progression or its specific signs/symptoms as drug-related AE per the usual reporting requirements.

8.4.6.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, expedited reporting by the study sponsor to other parties (eg, regulators) might be warranted.

The communication requirements for AESIs are detailed in the table below. Any AESI should be followed until full recovery or until there is no further improvement.

AESI	Definition	Data collection and rapid communication requirements
CRS	CRS of Grade 2 or higher per ASTCT grading (see Section 6.6.3.1 for details on CRS)	Event can be serious or non-serious: • If serious, report as SAE^a • If non-serious, report as regular AE in eCRF but within 24 hours of awareness
ICANS	ICANS of Grade 2 or higher per ASTCT grading (see Section 6.6.3.2 for details on ICANS)	Event can be serious or non-serious: • If serious, report as SAE^a • If non-serious, report as regular AE in eCRF but within 24 hours of awareness

^a Follow all SAE reporting procedures and requirements, including reporting within 24 hours

8.4.7. Product Quality Complaint Handling

Definition

A 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.

8.4.8. 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.

8.5. Pregnancy and Postpartum Information

8.5.1. Participants Who Become Pregnant During the Trial

Pregnancy testing must be performed as specified in the SoA (Section 1.3). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Any participant who becomes pregnant during the study must discontinue further study treatment.

For reporting of participant pregnancy or participant partner(s) pregnancy refer to Section 8.4.5.

8.5.2. Participants Whose Partners Become Pregnant

All initial reports must be made to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Outcome of the reported pregnancy and any postnatal sequelae in the infant will be required. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as SAEs.

8.6. Pharmacokinetics

Serum samples will be collected according to the SoAs (Section 1.3) and used to evaluate the PK of JNJ-79635322. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, including but not limited to cytokines and/or other PD biomarkers. Serum samples will be analyzed to determine concentrations of JNJ-79635322 using a validated, specific, and sensitive method by or under the supervision of the sponsor. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Descriptive statistics may be used to summarize JNJ-79635322 serum concentrations at each sampling time point. Mean serum JNJ-79635322 concentration-time profiles may be plotted, and individual serum concentration-time profiles may also be plotted.

8.7. Pharmacodynamics

Sample collection and testing will comply with local regulations.

Bone marrow aspirate will be collected at baseline and during treatment per the relevant SoA (Section 1.3) and Table 18 to evaluate MRD and pharmacodynamic profiles of JNJ-79635322. Additional biomarker samples may be collected to help understand unexplained AEs.

8.8. Genetics

Sample collection and testing will comply with local regulations.

Genetic tests will include FISH in bone marrow PCs to evaluate cytogenetic risk. Additionally, genome and gene expression profiling may be performed for exploratory studies. However, information pertaining to genetic risk for other diseases or hereditary traits will not be obtained. Thus, no conclusions around incidental findings will be provided.

8.9. Biomarkers

Sample collection and testing will comply with local regulations.

Biomarker assessments may involve: (a) assessment of MRD negativity using NGF-based methodology; (b) evaluation of markers in bone marrow including, but not limited to, phenotypic (eg, GPRC5D+ and BCMA+ PCs, bone marrow microenvironment immune cell populations) and molecular markers (eg, gene expression, mutations, and deletions, including GPRC5D and BCMA) in tumor through implementation of flow cytometry, cytometry by time of flight, or other methodology, and DNA/RNA sequencing methods, among others.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Stopping Collections

Assessments or laboratory sampling related to exploratory endpoints may be reduced or stopped during the course of the study if enough data has been collected or is no longer deemed necessary by the sponsor.

8.10. Immunogenicity Assessments

Antidrug Antibodies

Antibodies to JNJ-79635322 (ADAs) will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. Other analyses may be performed to further characterize the immunogenicity of JNJ-79635322. The incidence of ADAs to JNJ-79635322 may be summarized for participants who are ADA-evaluable. Descriptive statistics for onset and duration of ADAs may also be presented for participants who are ADA-positive, if applicable. The potential impact of ADAs on PK, safety, and efficacy may also be evaluated.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Neutralizing Antibodies

All ADA-positive samples in ADA-positive participants will be tested for the presence of NAbs. The incidence of NAbs to JNJ-79635322 may be summarized for participants who are ADA-positive and have evaluable NAbs samples. Descriptive statistics for onset and duration of NAbs may also be presented, if applicable. The potential impact of NAbs on PK, safety, and efficacy may also be evaluated. Additional information for the collection, volumes, handling, storage, and shipment of biological samples can be found in the Laboratory Manual.

8.11. Medical Resource Utilization and Health Economics

MRU data, including the management of AEs and medical encounters related to MM, will be collected in the eCRF by the investigator and study site personnel for all participants, from start of administration of study treatment until PD, 30 days after the last dose of study drug(s) or at the start of subsequent therapy, whichever is later. The data collected may be used to conduct exploratory economic analyses and will include, but is not limited to:

- Number of outpatient department visits.
- Number and duration of hospitalizations and emergency department visits.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under its authority. A general description of the statistical methods to be used is outlined below; for more detail see the SAP, which will be finalized prior to database lock.

9.1. Statistical Hypotheses

See Section 3 for the primary statistical hypothesis. The multiplicity strategy for the primary and key secondary hypotheses is provided in Section 9.4.5.

9.2. Participant Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Screened	All participants who signed the ICF
Enrolled	All participants who signed the ICF and are not screen failures
Full	All participants who were randomized in the study
Safety	All participants who received at least 1 dose of study treatment
PK-evaluable	All participants who received ≥ 1 dose of JNJ-79635322 and have ≥ 1 post-treatment PK sample
Immunogenicity-evaluable	All participants who received ≥ 1 dose of JNJ-79635322 and have appropriate serum samples for detection of ADAs to JNJ-79635322 (≥ 1 sample after the start of the first dose of JNJ-79635322)

The Full Analysis Set will be used for efficacy analyses and the Safety Analysis Set will be used for safety analyses, unless otherwise specified.

