Janssen Research & Development *

Clinical Protocol

A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma

CARTITUDE-4

Protocol 68284528MMY3002; Phase 3
AMENDMENT 4

JNJ-68284528 (ciltacabtagene autoleucel)

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	18 August 2022
Amendment 3	14 June 2022
Amendment 2	02 July 2021
Amendment 1	20 March 2020
Original Protocol	25 October 2019

Amendment 4 (18 August 2022)

Overall Rationale for the Amendment: The reason for the amendment is to change the number of PFS events required to trigger the interim analysis. Per health authority request, the interim analysis will take place after approximately 75% of the total PFS events have been observed.

The changes made to the clinical protocol 68284528MMY3002 as part of Protocol Amendment 4 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
1.1. Synopsis, Statistical Methods	Removed reference to the interim analysis PFS events used in the sample size calculation.	The number of PFS events required for the interim analysis was modified following health authority request
4.1.2. Arm B; 9.5. Interim Analysis	The interim analysis for efficacy will occur at approximately 188 PFS events (change from approximately 165 events) which corresponds to 75% of the total planned 250 PFS events (modification from 66% of the total planned PFS events) The estimated number of OS events at PFS IA will be changed accordingly.	
1.3. Schedule of Activities (SoA), Table 1, Table 2, Table 3, Table 4, Table 5	Revisions to clarify that subjects will be tested for IgG, IgA, IgM, IgD, and IgE at screening. Only subjects identified as have IgD or IgE type myeloma at screening will need testing for IgD and IgE post screening.	Changes for clarity in collection and testing of samples for quantitative immunoglobulins.
1.3. Schedule of Activities (SoA), Table 3;Table 5 8.1.1. Myeloma Protein Measurements in Serum and Urine	Language added to provide clarity regarding when DSIFE testing is not needed for subjects in Arm A and Arm B.	Revisions for clarity
1.3. Schedule of Activities (SoA), Table 5; 8. Study Assessments and Procedures 8.9. Biomarkers	Added that sites will be notified if a subject has a sample that tests positive for RCL and that if a subject does not have a positive sample RCL will not be required to be collected after the 12-month visit	Addition for clarity
2.3. Benefit-Risk Assessment	The category of ‘other neurotoxicities’ was split into Movement and Neurocognitive Toxicity (ie, Parkinsonism), Cranial Nerve Palsies, Peripheral Neuropathy, and Guillain-Barré Syndrome.	Change to align with the current edition of the cilta-cel IB.
8. Study Assessments and Procedures	Added guidance regarding the types of procedures and documentation of procedures that	To provide guidance for home health care and telehealth visits.

Section Number and Name	Description of Change	Brief Rationale
	can be conducted via home health care on an exceptional basis.	

Amendment 3 (14 June 2022)

Overall Rationale for the Amendment: The reason for the amendment is to inform investigators that patients receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy, and to provide additional guidance for prevention and mitigation. Additional guidance for HLH and additional clarifications were also incorporated.

Section Number and Name	Description of Change	Brief Rationale
2.3 Benefit-Risk Assessment; 6.1.6.7 Serious Infections; 6.5.1.3 Prophylaxis for Infections; 10.29 Appendix 29: Study Conduct During a Natural Disaster	Added guidance on measures to prevent and mitigate COVID-19 infection, including the importance of vaccines and other preventative measures, the use of prophylaxis therapy (eg, Evusheld, if available), and the use of antiviral therapy (eg, Paxlovid, if available) for COVID-19 infection.	To provide additional prevention and mitigation guidelines for COVID-19 infections in patients treated with cilta-cel.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.30 Appendix 30: Adverse Event Reporting Guidance for Study 68284528MMY3002	Added text to indicate that events of COVID-19 infection will be reported during the first-year post-infusion of cilta-cel.	To expand the reporting timeframe for COVID-19 infections.
1.3 Schedule of Activities (SoA), Tables 4 and 5; 6.5 Concomitant Therapy; 10.29 Appendix 29: Study Conduct During a Natural Disaster	Specified that medications for the prevention and treatment of COVID-19, including vaccinations against COVID-19, will be reported until 1 year after cilta-cel infusion.	To expand the reporting timeframe for COVID-19 medications.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.30 Appendix 30: Adverse Event Reporting Guidance for Study 68284528MMY3002	For Arm B, added clarification of the requirement for expedited reporting (within 24 hours) of any grade movement and neurocognitive toxicity (ie, parkinsonism).	To ensure this risk is communicated in an expedited fashion, consistent with health authority feedback.
2.3 Benefit-Risk Assessment; 6.1.6.1 Management of Cytokine Release Syndrome	Added language regarding features of HLH that may put subjects at high risk of bleeding and included additional measures to be taken if HLH is suspected.	To increase awareness and provide additional guidance about the risk of HLH, consistent with health authority feedback.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information;	Removed statement that “Grade 1 or 2 AEs of CRS and neurotoxicity would not qualify for expedited reporting unless they meet SAE criteria”	For clarity.
1.3 Schedule of Activities (SoA), Table 5	The footnote for cytokine profiling (serum) was changed from “l” to “n”.	Correction to fix error.
1.3 Schedule of Activities (SoA), Table 5	Added Study Days for each specific month timepoint for MRD (bone marrow aspirate).	Revised for clarity.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Table 5	Added language regarding collection of RCL samples.	Revised to include additional information for the RCL requirement.
1.3 Schedule of Activities (SoA), Table 5; 10.2 Appendix 2: Clinical Laboratory Tests	Edits/footnotes added to clarify which subjects are required to do the CD4/CD8 lymphocyte panel. For Arm B in Table 5, the footnote 'r' was added for CD4/CD8 Lymphocyte panel.	Revised for clarity.
2.2.6.1 Pomalidomide, Bortezomib, and Dexamethasone; 8.3.3 Pregnancy; 10.12 Appendix 12: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Reference to the Pomalyst was revised to add the generic name.	Revision to clarify that generic pomalidomide can be used.
6.1.5.3 Conditioning Regimen	Text added: If required, approval from the relevant health authorities for use of the product will be obtained in compliance with local regulations regarding notification and approval.	Revised for clarity and consistency with other studies in the program.
6.1.6.1 Management of Cytokine Release Syndrome	Table 11 (Guidelines for the Management of Cytokine Release Syndrome) reorganized and modified to include organ toxicity.	Revised based on health authority feedback.
6.1.6.2.1 CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])	Added guidance in text for treatment if concurrent CRS is suspected during a neurologic event.	Added for clarity.
6.1.6.2.1 CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])	Table 12 (Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS]) reorganized and modified based on ASTCT consensus criteria.	Revised based on health authority feedback.
6.6.2 Pomalidomide and Bortezomib Dose Modification for Hematologic Toxicity	Added that for Grade 1 neuropathy change in bortezomib frequency may be considered based on clinical judgement and/or institutional practice. For Grade 1 with pain or Grade 2 added that a reduction of dosing by one level is a maximum dose of 1.0 mg/m^2	Revisions for clarity.
6.6.2 Pomalidomide and Bortezomib Dose Modification for Hematologic Toxicity (Table 21, footnote d)	Clarified that change in the schedule of bortezomib administration to once per week should occur on Days 1, 8, and 15.	Change made for clarity.
8 Study Assessments and Procedures	Updated the approximate blood volume to be collected from each subject.	Updated to address increase in volume for RCL and whole blood CyTOF samples.
8.1.2 Imaging	Added language regarding the diagnostic quality if a CT scan is used.	The sentence was previously removed in error.
8.9 Biomarkers	Added language regarding post-infusion samples and included additional measures to be taken if RCL is negative or positive.	Revised for consistency with other studies in the program.