9.3. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary efficacy endpoints. A detailed description of the statistical analyses will be provided in the SAP.

9.3.1. General Considerations

Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical variables will be summarized using number of observations and percentages, as appropriate. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

9.3.2. Primary Endpoint(s)/Estimands

This study has dual primary endpoints of PFS and CR or better. The study will be considered positive if at least one of these 2 dual primary endpoints achieves statistical significance. The estimand for each of these endpoints is defined as follows.

9.3.2.1. Progression-free Survival

9.3.2.1.1. Definition

PFS is defined as the duration from the date of randomization to either PD or death, whichever comes first. PD will be determined according to the IMWG response criteria. For participants who have not progressed and are alive, data will be censored at the last disease assessment before the start of any subsequent antimyeloma therapy. For participants who are lost to follow-up or who withdraw consent, and who have not progressed before loss to follow-up or withdrawal of consent, data will be censored at the last disease assessment. Participants without any post-baseline disease assessment will be censored at the date of randomization defined by the IMWG response criteria. For any PFS event (death or progression), if a participant missed at least 2 consecutive disease

evaluations immediately preceding the PFS event, this event will be censored at the date of last disease assessment before the missed visit.

9.3.2.1.2. Estimand

Primary Study Objective: To evaluate whether treatment with JNJ-79635322 will result in prolongation of PFS as compared to teclistamab, in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide.

Clinical Question of Interest: For participants with RRMM who have received 1 to 3 prior lines of therapy, what is the effect of assigning JNJ-79635322 versus teclistamab on reducing the risk of progression or death?

The estimand corresponding to this clinical question of interest is defined by the following attributes:

Study Treatment:

- Experimental: JNJ-79635322
- Control: teclistamab

Administered as specified in Section 6.1.

Population: RRMM patients as defined by protocol eligibility criteria.

Endpoint (variable): PFS: time from randomization to either PD or death, whichever comes first.

Population-level summary: HR versus control.

Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy	Description of Strategy for Addressing Intercurrent Events
Premature treatment discontinuation due to toxicity or reasons other than PD	Treatment Policy	Strategy targeting the effect of the treatment assignment, regardless of the occurrence of ICEs.
Subsequent antimyeloma therapy	Hypothetical	Strategy targeting a treatment effect in a hypothetical scenario in which participants would continue treatment as assigned. Therefore, participants who receive subsequent antimyeloma therapy prior to PD or death will be censored at the last disease assessment prior to subsequent therapy.

9.3.2.1.3. Analysis Methods

The non-parametric product-limit Kaplan-Meier survival estimation method will be used to summarize the distribution of PFS for each treatment arm. The stratified log-rank test will be used to make inference with regard to the superiority of JNJ-79635322 relative to teclistamab. The

stratified Cox-proportional hazards model with study treatment as the sole explanatory variable will be used to provide an estimate of HR of the treatment effect. The stratification factors are the ISS stage at screening (I vs. II/III), number of prior lines (1 vs. ≥ 2) and EMD status at baseline (yes vs. no).

9.3.2.2. CR or Better

9.3.2.2.1. Definition

CR or better is defined as the proportion of participants achieving CR or sCR prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment.

9.3.2.2.2. Estimand

Primary Study Objective: To evaluate whether treatment with JNJ-79635322 will improve the achievement of CR or sCR as compared with teclistamab, in participants with RRMM who have received 1 to 3 prior lines of therapy, including an anti-CD38 antibody and lenalidomide.

Clinical Question of Interest: For patients with RRMM who have received 1 to 3 prior lines of therapy, what is the effect of assigning JNJ-79635322 versus teclistamab, in the achievement of CR or better?

The estimand corresponding to this clinical question of interest is defined by the following attributes:

Study Treatment:

- Experimental: JNJ-79635322
- Control: teclistamab

Administered as specified in Section 6.1.

Population: RRMM patients as defined by protocol eligibility criteria.

Endpoint (variable): Overall response, where a participant is considered to have met overall response if achieving CR or better any time after randomization, but prior to any subsequent anticancer therapy.

Population-level summary: Odds ratio versus teclistamab.

Intercurrent events and their corresponding strategies:

Intercurrent Event	Strategy	Description of Strategy for Addressing Intercurrent Events
Premature treatment discontinuation due to toxicity or reasons other than PD	Treatment Policy	Strategy targeting the effect of the treatment assignment, regardless of the occurrence of the ICE (ie, response will be considered regardless of treatment discontinuation).

Subsequent antimyeloma therapy	While on treatment	Strategy targeting the treatment effect prior to the ICE, as reflected in the endpoint definition (ie, only response assessments prior to subsequent antimyeloma therapy will be used, as reflected in the endpoint definition).
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9.3.2.2.3. Analysis Methods

CR or better will be calculated for each treatment arm. The stratified Cochran-Mantel-Haenszel estimate of the odds ratio will be used to make inference with regard to the superiority of JNJ-79635322 relative to teclistamab. The analysis will be stratified for ISS stage at screening (I vs. II/III), number of prior lines (1 vs. ≥ 2) and EMD status at baseline (yes vs. no).

9.3.3. Secondary Endpoints

ORR: defined as the proportion of participants who achieve PR or better prior to subsequent antimyeloma therapy in accordance with the IMWG criteria.

VGPR or better: defined as the proportion of participants achieving VGPR, CR, or sCR prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment.

Duration of response: will be calculated among responders (with a PR or better response). It is defined as the time interval between the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD according to the IMWG response criteria or death due to any cause, whichever occurs first. Participants who have not progressed and are alive will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy

MRD-negative CR: defined as the proportion of participants with CR or better who achieve MRD-negative status, as determined by NGF with sensitivity of 10^{-5} , at any time point after randomization and prior to PD or subsequent antimyeloma therapy.

MRD-negative CR at 1 year: defined as the proportion of participants who achieve MRD-negative status at 12 months (± 3 months), as determined by NGF with sensitivity of 10^{-5} , prior to PD or subsequent antimyeloma therapy and who also achieve CR or better according to IMWG criteria. MRD-positive participants include participants for whom tested samples at 1 year were found to be MRD-positive, indeterminate, not evaluable, or missing. Participants who were not tested for MRD within the time window will also be considered as MRD-positive.

MRD-negative CR at 5 years: defined as the proportion of participants who achieve MRD-negative status at 5 years (± 6 months) as determined by NGF with sensitivity of 10^{-5} , prior to PD or subsequent antimyeloma therapy and who also achieve CR or better according to IMWG criteria. MRD-positive participants include participants for whom tested samples at 5 years were found to be MRD-positive, indeterminate, not evaluable, or missing. Participants who were not tested for MRD within the time window will also be considered as MRD-positive.

PFS2: defined as the time interval between the date of randomization and date of event, which is defined as PD as assessed by investigator on the first subsequent line of antimyeloma therapy, or death from any cause, whichever occurs first. Those who are alive and for whom a second PD has not been observed are censored at the last date of follow-up.

OS: measured from the date of randomization to the date of the participant's death due to any cause. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive.

TTNT: defined as the time from randomization to the start of subsequent antimyeloma treatment. Death due to PD without the start of any subsequent antimyeloma therapy will be considered as an event. Participants who withdraw consent to study, are lost to follow-up, or die due to causes other than PD will be censored at the date of death, or the last date known to be alive. Participants who are still continuing in the study at the time of analysis and have not started subsequent therapy will be censored at the date of their latest disease assessment.

PROs are defined in Section 8.2.4 and further details will be described in the SAP.

9.3.4. Tertiary/Exploratory/Other Endpoints

Analysis details for additional tertiary/exploratory and other endpoints, if any, will be described in the SAP.

9.3.5. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

The baseline value for safety assessment is defined as the value collected at the time point closest and prior to first study treatment. The incidence and severity of AEs, laboratory results, and other safety parameters will be reported by descriptive statistics. Treatment exposure and reasons for treatment discontinuation and study withdrawal will be tabulated.

Adverse Events

The verbatim terms in the eCRF to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. 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* 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 TEAEs 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 study treatment group.

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 AE or an SAE.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. ASTCT severity grading will be utilized for CRS and ICANS.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics, analyses of frequency tabulations, and change from baseline results will be specified in the SAP. Descriptive statistics will be used for selected laboratory analytes at baseline and at each scheduled time point. Changes from baseline to the worst grade experienced by the participant during the study will be provided in shift tables.

Vital Signs and Physical Examinations

Clinically significant abnormal changes will be summarized as AEs.

9.3.6. Other Analyses

The following data will be analyzed as specified in the SAP and may be presented in a separate report: PK, PD, MRU, biomarker, immunogenicity, symptomatic worsening of MM symptoms, and PROs.

9.4. Interim Analysis

A summary of the efficacy interim analyses for CR or better, PFS, and OS are provided below.

9.4.1. CR or Better

A single analysis for CR or better will be performed 9 months after the last participant is randomized.

9.4.2. PFS

The study design includes up to 2 interim analyses for efficacy and a final analysis for PFS:

- The first PFS interim analysis will be conducted at the time of the analysis for the dual primary endpoint of CR or better.
- The second PFS interim analysis is planned to be conducted when 75% of the total PFS events have accumulated. However, if at least 65% of the total planned PFS events are observed at the time of the first PFS interim analysis (ie, the time of the CR or better final analysis) this interim analysis will be omitted.
- The PFS final analysis will be conducted when the total planned PFS events have accumulated, which will be between 198 and 258 events depending on the ERE.

ERE will occur at a PFS interim analysis when at least 65% of the initial total planned PFS events are observed.

The initial significance level for the test of superiority with respect to PFS will be determined based on the actual number of observed PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method ([O'Brien 1979](#); [Lan 1983](#)), subject to ERE.

9.4.3. OS

The study design includes up to 4 interim analyses for efficacy and a final analysis for OS:

- The first OS interim analysis will be performed at the time of the CR or better analysis (ie, at the time of the first PFS interim analysis).
- The second OS interim analysis will be performed at the time of second PFS interim analysis, ie, if less than 65% PFS IF is observed at the time of the CR or better analysis, otherwise this analysis will be omitted.
- The third OS interim analysis will be conducted at the time of the PFS final analysis. However, if the study is unblinded prior to the planned PFS final analysis, this interim analysis for OS will be triggered upon reaching 80% of the target number of OS events.
- The fourth OS interim analysis will be conducted when 85% of the total planned OS events have accumulated. If at least 75% of the total planned OS events are observed at the time of the third OS interim analysis for efficacy (ie, the time of the PFS final analysis) this interim analysis will be omitted.
- The OS final analysis will be conducted when the total planned OS events have accumulated, which will be between 181 and 222 events depending on the ERE.

ERE will occur at an interim analysis when at least 75% of the initial total planned OS events are observed.

The initial significance level for the test of superiority with respect to OS will be determined based on the actual number of observed OS events at the interim analysis, using the Kim-DeMets spending function with parameter equal to 2, subject to ERE.

OS will also be monitored for a potential detrimental effect. Further details of the monitoring rule will be provided in the SAP.