Section Number and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Added a request to provide COVID-19 antibody titers, if available, post cilta-cel infusion for up to 1 year.	Request for clarity regarding COVID-19 antibody reporting, including timeframe.

Amendment 2 (02 July 2021)

Overall Rationale for the Amendment: Overall reasons for the amendment are to provide guidance on study conduct during the COVID-19 pandemic, to enable increased patient access via the lowering of inclusion criteria for study entry (ie, reduced serum monoclonal paraprotein levels), and to revise safety reporting requirements to allow extended data collection.

Revisions noted below are representative of the changes. In some cases, new text is displayed in bold font and deleted text noted with strikethrough.

Section Number and Name	Description of Change	Brief Rationale
10.29 Appendix 29 Study Conduct During a Natural Disaster	Natural Disaster/COVID-19 appendix added.	Added to provide guidance on study conduct during the COVID-19 pandemic, including considerations for vaccine administration.
5.2 Exclusion Criteria	Criterion 6 was updated to indicate that vaccination with live attenuated vaccines is not permitted 6 weeks prior to randomization.	Updated to maintain consistency with other sections and other studies in the program.
5.1 Inclusion Criteria	Criterion 2 was edited for the following reasons: • To indicate a change in the serum monoclonal paraprotein (M-protein) level from ≥ 1.0 g/dL to ≥ **0.5 g/dL** • To add a note that '**If central and local laboratory studies are performed the same day, only the central laboratory results will be considered.**'	Updated and clarified the criteria of measurable disease at screening necessary for a documented diagnosis of multiple myeloma (MM).
5.2 Exclusion Criteria	Criterion 18 was revised to remove 'history of autoimmune disease within 2 years'	To increase patient access by providing a more inclusive patient population
10.7 Appendix 7: Criteria for Response to Multiple Myeloma Treatment	Footnote added to the table to indicate that patients with <0.5 g/dL at baseline cannot be assessed for minimal response.	Clarification and alignment with other sections of the protocol.
5.1 Inclusion Criteria	Criterion 6.1 was updated to Criterion 6.2 in order to clarify that subjects must be refractory to lenalidomide in at least one prior line.	Clarification.
4.1.2 Arm B	Updated section for the following: • To provide information on additional cycles of bridging therapy • To clarify that after PD, subjects will be followed for delayed adverse events (Arm A) and delayed adverse events including SPMs (Arm B) • To provide further monitoring details for subjects who progress in Arm B prior to receiving cilta-cel	Clarification and alignment with other sections of the protocol.

Section Number and Name	Description of Change	Brief Rationale
	• To provide the study number (ie, Study 68284528MMY4002) of the subsequent long-term follow-up study for the continued monitoring of subjects treated with cilta-cel.	
7.1.2 Discontinuation of Study Treatment for Arm B	Updated section to clarify that after PD, subjects will be followed for delayed adverse events (Arm A) and delayed adverse events including SPMs (Arm B).	Clarification and alignment with other sections of the protocol.
1.1 Synopsis, Intervention Groups and Duration	Text clarified to note that: 'After confirmed PD, subjects will be followed for survival, subsequent anti-myeloma therapies, and **delayed AEs including** SPMs every 16 weeks until the end of the study.'	Clarification and alignment with other sections of the protocol.
1.3 Schedule of Activities (SoA), Table 1	Text for bone marrow aspirate and core biopsy procedure was revised to note sampling conditions for rescreened patients.	Clarification
1.3 Schedule of Activities (SoA), Tables 1, 2, 3, and 4	Table 1: Deleted the assessment of 'secondary primary malignancy' from the screening phase as it is assessed from randomization onwards, not from the signing of the Informed Consent Form (ICF). Tables 2, 3, and 4: Text for assessment of 'secondary primary malignancy' was clarified to note that assessment is from the time of randomization, and not from signing of the ICF.	Correction
1.3 Schedule of Activities (SoA), Tables 2, 3, and 5	In order to indicate that collection of the EQ-5D-5L questionnaire in the post-treatment follow-up phase (ie, Post-PD) has been revised from every 6 months until EOS to every 16 weeks ±14 days, the footnote (and corresponding in-table cross-reference) was deleted.	Revision of collection period.
1.2 Schema; 1.3 Schedule of Activities (SoA), Tables 2 and 3	Revised text to indicate that the end of treatment is to occur within 30 days of the last dose.	Clarified timing of the end of treatment.
1.2 Schema	Text revised to indicate that patients will be followed-up for survival status, serious adverse events, and delayed adverse events.	Updated assessments made during the follow-up period.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Tables 2, 3, 4, and 5	Revised timing of plasmacytoma assessment via radiology to: Table 2: '~~C4D1~~**C5D1** (±~~7~~ **14** days) and then every 12 weeks **(**±~~7~~ **14** days)'. Table 3: '~~C3D1~~**C4D1** (±~~7~~ **14** days) and then every 12 weeks (±~~7~~ **14** days) In Table 4, a window of ≤72 hours was added for plasmacytoma assessment at Apheresis. Information was added regarding the timing of on plasmacytoma assessment during the Treatment Phase. In Table 5, the window for plasmacytoma assessment via radiology was revised to ±14 days.	Clarified information regarding plasmacytoma assessment, including updates to timing and extension of the assessment window; revisions were made to harmonize assessment across treatment arms where possible.
1.3 Schedule of Activities (SoA), Tables 2, 3, and 4	Timing of Quantitative immunoglobulins, SPEP and UPEP procedures to be conducted on Day 1 of Cycles 1 to 8 (Table 2) and Cycles 1 and 2 (Table 3) was revised to note an assessment window of **'(±7 days starting with Cycle 2)**'. The timing for the conduct of the aforementioned evaluations on Day 1 of Cycles 9 and beyond (Table 2) and for Cycles 3-6 and Cycles 7 and beyond (Table 3) was revised for an assessment window of **'(±7 days)**'. Timing of the Serum FLC and SIFE/UIFE assessment was revised in Tables 2 and 3 to note an assessment window of '**(±7 days starting with Cycle 2)**'. In Table 4 a window of '**(±7 days)**' was added for the assessment of SPEP, UPEP, Serum FLC and SIGE/UIFE.	Clarification of timing and extension of assessment window.
1.3 Schedule of Activities (SoA), Tables 2 and 3	For Bone marrow aspirate and core biopsy, deleted the following: "To confirm CR (including sCR) ~~and at the time of PD. A portion of aspirate collected at PD should be sent to the central laboratory~~.: Also deleted from Notes: "~~Send fresh aspirate samples to central laboratory (Section 8.1.4).~~"	A bone marrow sample at the time of PD is only needed for subjects in Arm B
1.3 Schedule of Activities (SoA), Tables 2 and 3	For MRD (bone marrow aspirate) assessment, a cross-reference to the footnote stating 'A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.' was added for sample collection at time of suspected CR or sCR.	Clarification