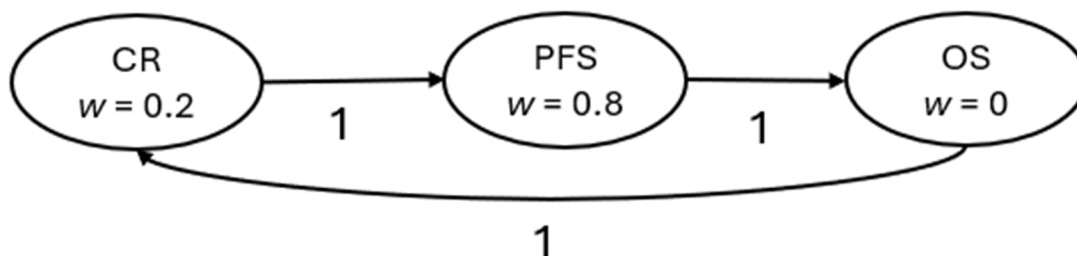
9.4.4. IDMC

An IDMC will be established as noted in the Committee Structure in Section 10.2.7. The IDMC will review the efficacy interim analyses and ongoing safety data as specified in the IDMC charter. The IDMC may also recommend increasing the planned number of events for the PFS and OS analyses according to the prespecified ERE rule.

Further details of these interim analyses will be provided in the SAP.

9.4.5. Multiplicity Strategy

The multiplicity strategy will be applied to the 2 primary superiority hypotheses (CR or better and PFS) and one key secondary superiority hypothesis (OS), and follows the graphical approach for group sequential designs of [Maurer and Bretz 2013](#) which provides strong control of Type I error at the one-sided 0.025 level ([Cui 1999](#)). The diagram of the graphical procedure is shown in [Figure 2](#) and details of the testing procedure will be specified in the SAP.

Figure 2: Strategy Diagram of the Graphical Procedure

9.5. Sample Size Determination

The total sample size is calculated based on the following assumptions. The primary hypothesis is to demonstrate the superiority of JNJ-79635322 over teclistamab, in terms of at least one of the dual primary endpoints of PFS and CR or better. The initial one-sided significance levels allocated to test the superiority for PFS and CR or better will be 0.02 and 0.005 respectively.

It is hypothesized that JNJ-79635322 will reduce the risk of PD or death by 38% compared with standard treatment (HR=0.62). The median PFS for teclistamab for this study population is estimated to be 35 months, based on data from MajesTEC-9 ([Johnson & Johnson TECVAYLI® Press Release 2026](#)). Based on a log-rank test with one-sided alpha of 0.02, for an HR of 0.62, a total of 198 PFS events are needed to achieve a cumulative power of approximately 90%. With an 18-month accrual period and an annual drop-out rate of 5% for PFS, the total sample size is approximately 700 participants (350 per arm with 1:1 randomization).

With 700 participants (350 per arm), there will be at least 97% power to detect a 15% absolute difference in CR or better at a 1-sided alpha of 0.005, where the CR or better for teclistamab in this study population is assumed to be 66% based on data from MajesTEC-9.

It is estimated that the median OS for teclistamab in this study population is 53 months based on data from MajesTEC-9. With 180 OS events, this study can achieve approximately 80% power to detect a 35% reduction in the rate of death (HR=0.65), based on a log-rank test using a one-sided alpha of 0.025.

The number of PFS and OS events for the final PFS and OS analyses may be re-estimated at an interim analysis, following the ERE procedure. Details of the interim analyses are provided in Section 9.4 and further details of the ERE procedure will be provided in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed according to the SoA (Section 1.3) by the local laboratory with exceptions noted:

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Hemoglobin White blood cell count with differential ANC Absolute lymphocyte count
Coagulation	Prothrombin time or (international normalized ratio) Activated partial thromboplastin time Fibrinogen
Clinical Chemistry	• Potassium • Sodium • Creatinine • AST • ALT • Gamma glutamyl transferase • Total bilirubin (direct bilirubin if Gilbert's disease) • Alkaline phosphatase • Lactic acid dehydrogenase • Phosphate • Uric acid • Calcium (total) • Albumin • Lipase or amylase
	For potential and confirmed Hy's Law case reporting requirements: see Section 8.4.2.2.

Laboratory Assessments	Parameters
Other Laboratory Tests	• Serum or urine pregnancy testing for participants of childbearing potential only (see Section 8.3.7) • Serology: – Hepatitis B: HBsAg, anti-HBs, anti-HBc, HBV-DNA PCR (see Section 10.6) – Hepatitis C: anti-HCV and HCV-RNA if anti-HCV is positive (see Section 8.3.5) – HIV: HIV PCR and CD4-count (see Section 8.3.6) • C-reactive protein, ferritin, cytokines, arterial blood gases testing might be required during workup of severe cases of CRS, to monitor for disseminated intravascular coagulation and for potential evolution to HLH/MAS. B-type natriuretic peptide assessment to be performed if clinically indicated (local laboratory testing) (see Section 6.6.3.1).

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

10.2.1. Regulatory and Ethical Considerations

- **The investigator is responsible** for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country- or territory-specific requirements.
- **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.
- **Protocol Amendments:** No modification to this protocol will occur without a formal amendment issued by the sponsor and signed and dated by the investigator. Amendments cannot be implemented without prior approval by IEC/IRB and relevant competent authority, except to eliminate immediate hazards to the participants (promptly submit amendment to the IEC/IRB and relevant competent authority). Documentation of amendment approvals must be provided to the sponsor.
- **Departure from the Protocol:** In situations where a departure from the protocol is unavoidable during the study, the investigator or delegate will contact the appropriate sponsor representative listed in the Contact Information page(s) to discuss the situation and agree on an appropriate course of action prior to such departure, except in emergency situations. The departure and its rationale must be recorded in source documents and be reflected in the eCRF data.
- **Required Prestudy Documentation:** Documentation that must be provided to the sponsor before shipment of study treatment to the study site are specified in the appropriate documents such as the Clinical Trial Agreement. Additional documentation might need to be provided prior to enrollment of the first participant.
- **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 all documents as required by local regulations. Required documents are specified in the appropriate documents such as the Clinical Trial Agreement.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, which should be submitted promptly, 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 dated approval, with clear identification of the IEC/IRB and the documents approved.

During the study the investigator (or sponsor where required) will send documents and updates to the IEC/IRB for their review and approval, where appropriate, as specified in the appropriate documents such as the Clinical Trial Agreement.

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 (if applicable, the notification will be submitted through the head of investigational institution).

- **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.
- **Other Ethical Considerations:** For study-specific ethical design considerations, refer to Section 4.2.1.

10.2.2. Financial Disclosure

During the study and for 1 year after completion of the study, investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations. Refer to appropriate documents such as the Clinical Trial Agreement for details.

10.2.3. Informed Consent Process

Each participant (or a legally designated representative) must give consent according to local requirements after the nature of the study has been fully explained and a response to all questions regarding the study was given. The ICF(s) must be signed before any study-related activity.

The consent must be appropriately recorded by means of either the participant's or their legally designated representative's personally dated signature; the authorized person obtaining the consent must also sign the ICF. After consent, a copy of the ICF must be given to the participant. The medical records must include a statement that consent was obtained as required.

If the participant or legally designated representative is unable to read or write, an impartial witness must be present for the entire process and must personally date and sign the ICF after the oral consent of the participant or legally designated representative is obtained.

Participants who are determined to be eligible for rescreening must sign a new ICF and will be assigned new participant numbers.

Where local regulations require, a separate ICF may be used for the specific component(s), such as DNA analysis, of the study.

When applicable, during the study, participants must be re-consented to the most current version of the ICF(s).

10.2.4. Recruitment Strategy

Refer to Recruitment and Informed Consent Procedure Template for details.

10.2.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant data that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects, including notification to appropriate authorities in accordance with applicable law.

10.2.6. Storage, Use, Transfer, and Retention of Data and Samples

- Study samples will be coded (or anonymized) at all times in accordance with the informed consent; no personal identifiers will be used.
- Investigator and study site will only store, use, transfer and retain data and (optional) study samples, in accordance with the informed consent, applicable law, and any written agreement with sponsor. Other than what is specified in this written agreement with sponsor, study site and investigator shall not conduct or facilitate any research not required by the protocol (i) on participants, or (ii) on samples or data collected from study participants during the study, if the research relates to JNJ-79635322.
- Sponsor may store, use, transfer or retain the data and (optional) study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.
- The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer disks or tapes. They will be retained for the longer of the maximum period required by the country/territory and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.
- If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.2.7. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor study data and to ensure the continuing safety of the participants enrolled in this study. The composition, detailed objectives and procedures will be documented in its charter.

10.2.8. Use of Information, Registration of Study and Publication

- All information, including but not limited to information regarding JNJ-79635322, supplied by the sponsor to the study site or investigator and not previously published, and any data generated as a result of this study, are considered confidential and the sole property of the sponsor. The study site and investigator shall not use nor disclose this information except as needed for the conduct of the study, and then only on like terms of confidentiality and non-use.
- The study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and study site or investigator.
- The sponsor will register the study and publish the study results in compliance with applicable law. The disclosure of the study results will be performed after the end of study. The sponsor will generally support publication of multicenter studies only in their entirety.

- Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.
- The summary of the results from the interim analyses as described in Section 9.4, may be submitted to the EU database within one year of the intermediate data analysis date.

10.2.9. Data Quality Assurance, Monitoring and Audits

- Data quality will be ensured by selection of qualified investigators and study sites, review of protocol procedures and guidelines for CRF completion with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Review and verification of CRF data may occur, as appropriate.
- Written instructions will be provided for collection, handling, storage, and shipment of samples.
- The sponsor will use monitoring techniques such as central, remote, or on-site monitoring to monitor this study as frequently as necessary. It is expected that during remote contacts, study site personnel will be available to provide an update on the study.
- Representatives of the sponsor's clinical quality assurance department may conduct an on-site audit of the study in compliance with regulatory guidelines and company policy. Study site personnel must be available for consultation. These audits will require access to all study records, including source documents. Participant privacy must, however, be respected.
- Similar auditing procedures may also be conducted by agents of any regulatory body; the investigator must immediately notify the sponsor if they were contacted concerning such inspection.

10.2.10. Source Documents and Case Report Form Completion

- For each participant, the sponsor provides CRFs in electronic format for recording, in English, of all data relating to the study by the investigator or authorized study site personnel. Worksheets, which are considered part of participant's source documents, may be used for the capture of some data to facilitate completion of the CRF. The CRF must be completed as soon as possible after a participant visit. The investigator must verify that all data entries in the CRF are accurate and make corrections as appropriate. Study-specific data will be transmitted in a secure manner to the sponsor. If necessary, queries will be generated in the electronic data capture tool.
- All participative measurements (eg, pain scale information or other questionnaires) will be completed, whenever possible, by the same assessor who made the initial baseline determinations.
- Source documents, on paper to be filed or using any eSource system to be maintained at the study site, provide evidence for the existence of the participant and substantiate the integrity of all study data collected, with at minimum the level of detail as commonly recorded at the study site.
- The author of an entry in the source documents must be identifiable.

- Specific details required as source data for the study and source data collection methods will be reviewed with the study staff before the study and will be described in the monitoring guidelines (or other equivalent document). This will include the list of any data recorded directly into the CRF that will be considered source data.

10.2.11. Study and Site Start and Closure

Study Start Date is defined as the date the first participant is screened (ie, signed the ICF).

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.

10.3. Appendix 3: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures (Section 5.1). In case a pregnancy occurs while on study treatment, pregnancy information will be collected and reported as noted in Section 8.4.5.