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Tables 2, 3	Reporting of adverse events and concomitant therapy will be extended until '30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier'.	Extension of reporting period.
1.3 Schedule of Activities (SoA), Table 5	Additional language was added to Table 5 regarding reporting of non-serious, all serious, and delayed AEs until EOS.	Clarification
1.3 Schedule of Activities (SoA), Table 4	Timing for Physical examination and ECOG procedures was revised to indicate that the assessment window during apheresis will be '**(≤72 hrs prior to apheresis)**'.	Clarification of timing.
1.3 Schedule of Activities (SoA), Table 4	Plasmacytoma assessment in Arm B, prior to JNJ-68284528 infusion, revised to state assessment by physical exam (not by PET/CT)	Assessment by radiology does not occur until Day 84
1.3 Schedule of Activities (SoA), Table 4	Notes regarding the assessment of vital signs were updated to state that vital signs can be omitted on days where bortezomib or daratumumab administration is planned to be omitted. Updated notes for complete blood count (CBC) with differential and full metabolic panel to indicate that if bortezomib or daratumumab administration is planned to be omitted, both CBC and chemistry assessments on those days can be done locally but need to be reviewed by the Investigator.	To minimize the need for patients to travel to the site.
1.3 Schedule of Activities (SoA), Table 5	Removed "~~At 6 months (D196) post CAR-T infusion (unless done w/n last 3 months (bone marrow aspirate).~~" Also clarified that the bone marrow biopsy and aspirate to confirm CR is for the local lab.	The D196 bone marrow aspirate is for flow cytometry and CyTOF not disease assessment.
1.3 Schedule of Activities (SoA), Table 4; 6.1.5.2 Criteria for Apheresis	Edits/footnotes added to indicate that blood samples for immunophenotyping and flow PK CAR+ T cells, and CyTOF/PBMC (TCRSeq)/plasma will be recollected prior to the second apheresis.	To provide instruction on blood sample collection for biomarker assessment for subjects requiring a repeat apheresis.
2.3 Benefit-Risk Assessment	Removed footnote 'a' from TLS in Table 6.	TLS is no longer an adverse event of special interest
6.1.5.3 Conditioning Regimen	Revised to note cilta-cel administration will follow directions described in the cell therapy product procedures manual (CTPPM), and not the site investigational product procedures (SIPPM).	Revised for administrative purposes and clarity.
	Revised to clarify the product release criteria, including instruction that '**Products provided through this exceptional release or similar process that exceed the protocol maximum dose will not qualify for overdose reporting**'.	
6.1.1 Dexamethasone	Instruction added for the administration of dexamethasone in subjects on Arm A receiving dexamethasone as part of the standard therapy PVd.	To clarify timing and doses of oral dexamethasone to be administered to subjects

Section Number and Name	Description of Change	Brief Rationale
		≤75 years of age or >75 years of age.
6.1.5.1 Apheresis and Bridging Therapy	Added '**If for logistical reasons apheresis cannot be performed 3-6 days after randomization, shorter timeframe will be accepted when possible.**'	Clarification
6.1.5.4 Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine) Dosing	Text updated to note that prior to the start of the conditioning regimen, subjects may not have received: • **Dexamethasone within 7 days** • No live, attenuated vaccines within **6** weeks	Updates were made for changes in the conditioning regimen and for alignment with other sections of the protocol.
6.5.3 Prohibited Therapies	Updated text for Arm B to note: • Corticosteroid use is to be avoided after the start of lymphodepletion and prior to Day 112 • No vaccination with live, attenuated vaccine ≤6 weeks before starting the conditioning regimen	Updated for safety concerns and to maintain consistency both within the protocol and with other studies in the program.
6.6.2 Pomalidomide and Bortezomib Dose Modification for Hematologic Toxicity; 6.6.4 Pomalidomide and Daratumumab Dose Modification for Hematologic Toxicities	Updated guidance on dose modification for pomalidomide and/or bortezomib and daratumumab.	Updated to address dose delays/skipped doses.
6.1.6.6 Hypogammaglobulinemia	Section updated to note that: • Subjects with IgG <400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or SC IgG as per institutional guidelines. • Vaccination with live attenuated virus vaccines is not permitted for at least 6 weeks prior to the start of the conditioning regimen	Revised for consistency with other studies in the program
6.1.6.8. Hypersensitivity Reactions	Ampicillin was deleted.	
1.3 Schedule of Activities (SoA), Table 5	Table revised to indicate that handwriting analysis will be collected on Day 56. Starting from Day 84, handwriting analysis will be performed every 28 days up to and including Day 196.	Clarification regarding timing.
1.3 Schedule of Activities (SoA), Table 5; 8.2.4 Clinical Safety Laboratory Assessments; 10.2 Appendix 2: Clinical Laboratory Tests	Added the laboratory assessment 'CD4/CD8 Lymphocyte panel'.	Safety assessment added as certain opportunistic infections are common in patients with low CD4 count counts.
1.3 Schedule of Activities (SoA), Table 5	Additional assessment of CAR-T chemistry will be performed at Days 84 and 112.	Safety parameter added in order to closely monitor patients after cilta-cel administration.
1.3 Schedule of Activities (SoA), Table 5	Bone marrow core biopsy at Day 56 was deleted.	Typo correction and clarification of repetitive text.