Definitions

Participants of Childbearing Potential

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

Participants Not of Childbearing Potential

- **premenarchal**
A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in participants on HRT, the participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study.
- Permanent absence of reproductive potential (for the purpose of this study).
 - Has undergone a procedure that precludes reproductive potential.
 - Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active where pregnancy can occur), a 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.

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

If applicable, study participants should be counselled about donation and cryopreservation of gametes prior to starting study treatment.

Examples of Contraceptives

EXAMPLES OF HIGHLY EFFECTIVE METHODS OF CONTRACEPTIVES^a:
USER INDEPENDENT Highly Effective Methods^a
Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Intrauterine device
Intrauterine hormone-releasing system
Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
Azoospermic partner (vasectomized or due to medical cause) <i>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)</i>
USER DEPENDENT Highly Effective Methods^a
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b: oral, injectable, transdermal or intravaginal
Progestogen-only hormone contraception associated with inhibition of ovulation^b: oral or injectable
Sexual abstinence from intercourse where pregnancy could occur <i>(Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse where the possibility of pregnancy exists during the entire period of risk associated with exposure to the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.)</i>
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (Not Considered to be Highly Effective - Failure Rate of $\geq 1\%$ Per Year)^a
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Condom with or without spermicide (do not use multiple condoms together because of risk for failure due to friction)
Cap, diaphragm, or sponge with spermicide
A combination of external condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)
Periodic abstinence (calendar, symptothermal, post-ovulation methods)
Withdrawal (coitus-interruptus)
Spermicides alone
Lactational amenorrhea method

^a Highly Effective Methods have a failure rate of $<1\%$ per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should 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. A participant using oral contraceptives must use an additional contraceptive method.

10.4. Appendix 4: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies

It is recognized that major disruptions may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of 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 judgment 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 treatment will be followed.

If as a result of the major disruption 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 treatment, 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 treatments and withdrawal from the study should be documented with the prefix "Major Disruption-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the major disruption should be summarized in the clinical study report.

10.5. Appendix 5: Cytokine Release Syndrome – Severity Grading and Management

ASTCT CRS Consensus Grading				
CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever^a	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
Hypotension	With None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	And/Or ^b None	Requiring low-flow nasal cannula ^c or blow-by	Requiring high-flow nasal cannula ^c facemask, nonbreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading

- ^a Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
- ^b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
- ^c Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L/minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L/minute}$.

Source: [Lee 2019](#)

High-dose Vasopressors ^b	
Pressor	Dose
Norepinephrine monotherapy	$\geq 20\text{ }\mu\text{g/min}$
Dopamine monotherapy	$\geq 10\text{ }\mu\text{g/kg/min}$
Phenylephrine monotherapy	$\geq 200\text{ }\mu\text{g/min}$
Epinephrine monotherapy	$\geq 10\text{ }\mu\text{g/min}$
If on vasopressin	Vasopressin + norepinephrine equivalent of $\geq 10\text{ }\mu\text{g/min}^{\text{a}}$
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of $\geq 20\text{ }\mu\text{g/min}^{\text{a}}$

Source: [Lee 2014](#)

10.6. Appendix 6: Hepatitis B Virus Screening

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

- Individuals who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) **are eligible** for this protocol.
- Individuals who test **negative** for surface antigen (HBsAg-) and **positive** for core antibody (anti-HBc+) **and either positive or negative** for surface antibody (anti-HBs+ or anti-HBs-) **must undergo further testing for the presence of HBV DNA.**
 - If the HBV DNA test is **negative**, the participant is eligible for this protocol. However, testing for the presence of HBV DNA should be performed Q3M in addition to the ALT/AST laboratories according to the SoA while receiving study treatment until EoT. HBV DNA should be continued Q3M along with ALT/AST monthly in the follow-up period, if one exists, up to 6 months or before the start of new anticancer treatment. If there is evidence of HBV reactivation, hold study treatment, if applicable, and initiate treatment for HBV infection as appropriate per institutional guidance.
 - If the HBV DNA test is **positive**, the individual is **NOT eligible** for this protocol. In the event the HBV DNA test cannot be performed, the individual is **NOT eligible** for this protocol.
- Individuals who test **positive only** for **surface antibody** (anti-HBs+) and have a known history of prior HBV vaccination **are eligible** for this protocol. In case HBV vaccination status is unknown or without history of vaccination, an HBV-DNA test must be performed and negative to be eligible for this study.
- Individuals who test **positive** for surface antigen (HBsAg+) **are NOT eligible** for this protocol, regardless of the results of other hepatitis B tests.

Eligibility Based on Hepatitis B Virus Test Results				
Hepatitis B Test Result				
Action	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs or HBsAb)	Hepatitis B core antibody (anti-HBc or HBcAb)	Hepatitis B DNA
Exclude	Positive	Negative <i>or</i> positive	Negative <i>or</i> positive	NA
	Negative	Negative <i>or</i> positive	Positive	Positive
Include	Negative	Negative	Negative	NA
	Negative	Negative <i>or</i> positive	Positive	Negative
	Negative	Positive	Negative	NA*

NA: Not applicable or no need to test. A negative test (or antibodies/DNA below the level of quantification) is denoted as “negative”; a positive test (or presence of antibodies/DNA above laboratory thresholds) is denoted as “positive”.

* For participants with a known history of prior HBV vaccination. In case HBV vaccination status is unknown or without history of vaccination, an HBV-DNA test must be performed and negative to be eligible for this study.

Modified from source: <https://www.hepb.org/assets/Uploads/understanding-blood-tests.pdf>. Accessed 11 February 2026.

10.7. Appendix 7: Prior Cancer Therapy for Multiple Myeloma

A line of therapy is defined as 1 or more cycles of a planned treatment regimen. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of PD, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease ([Rajkumar 2011](#); [Rajkumar 2015](#)).