Section Number and Name	Description of Change	Brief Rationale
	Text regarding the collection of bone marrow assessment and core biopsy samples for Day 84 through Day 196 was revised.	
10.2 Appendix 2: Clinical Laboratory Tests	The list of laboratory tests was updated; changes included additions to the list of CAR-T Chemistry assessments (ie, triglycerides and fibrinogen), and Tests at Screening only (ie, to clarify Hepatitis C virus (HCV) infection).	Safety parameter added to closely monitor patients after cilta-cel administration.
1.3 Schedule of Activities (SoA), Table 5	The laboratory assessment 'Full Metabolic Panel' was deleted.	Deleted as redundant; the CAR-T chemistry assessment evaluates the same parameters as the full metabolic panel, as well as additional parameters that aid in the diagnosis and monitoring of hemophagocytic lymphohistiocytosis (HLH).
1.3 Schedule of Activities (SoA), Table 5	Flow cytometry and CyTOF instructions for the period of Day 35 to 196 were updated to for collection 'at time of suspected CR/sCR'.	Clarification of timing
1.3 Schedule of Activities (SoA), Table 5	The following footnote (m) was added for PK CAR Transgene levels: **'After Day 112, CAR transgene levels, and CAR+ T cell counts will be measured every 8 weeks through 1 year. After 1 year, PK CAR transgene levels and CAR+ T cell counts (immunophenotyping) will be measured at least annually until EOS or PD, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.'** Footnote 'm' also added as a cross reference to Immunophenotyping (whole blood)	Text added to clarify CAR transgene sampling conditions in alignment with FDA guidance.
6.1.5.7 JNJ-68284528 Administration	Clarification of cilta-cel administration criteria, including information on the quantity of the dose, and dosing instructions (ie, units of weight).	Revised for clarity and to be consistent with other studies in the program.
8 Study Assessments and Procedures (Overview)	Updated the approximate blood volume to be collected from each subject.	Blood volume updated to reflect changes
7.1.2 Discontinuation of Study Treatment for Arm B	Text added to include '**signs of active infection**' as a reason for discontinuation.	Update made to align discontinuation criteria with that noted in Section 6.1.5.5.
9.4.4 Safety Analyses; 10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, Severity Criteria	A paragraph was added regarding the summarization and grading of both CRS and CAR-T cell-related neurotoxicity, their individual symptoms, and neurotoxicity not temporally associated with CRS or any other neurologic AEs that do not qualify as ICANS.	Text added to clarify grading and to note that the analysis of adverse events for CRS and neurotoxicity will separate the symptoms.
2.2.5 Summary of Nonclinical and Clinical Studies; 2.3 Benefit-Risk Assessment; 6.1.6.2.2 Other Neurotoxicities	Updated section with (or provided cross-reference to) current safety and efficacy data.	Updated based on current clinical data and to align with other studies in the program.

Section Number and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, Severity Criteria, Special Reporting Situations	Instruction added on the assessment, reporting, and monitoring of special reporting situations, including those that meet the criteria of an adverse event (including serious adverse events [SAEs]) and death not related to progressive disease (PD).	Clarification of reporting and monitoring procedures.
6.1.6.3 Tumor Lysis Syndrome	Deleted tumor lysis syndrome as an adverse event of special interest (AESI).	Clarification of AESIs.
6.1.6.4 Second Primary Malignancy	Noted that that second primary malignancies (SPMs) on both arms of the study will be AESIs.	Clarification of AESIs.
8 Study Assessments and Procedures	Section updated with the following revisions: • 'Local laboratory data may be collected if central laboratory data is not available at a particular timepoint, (Section 8.1.6), ~~however, this does not include screening assessments~~.' • The list of study specific materials was updated: 'IPPI/SIPPM **(now known as CTPPM)**' • Revised sentence in Apheresis (Arm B only): 'Apheresis should be performed according to institutional standards~~, with a collection target of 6 x 10^9 PBMCs (range: 2 to 20 x 10^9 PBMCs); 2 apheresis collections may be performed to attain this target~~. Instructions for processing and shipping apheresis product are provided in the ~~SIPPM~~**CTPPM.'** • Added the following sentences to Treatment Phase-Bridging therapy, Conditioning Regimen, and JNJ-68284528 Administration (Arm B): '**Cycles beyond Bridging Cycle 1 may be truncated to allow for adequate washout and minimize time off therapy.**' **'Prior to dosing with JNJ-68284528, review of safety assessments and disease characteristics should be completed per Section 6.1.5.5.'** • Revised sentence in Post-infusion Follow-up Phase and Post-treatment Follow-up Phase (Arm B): 'In addition, **assessment for other delayed AEs, and assessment** ~~yearly until assessment~~ for RCL will be collected ~~yearly~~ until end of study and will continue to be collected yearly ~~until~~ **for up to** 15 years after the JNJ-68284528 administration in a	Updated to maintain consistency within the protocol and with other studies in the program.

Section Number and Name	Description of Change	Brief Rationale
	separate long-term follow-up study **(Study 68284528MMY4002)**.'	
8.1.2 Imaging	Text revised as follows: • 'Positron emission tomography (PET)/CT with diagnostic CT component. ~~If a CT scan is used it must be of diagnostic quality (see the disease response criteria in Section10.7).~~' • '~~If cross-sectional i~~**I**maging **reports** ~~was obtained, images~~ must be made available to sponsor for central team review upon request.' Additional instructional text was added to note that de-identified imaging reports (where permitted by local regulations) should be sent to the sponsor for review.	Updated to clarify imaging requirements.
8.1.3 Documentation of Soft Tissue Plasmacytomas	Text was revised to note imaging requirements (ie, remediation steps for poor quality CT, method documentation, and report availability). Additional changes were made to note that 'Assessments will continue every 4 weeks **or every 12 weeks** until development of confirmed CR or confirmed disease progression as long as the soft tissue plasmacytoma remains measurable on physical or **radiological** examination.'	Clarification of imaging and documentation requirements.
8.1.4 Bone Marrow Examination	Identified alternative analyses to be used in case of issues with sample availability or quality (ie, cytogenetics from central lab, diagnostic results from FISH analysis).	Clarification
8.1.5 Minimal Residual Disease Evaluations	Added text that bone marrow evaluations aimed at MRD detection do not need to be continued if a clone for MRD detection cannot be identified.	Clarification of next steps in case of issues with MRD detection.
8.1.6 Local Laboratory Assessments	Text added to clarify the role of central versus local labs (ie, preference/precedence for central lab collection).	Revised to provide direction/alternatives and clarify preference.
4.4 End of Study Definition	Section revised to note that all subjects who received JNJ-68284528 may participate in a long-term follow-up study; information on transition and monitoring was provided.	Text was added to allow the transition of subjects from MMY3002 to the LTFU study MMY4002.
6.8 Intervention After the End of the Study	Text modified to note delayed AEs will be an additional parameter assessed in the long-term follow-up study.	Clarification
7.2 Subject Discontinuation/Withdrawal from the Study	Added text that a subject who declines to continue study treatment hasn't necessarily withdrawn consent.	Clarification of withdrawal of consent.