A single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered a prior line of therapy.

A participant must have undergone ≥ 1 complete cycle of treatment for each treatment that is considered as an individual prior line, unless PD was the best response to the line of therapy.

10.8. Appendix 8: Anticipated Events

Purpose

This appendix applies only to the reporting of anticipated events by the sponsor to the US FDA, and US-based Investigators and IECs/IRBs, in accordance with the FDA's guidance. The intent is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

Definition of an Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen.

Background

The FDA acknowledges that certain SAEs can be anticipated to occur commonly in the study population regardless of drug exposure. Although these anticipated SAEs may meet the definition of unexpected (ie, SUSARs), because they are not listed in the IB, they do not warrant expedited reporting as individual cases, or even in aggregate if the incidence is consistent with the expected background rates in the study population.

Analysis and Reporting of Anticipated Events

All AEs and SAEs will be recorded and reported by the investigator to the sponsor as described in Section 8.4.

The sponsor's SAC is an established safety committee, independent of the study team. To meet US safety reporting, the SAC will periodically perform aggregate analysis of anticipated events per the Anticipated Events Safety Monitoring Plan, which details the statistical analysis, the frequency of review and thresholds to trigger an aggregate analysis of anticipated events.

If an anticipated event is determined to occur more frequently in the experimental arm(s) of the study and there is a reasonable possibility that the anticipated event could be drug-related, the sponsor will prepare an aggregate safety report for FDA and US-based IRBs/ECs and Investigators.

Anticipated Events for the Study

The below list includes AEs that are commonly anticipated for the disease stage, study population and background treatment, for which the sponsor does not plan to report individual cases, regardless of the assessment of causality. This list is limited to those events for which an individual occurrence, or even an aggregate incidence consistent with the background rate in the study population, is inconsequential in the developing safety profile of the study treatment.

For the purposes of this study, the following events will be considered anticipated events:

- Bleeding
- Bone disease

- Hypercalcemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection
- Renal failure and insufficiency
- Anemia
- Neutropenia
- Thrombocytopenia

10.9. Appendix 9: Long-term Extension Phase

The purpose of this LTE phase is to provide continued treatment to participants who have not discontinued study treatment and follow-up of patients who have ended study treatment. This phase will begin upon notification from the sponsor to the site to initiate the LTE guided by planned analyses.

Participants who were randomized to receive JNJ-79635322 or teclistamab and are still on study treatment (ie, who are in Treatment Phase) will be offered the option to continue to receive study drug(s) as specified in Section 6.7. Participants who have already ended study treatment altogether and are in the Follow-up Phase will remain in follow-up and not restart any study treatment, following the below SoA (LTE; Table 20).

Study Treatment Administration

Open-label Study Treatment

Study treatment should continue to be administered as described in Section 1.3 and Section 6 of the protocol.

Prohibitions and Restrictions

Refer to Section 5.3 and Section 6.9.

Study Procedures for the Long-term Extension

Eligible participants will continue treatment beginning with Cycle X+1, where X is the last cycle that the participant completed during the Treatment Phase. The sponsor recommends investigators follow the guidance on concomitant therapies (Section 6.9), pretreatment medication (Section 6.1.1), dose modification (Section 6.6), and management of toxicities (Section 6.6.3) as described in the main body of the protocol. Disease evaluations should be completed by a local laboratory per Table 20.

All participants continuing in the LTE should follow the SoA (LTE; Table 20).

Blood samples for serum chemistry and hematology should be collected from a local laboratory as specified in the SoA (LTE; Table 20). Additional local laboratory tests may be performed as necessary. The investigator should review the laboratory report, document this review, and record any clinically relevant changes in the AE section of the eCRF (see Section 8.4.1 of the protocol for details).

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

Table 20: Schedule of Activities (Long-term Extension)

Procedures	Participants Remaining on Previously Received Study Treatment	Participants Off Study Treatment
Visit window during the LTE phase ^a is ± 1 week.		
Screening		
Informed consent for the LTE phase	X	
Study Drug Dispensing		
JNJ-79635322 or teclistamab	JNJ-79635322: Continuous to maximum of 36 months. Teclistamab: Continuous until PD.	
Visit Frequency		
Participant should visit the study site	Per treatment schedule, including EoT visit.	
Clinical Laboratory		
Safety Laboratory Assessments	Local laboratory assessments on the same day as treatment.	
Safety		
Physical examination, ECOG and vital signs ^b	On the same day as treatment.	
AE/SAE/SPM	Continuous ^a	
Survival ^c		Q4M ($\pm$ 14 days)
Efficacy		
Efficacy assessments	As per local SoC. Date of PD will be collected.	
Bone marrow aspirate	For disease evaluation, and MRD. Refer to Table 18 for collection time points (no molecular markers should be taken during the LTE).	
SST	Continuous	

^a Continuous during this period and until 30 days after the last dose if discontinued treatment during this period. (S)AEs considered related to the study treatment should be reported until the end of the study.

^b Clinically relevant abnormalities should be reported as AEs.

^c May be obtained by telephone or chart review.

10.10. Appendix 10: Outpatient JNJ-79635322 and Teclistamab Administration Through the First Treatment Dose

If allowed by local regulations and institutional guidance, investigators should assess the participant's clinical status and the healthcare facility's capability to safely manage outpatient logistics. General recommendations for each of these considerations are provided below.