Section Number and Name	Description of Change	Brief Rationale
6.1.5.5 Evaluation Prior to Administration of JNJ-68284528	Provided information on and cross-reference to safety monitoring and reporting procedures for subjects in Arm B who have confirmed PD after bridging therapy and have proceeded forward with JNJ-68284528 infusion.	Clarification
10.6 Appendix 6: Hepatitis B Virus Screening	Text was added to specify when HBV-DNA and AST/ALT laboratories should be performed.	Clarifications were made in alignment with the SOA.
10.28 Appendix 28: Anti-microbial Prophylaxis Recommendations	Information on recommended anti-microbial prophylaxis therapies was updated; changes included revisions to timing (ie, start and stop) and the inclusion of pentamidine as a treatment for *Pneumocystis* Pneumonia (PCP).	Update/clarification.
8.3.6 Anticipated Events	Text on the reporting of anticipated events was updated (ie, added cross-reference to instructions on reporting; provided a reminder of differing regulatory reporting requirements).	Provided clarification on the reporting of anticipated events.
10.30 Appendix 30: Adverse Event Reporting Guidance for Study 68284528MMY3002	Appendix added.	To provide guidelines for the reporting of AEs and expedited reporting.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Provided updates for AE reporting in Arm B (ie, clarified timing and AEs to be reported until the end of the study, deleted information on the reporting of events of neurotoxicity/existing neurologic AEs, AESIs and SPMs; provided cross-reference to Section 10.30 for additional guidance).	To be consistent with FDA guidance regarding long term follow-up of patients after CAR-T dosing.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 8.3.7 Adverse Events of Special Interest	Information on delayed AEs was added to Section 8.3.1. Section 8.3.7 was deleted. Text for AESIs updated and moved to Section 8.3.1, and Section 8.3.1 reorganized so that information on all AEs is provided before that on AESIs, delayed AEs, and serious AEs.	Readability; updated to provide information about AE reporting in one section in a logical order of presentation.
8.2 Safety Assessments	Physical examination findings will include findings from neurologic exams.	Clarification regarding safety assessments measured.
8.4 Treatment of Overdose	Provided cross-reference to product information, direction on dosing, and instruction on product evaluation if the maximum dose is exceeded.	Clarifications added
2.2.6.2 Daratumumab, Pomalidomide, and Dexamethasone 4.2.1 Study-Specific Ethical Design Considerations	Information was updated for Study 54767414MMY3013 (APOLLO).	To provide updated information for comparator agents (ie, daratumumab in combination with pomalidomide and dexamethasone [DPd]).
6.1.6.1. Management of Cytokine Release Syndrome	Minor updates were made (ie, for verbiage, Study MMY2001 results). Text was further updated to note that laboratory testing conducted for cases of	Revised for alignment with other studies in the program.

Section Number and Name	Description of Change	Brief Rationale
	severe CRS may reveal high serum levels of triglycerides.	
8.9.2 High-risk Classification by Cytogenetics	Amp 1q was added to the list of specific molecular subgroups.	Information update.
1.3 Schedule of Activities (SoA), Table 4	The table title was revised.	To clarify that the treatment phase in Arm B is: 'SBCM and Bridging Therapy'.
6.1.6.5 Prolonged Cytopenia	The section title was revised from 'Cytopenia' to '**Prolonged Cytopenia**'.	Clarification
6.1.6.7 Serious Infections	The section title was revised from 'Infections' to '**Serious** Infections'	Clarification
Title page; 1.1 Synopsis; 2 Introduction	Added generic name (cilta-cel) to the document and removed JNJ-68284528.	Added generic name
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Additional minor changes included: • The replacement of 'JNJ-68284528' with 'cilta-cel' in any new areas of text. • Revision of 'extramedullary plasmacytomas' to 'plasmacytomas' or 'soft tissue plasmacytomas' • CTPPM has been added. • References to the Attachments added in the relevant sections. • The study number of the long-term follow-up study was added as applicable.	Minor errors were noted, and additional minor clarifications/edits made

Amendment 1 (20 March 2020)

Overall Rationale for the Amendment: To add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for JNJ-68284528.

Section number and Name	Description of Change	Brief Rationale
Title Page	Study number was corrected to remove the JNJ- prefix: ~~JNJ-~~68284528MMY3002	Correction of error
1.3. Schedule of Activities	For Arm B in Table 5, collection of a handwriting sample and frequency of testing was added to the study procedures. Study Day 35 and Day 42 were added to the table as additional assessment days for collection of handwriting samples.	Update of safety information to include other neurotoxicities
	For Arm B in Table 5, extend ICE neurologic test to be performed at least daily until **ICANS is** resolved.	
	For Arm B in Table 5, Reporting of neurologic adverse events or exacerbation of existing neurologic adverse events will be extended to up to 12 months after JNJ-68284528 infusion	
2.2.5. Summary of Nonclinical and Clinical Studies	Added to summary of data for Study 68284528MMY2001 a description of 6 cases of other neurotoxicities.	
2.3. Benefit-Risk Assessment	Added other neurotoxicities to Table 6 (Risks Associated with JNJ-68284528 and Mitigation Strategies) as a subsection of neurological adverse events	
3. Objectives and Endpoints	Added exploratory objective and endpoints to characterize potential early predictive markers for neurotoxicity	
5.2. Exclusion Criteria	Revised Criterion #18 to add: Any history of Parkinson's disease or other neurodegenerative disorder	
6.1.6.2. Neurologic Adverse events	Divided section into overall neurologic adverse events with sub-sections of CAR-T cell related neurotoxicity (ICANS) (Section 6.1.6.2.1) and other neurotoxicities (Section 6.1.6.2.2)	
6.1.6.2.1. CAR-T Cell-related Neurotoxicity (ICANS)	Added "Consider performing neuroimaging (eg, MRI)…" Clarified that hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity temporally associated to CRS. Added recommendation to rule out alternative etiologies at first sign of neurotoxicity. Table 12 (Guidelines for Management of ICANS) – added to row 1 (ICE score 7-9) when no concurrent CRS dexamethasone can be considered	
6.1.6.2.2. Other Neurotoxicities	New section with guidance to monitor for other neurotoxicities	
8.2.7. Neurologic Examination	Added the following:	

Section number and Name	Description of Change	Brief Rationale
	For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of the brain and an EEG.	
8.2.7. Neurologic Examination; 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Added a section describing the assessment for qualitative changes in handwriting.	
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Text updated to include additional guidance regarding the reporting of neurotoxicity events.	
10.27: Appendix 27: CCI [redacted]	Table for added for qualitative grading of handwriting sample	
1.3. Schedule of Activities	Table 1, Screening Phase for All subjects, Hepatitis B recommendation revised as follows: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are **anti-HBc positive with or without** anti-HBs positive ~~and anti-HBc positive~~). For Arm A Table 2, Arm A Table3, and Arm B Table 5, Added "**For subjects at risk for HBV activation, monitor HBV DNA and AST/ALT** every 12 weeks (±7 days) until 1-year post-dose of JNJ-68284528" to HBV-DNA row.	Revisions to enrich the clinical trial population by allowing inclusion of subjects who are anti-HBc positive with or without anti-HBs positive
5.2. Exclusion Criteria	Revised criterion #17 (bullet 'b') to state "Subjects who are anti-HBs positive and without history of vaccination or for subjects who are **anti-HBc positive with or without** anti-HBs positive ~~and anti-HBc positive"~~ should have HBV DNA quantification test done.	
10.2. Appendix 2: Clinical Laboratory Tests	Revisions made to Hepatitis B serology: Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are **anti-HBc positive with or without** anti-HBs positive ~~and anti-HBc positive~~)	
10.6. Appendix 6: Hepatitis B Virus Screening	Revised hepatitis B screening guide to allow subjects who are anti-HBc positive only to participate in the study Added "If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance".	
1.3. Schedule of Activities	For Arm B, Table 5 moved MRD testing from Day 28 to Day 56	Change to align MRD testing with timing that is more clinically meaningful