Clinical Consideration

General guidance and clinical considerations for a participant who is suitable for outpatient administration and follow-up includes the following:

- No packed red blood cell or platelet transfusions within the last 7 days prior to step-up dosing and first treatment dose.
- No fever or active infection (bacterial, fungal, viral) requiring ongoing antiviral, antibacterial, or antifungal treatment since study enrollment.
- No Grade ≥ 3 neutropenia, anemia, and thrombocytopenia or Grade ≥ 3 , clinically significant non-hematologic AEs.
- No clinically significant coagulopathy that would increase the risk of bleeding in the setting of cytopenia.
- Participants who have high tumor burden as defined in Section 6.6.3.11 and who are receiving prophylactic treatment for TLS are eligible for outpatient administration with optional consideration for tocilizumab premedication, if deemed appropriate by the investigator.
- No rapidly progressing disease per investigator assessment.
- No deterioration in neurologic status, including mental status changes such as confusion or increased somnolence. The only exception is confusion or somnolence that has resolved and must be attributed to medications known to cause confusion or somnolence.
- The following laboratory parameters:
 - eGFR >30 mL/min.
 - AST and ALT $<2.5 \times \text{ULN}$.

Logistical Consideration for Qualified Healthcare Facility

Outpatient administration and post-JNJ-79635322 and teclistamab administration follow-up must take place at a qualified healthcare facility. The following should be considered for outpatient administration and follow-up:

- Participant should stay within 30 minutes of transportation to the site and remain in the company of a competent adult at all times for a minimum of 2 days after each SUD of JNJ-79635322 or 2 days after each SUD of teclistamab and after the first treatment dose of JNJ-79635322 or teclistamab (see Section 6.1.3).
- Site should prepare a documented plan to ensure timely management of CRS/ICANS if these occur in an outpatient setting, including a mechanism to notify the hematology team and treat in a timely manner if clinically indicated.

- Participant and accompanying competent adult should be made aware of the presenting signs and symptoms of JNJ-79635322 or teclistamab-associated toxicities, including but not limited, to CRS, ICANS and infections.
- Site should provide the participant with a thermometer, educational material, diary, and wallet card, including but not limited to, notification of enrollment in a clinical study and emergency contact information.
- Participant should carry a wallet card for study participant identification at all times.
- Participant should comply with all the protocol requirement procedures, including measuring and recording of oral temperature twice daily (≥ 8 hours apart) and coming to the site for safety assessments according to the relevant SoA (Section [1.3](#)).

10.11. Appendix 11: Criteria for Response to Multiple Myeloma Treatment (2016 IMWG response criteria)

Response	Response Criteria
sCR	- CR as defined below, <i>plus</i> - Normal FLC ratio, <i>and</i> - Absence of clonal PCs by immunohistochemistry (κ/λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ patients, respectively, after counting ≥ 100 PCs) or negative 2-4 color flow cytometry.
CR ^a	- Negative immunofixation of serum and urine, <i>and</i> - Disappearance of any soft tissue plasmacytomas, <i>and</i> $<5\%$ PCs in bone marrow - No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine^b.
VGPR ^a	- Serum and urine M-component detectable by immunofixation but not on electrophoresis, <i>or</i> $\geq 90\%$ reduction in serum M-component plus urine M-component <100 mg/24 hours. - In addition to the above criteria, if present at baseline $>90\%$ reduction in the sum of the maximal perpendicular diameter (SPD) compared with baseline for soft tissue plasmacytoma.
PR	$\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to <200 mg/24 hours. - If serum and urine M-protein are not measurable, a decrease $\geq 50\%$ in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. - In addition to the above criteria, if present at baseline, $\geq 50\%$ reduction in the size (SPD) of soft tissue plasmacytomas is also required.
MR	$\geq 25\%$ but $\leq 49\%$ reduction of serum M-protein <i>and</i> reduction in 24-hour urine M-protein by 50% to 89%. - In addition to the above criteria, if present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required.
Stable disease	Not meeting criteria for sCR, CR, VGPR, PR, MR, or PD.

PD ^c	Any one or more of the following criteria: • Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL), <i>and/or</i> – Urine M-component (absolute increase must be ≥ 200 mg/24 hours), <i>and/or</i> – Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD of >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion >1 cm in short axis. • Definite development of new bone lesions or definite increase in the size of existing bone lesions.
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^a Clarifications to the criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 (or reference range in testing laboratory) in addition to CR criteria listed above. VGPR in such subjects requires a $\geq 90\%$ decrease in the difference between involved and uninvolved FLC levels.

^b In some cases, it is possible that the original M-protein light chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered as a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a subject has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.).

^c Clarifications to the criteria for coding PD: bone marrow criteria for PD are to be used only in subjects without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, and FLC, and does not refer to bone lesions, or soft tissue plasmacytomas and the “lowest response value” does not need to be a confirmed value.

Notes: All response categories (CR, sCR, VGPR, PR, MR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if lowest M-component is ≥ 5 g/dL.

Source: Adapted from [Durie 2015](#), [Rajkumar 2011](#), and [Kumar 2016](#)

10.12. Appendix 12: Renal Function

Refer below for the CKD-epi creatinine formula to calculate eGFR:

$$\text{eGFR (in ml/min)} = 142 \times (\text{SCr}/\kappa)^{\alpha} \times 0.9938^{\text{Age}} \times 1.012 [\text{if female}] \times (\text{patient BSA}/1.73)$$

with:

$\alpha = -0.241$ if female and sCR ≤ 0.7 mg/dL

$\alpha = -0.302$ if male and sCR ≤ 0.9 mg/dL

$\alpha = -1.2$ if female and sCR > 0.7 mg/dL, or if male and sCR > 0.9 mg/dL

$\kappa = 0.7$ if female

$\kappa = 0.9$ if male

Age in years

SCr = standardized serum creatinine in mg/dL

Reference: [Inker 2021](#).

10.13. Appendix 13: New York Heart Association Functional Classification

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

10.14. Appendix 14: Protocol Amendment History

Changes made in this amendment are detailed in the Protocol Amendment Summary of Changes table.

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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): Thomas Renaud

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(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
Renaud Thomas 1069156	20-Feb-2026 13:32:26 (GMT)	Document Approval