Section number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Bone marrow aspirate and core biopsy requirement for Arm A in Table 2 and Table 3 was changed to reflect a portion of the aspirate collected at PD should be sent to the central laboratory.	Revised for clarity
1.3. Schedule of Activities	For Arm A Table 2 (PVd), Table 3 (DPd) and Arm B Table 5: MRD (bone marrow aspirate) required of all dosed subjects at defined timepoints regardless of status and for subjects with suspected CR, at the time of CR and then yearly for subjects that remain on study up to PD.	
1.3. Schedule of Activities	For Arm A, footnote "a" for Table 2 and Table 3 was updated with the following text "Assessments and procedures on Cycle 1 Day 1 to be performed prior to administration of study intervention."	
1.3. Schedule of Activities	For Arm B, Table 4, infectious disease testing during the Apheresis phase of the study will be performed for other countries as required by country or per local regulations	
1.3. Schedule of Activities	For Arm B, Table 4, added the following to footnote "a": Safety laboratory assessments may be performed prior to initiating bridging therapy.	
1.3. Schedule of Activities	For Arm B, Table 4, added footnote "c" to Apheresis heading stating that "Assessments and procedures to be performed prior to apheresis"	
1.3. Schedule of Activities	For Arm B in Table 5, the frequency of CBC with differential was updated to every 12 weeks (=/- 7 days) **on 2 occasions** and then every 6 months (+/- 14 days) until PD or EOS, whichever is earlier.	
1.3. Schedule of Activities	For Arm B in Table 5, the bone marrow aspirate and core biopsy requirement was updated to "At time of PD **or** ~~and~~ EOS (bone marrow biopsy and aspirate)". Also added that bone marrow biopsy should be obtained at PD and sent to the central laboratory.	
1.3. Schedule of Activities	For Arm B in Table 5, the footnote 'l' was added for Immunophenotyping	
1.3. Schedule of Activities	For Arm B in Table 5, PK CAR transgene samples, soluble BCMA samples, and immunogenicity samples will be collected at PD or EOS.	
1.3. Schedule of Activities	For Arm B in Table 5 footnote 'd', provision of window at end of infusion for vital signs was deleted	
2.3. Benefit-Risk Assessment	Added guidance to CRS and neurologic adverse events to "Notify the sponsor if subject is experiencing Grade 2 or higher CRS".	
5.1. Inclusion Criteria	Revised inclusion criterion 6 to clarify definition of refractory to lenalidomide, to include failure to achieve minimal response.	

Section number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Revised exclusion criterion 10 to provide guidance to subjects with contraindications to DPd or PVd.	
6.1. Study Interventions Administered	Formatting change to Table 8 to add a row titled "Either DPd or PVd followed by" Revised table footnotes to provide guidance if additional cycles are indicated	
6.1.2. Bortezomib	Added guidance for consideration of additional cycles of bridging therapy	
6.1.5.7. JNJ-68284528 Administration	Clarified in hospitalization requirements in Table 10 that hospitalization is required for Grade 2, 3, or 4 ICANS **temporally associated to CRS**. Added that hospitalization for neurotoxicity that is not temporally associated with CRS is at the discretion of the investigator.	
6.2.1. Accountability	Added clarification that information in this section relates to study treatment that is supplied to investigational sites from the sponsor.	
6.5. Concomitant Therapy	Revised concomitant chemotherapy entry as follows: Chemotherapy (~~including any~~ given for **CAR-T cell related toxicity** ~~HLH~~)	
6.5.2. Permitted Medications	Added that chemotherapy agents used to treat CAR-T cell related toxicities are permitted upon consultation with the sponsor. Removed exception for therapy to treat CAR-T cell related toxicity from prohibited therapies in Section 6.5.3.	
6.6.1. Dexamethasone	Clarified statement that for subjects whose dexamethasone treatment is discontinued, they may continue to receive pomalidomide/bortezomib or daratumumab/pomalidomide	
8.1.4. Bone Marrow Examination	Clarified that portion of bone marrow aspirate to be sent to central laboratory for immunophenotyping and to monitor BCMA is specific to subjects in Arm B.	
8.1.5. Minimal Residual Disease Evaluations	Clarification of collections for MRD	
8.3.6. Anticipated Events	Moved Anticipated Events into its own section (from Section 8.3.5) as it is not a regulatory reporting requirement for all countries	
8.3.1. Adverse Events of Special Interest	Added other neurotoxicities	
8.5.3. Pharmacokinetic Parameters and Evaluations	Clarification to existing text.	
8.9. Biomarkers	Defined that additional biomarker samples include but are not limited to serum or PBMCs from whole blood. Clarified that a tumor sample should be collected from subjects in Arm B diagnosed with a SPM.	

Section number and Name	Description of Change	Brief Rationale
8.9. Biomarkers	Added that if a subject dies and an autopsy is preformed, specimens may be requested by the sponsor for analysis.	
9.3. Populations for Analysis	Safety analysis set consists of All randomized subjects who received ~~at least one dose~~ **any part** of study treatment.	
9.4.6. Biomarkers Analyses	Clarified that core biopsy sample from bone marrow biopsy performed at disease progression should be sent to the central laboratory.	
1.3. Schedule of Activities	For Arm B in Table 5, post-infusion follow-up assessment Days revised: Day 8 assessment changed to Day 7 and Day 22 assessment changed to Day 21	Revised for consistency with other studies in the program
1.3. Schedule of Activities	For Arm B in Table 5, removed post end of infusion collections for PK CAR transgene levels sample and soluble BCMA sample.	Reduction in sample collection
1.3. Schedule of Activities; 8.1.6. Local Laboratory Assessments; 8. Study Assessments and Procedures; 8.1. Efficacy Assessments; 8.1.1. Myeloma Protein Measurements in Serum and Urine	Table 2 (footnote d), Table 3 (footnote e), Table 4 (footnote d), Table 5 (footnote o): Added that local laboratory assessments may be used under specified circumstances. Guidance added that all efforts should be made to collect efficacy data centrally, however local data may be collected if central data is not available at a particular time point.	Revisions to allow for flexibility in collecting laboratory data
1.3. Schedule of Activities	Dexamethasone treatment in Table 3 revised for clarity to state “Days 1, 8, 15, and 22 of each 28-day cycle”	Correction of error
	For Arm B in Table 5, Assessment of plasmacytomas by physical examination if applicable was added at the time of conditioning regimen. Footnote “n” added to indicate that the assessment should occur as close to prior to the first dose as possible.	
4.4. End of Study Definition	Correction made to the study completion definition: A subject will be considered to have completed the study if he or she has either died before the end of the study, is **not** lost to follow-up, has **not** withdrawn consent for study participation or study terminated by sponsor.	
6.1.6.1. Management of Cytokine Release Syndrome	In second row of Table 11, footnote for low-flow nasal cannula was corrected from “a” to “d”.	
6.5.1.3. Prophylaxis for Infections	Prophylaxis to prevent herpes zoster reactivation should continue for at least ~~3 months~~ **6 months** following last dose of study treatment.	

Section number and Name	Description of Change	Brief Rationale
8.12 Medical Resource Utilization and Health Economics	Deleted the statement "Health Economics parameters are not evaluated in this study" and added "All health economic data will be used only in a de-identified manner". Added "**Health economics data such as** medical resource utilization data associated with medical encounters…."	
10.2. Appendix 2: Clinical Laboratory Tests	Correction made to Laboratory Assessments: "Tests within 60 days prior to ~~apheresis~~ **randomization**"	
10.4 Appendix 4: Adverse Events	Daratumumab safety information reference changed from PI or SmPC to IB	
2.3. Benefit-Risk Assessment	Removed statement "Clinical experience with JNJ-68284528 and LCAR-B38M CAR-T cells is limited" as to date almost 100 subjects have received an infusion of JNJ-68284528	Update based on current clinical data
2.3. Benefit-Risk Assessment; 6.1.6.7. Infections	Added that JNJ-68284528 should not be administered to subjects with active infections Added recommendation for extended use of anti-microbial therapies	Revised guidance for infections
10.28. Appendix 28 (Anti-microbial Prophylaxis	Added table with anti-microbial prophylaxis recommendations	
3. Objectives and Endpoints	Added a separate secondary endpoint for time to worsening of symptoms as captured by the MySIm-Q total symptoms score (separate from the overall PRO endpoints) as it is defined specifically in Section 9.4.3.	Revision for consistency
6.1.2. Bortezomib	Additional cycles of bridging therapy may be considered based on subject's clinical status and timing and availability of JNJ-68284528	Addition of guidance for the consideration of bridging therapy
6.1.3. Daratumumab	Additional cycles of bridging therapy may be considered based on subject's clinical status and timing and availability of JNJ-68284528	
6.1.5.1. Apheresis and Bridging Therapy	Additional cycles of bridging therapy may be considered based on subject's clinical status and timing and availability of JNJ-68284528	
6.1.5.5. Evaluation Prior to Administration of JNJ-68284528	Language added to allow for subjects with confirmed PD after bridging therapy to receive JNJ-68284528 after consultation with the sponsor and evaluation of risks and benefits to the subject.	Addition to allow for subjects with confirmed PD after bridging therapy to receive JNJ-68284528 if requested by investigator
6.2.5. Cytopenia	Added consideration of parvovirus B19 monitoring	Additional guidance for cytopenia and hypogammaglobulinemia
6.2.6. Hypogammaglobulinemia	Added that subjects IG <400 mg/dL and recurrent infections may receive prophylactic IVIG	
6.8. Intervention After the End of the Study	Revised language to state that subjects benefiting from treatment will be able to continue treatment after the end of study.	Revision to be consistent with Janssen policy
10.12. Appendix 12: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Revised definition of postmenopausal as no menses for 24 months without an alternative medical cause.	Revised to be consistent with pomalidomide pregnancy prevention program

Section number and Name	Description of Change	Brief Rationale
10.20. Appendix 20: Multiple Myeloma Symptom and Impact Questionnaire	Updated sample of MySIm-Q with latest version	Update to current version of questionnaire
6.1.6.1. Management of Cytokine Release Syndrome	Added column for CRS grade to Table 11	Grading added to CRS and ICANS management tables to reflect adoption of ASBMT criteria across study protocols
6.1.6.2.1. CAR-T Cell-related Neurotoxicity (ICANS)	Added column for ICANs grade to Table 12	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma

JNJ-68284528 (ciltacabtagene autoleucel [cilta-cel]) is an autologous CAR-T therapy that targets B-cell maturation antigen (BCMA), a molecule expressed on the surface of mature B lymphocytes and malignant plasma cells. Results from the Phase 1b portion of Study 68284528MMY2001 indicate that cilta-cel has anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	• Progression-free survival (PFS)

Hypothesis

The primary hypothesis is that cilta-cel will significantly improve PFS compared with standard therapy (PVd or DPd), in subjects who have previously received 1 to 3 prior line(s) of therapy, that included a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) and who are refractory to lenalidomide.

OVERALL DESIGN

This is a Phase 3, randomized, open-label, multicenter study to determine whether treatment with cilta-cel will provide efficacy benefit compared to standard therapy (PVd or DPd) in subjects with relapsed and lenalidomide-refractory multiple myeloma (MM).

NUMBER OF SUBJECTS

Approximately 400 subjects will be randomized 1:1 to Arm A or Arm B:

- Arm A: standard therapy with either PVd or DPd
- Arm B: Cilta-cel

INTERVENTION GROUPS AND DURATION

The choice of whether the subjects will be treated with PVd or DPd as standard therapy or part of the bridging therapy will be determined by the investigator prior to screening and will be dependent on the subject's prior exposure to anti-myeloma therapies.

Subjects randomized to Arm A will receive PVd or DPd until confirmed progressive disease (PD), death, intolerable toxicity, withdrawal of consent, or end of study. Subjects who discontinue PVd or DPd for any reason, other than PD or withdrawal of consent, will continue to be followed for response assessment until confirmed PD or the start of a subsequent anti-myeloma therapy. After confirmed PD, subjects will be followed for survival status, subsequent anti-myeloma therapies, and the occurrence of second primary malignancies (SPMs) every 16 weeks until the end of the study.

Subjects randomized to Arm B will undergo apheresis to acquire peripheral blood mononuclear cells (PBMCs). Subjects will receive PVd or DPd as bridging therapy, following apheresis. After cilta-cel production and product release, subjects will receive a conditioning regimen of cyclophosphamide and fludarabine. Cilta-cel will be administered 5 to 7 days after the start of the conditioning regimen. Subjects will have intensive monitoring for safety, pharmacokinetics, biomarkers, and efficacy during the first 112 days after cilta-cel administration (post-infusion follow-up). During the post-treatment follow-up, subjects will continue to be monitored for efficacy until confirmed PD, death, or withdrawal of consent. After confirmed PD, subjects will be followed for survival, subsequent anti-myeloma therapies, second primary malignancies (SPMs) for both Arms, and other delayed adverse events for Arm B every 16 weeks until the end of the study. All subjects who received cilta-cel will continue to be monitored for long-term safety under a separate study for up to 15 years after cilta-cel administration.

Subjects who are unable to receive PVd or DPd standard therapy for Arm A, or unable to be apheresed, or receive bridging therapy, conditioning regimen or cilta-cel infusion for Arm B, will be followed until confirmed PD, start of a new anti-myeloma therapy, withdrawal of consent, or end of the study whichever occurs first. After PD, subjects will be followed for survival status, subsequent anti-myeloma therapies, and SPMs until the end of the study.

EVALUATIONS

For both Arm A and Arm B, disease status will be evaluated according to the International Myeloma Working Group (IMWG) consensus recommendations for MM. Minimal residual disease (MRD) will be monitored in subjects using Next Generation Sequencing on bone marrow aspirate DNA.

Subjects randomized to Arm B will have blood and serum samples collected for assessment of cilta-cel pharmacokinetics, immunogenicity, and biomarkers.

Data regarding subjects' health-related quality of life, will be captured using patient-reported outcome measures in both Arm A and Arm B. Medical resource utilization data, associated with medical encounters, will also be collected for both treatment arms.

Safety evaluations will include a review of adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurological examination), and assessments of cardiac function, Immune Effector Cell-associated Encephalopathy (only for Arm B), and Eastern Cooperative Oncology Group performance status.

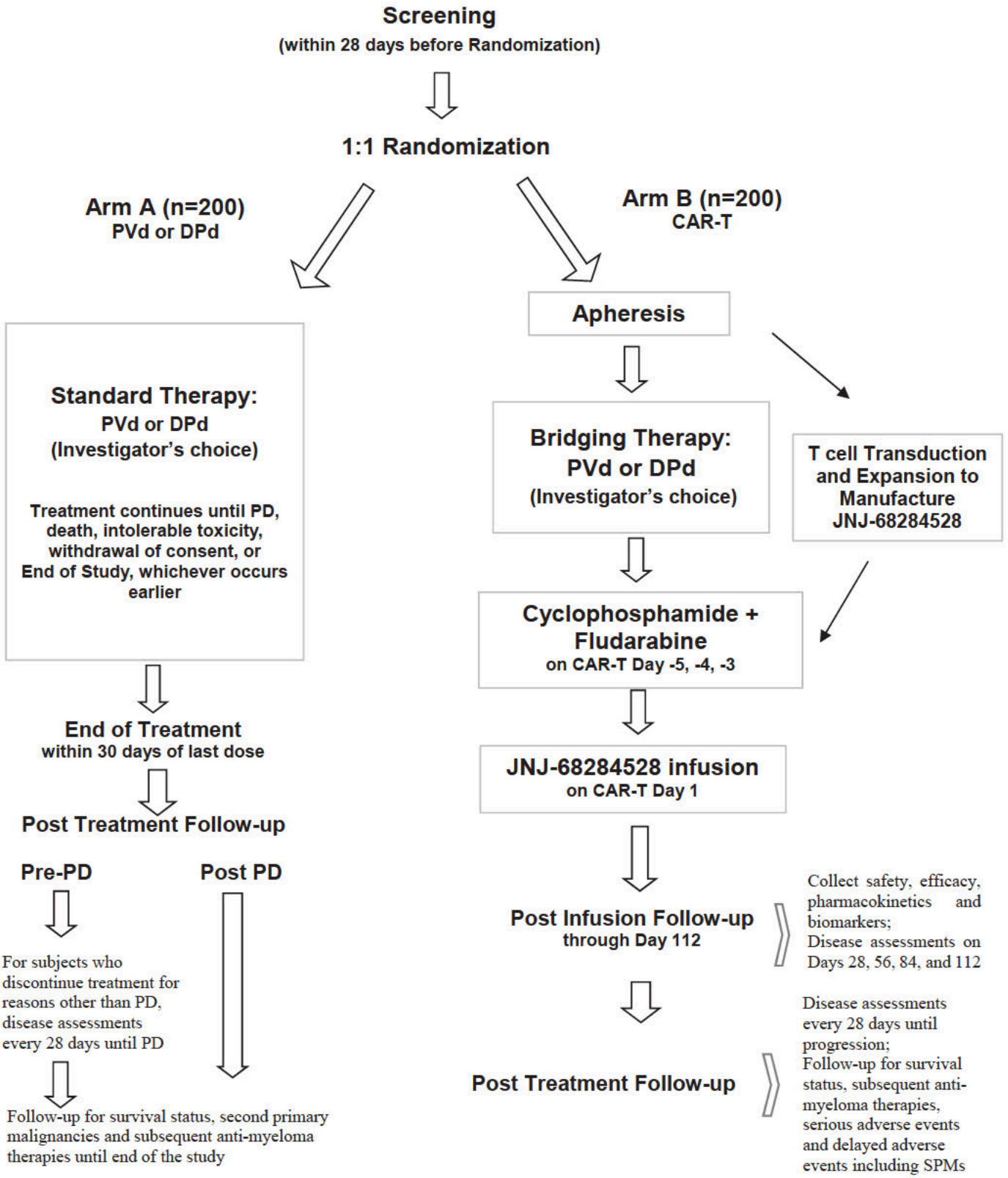
Safety and efficacy data will be periodically reviewed by an Independent Data Monitoring Committee.

STATISTICAL METHODS

The sample size calculation is performed based on the assumption that cilta-cel can reduce the risk of PD or death by 35%, ie, hazard ratio (cilta-cel vs. standard therapy) of 0.65, which translates into a median PFS of 20 months for the cilta-cel group, assuming the median PFS for the standard therapy arm is 13 months. Approximately 400 (200/treatment arm) subjects will be randomized to observe a total of 250 PFS events to achieve approximately 90% power to detect this hazard ratio with a log-rank test (2-sided alpha of 0.05). The sample size calculation has taken into consideration an estimated annual dropout rate of 5% and one interim analysis for efficacy.

1.2. Schema

Figure 1: Schematic Overview of the Study



Key: DPd=daratumumab, pomalidomide, dexamethasone; PD=progressive disease; PVd=pomalidomide, bortezomib, dexamethasone

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities for Screening Phase for All Subjects

	Notes	Screening (≤28 days before randomization)
STUDY PROCEDURES		
Informed consent	Before the 1st study-related procedure	X
Eligibility criteria		X
Demographics and medical history		X
Disease characteristics		X
Physical examination	Complete physical examination including neurologic examination	X
ECOG		X
TTE or MUGA Scan	Including left ventricular ejection fraction; ≤8 weeks before randomization	X
12-lead electrocardiogram		X
Spirometry test (ie, FEV1)	Only for subjects intended to receive DPd who have known or suspected COPD	X
Vital signs	Including oxygen saturation, height and weight	X
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY		
Complete blood count with differential	See Section 10.2; ≤72 hours prior to randomization	X
Full metabolic panel	See Section 10.2; ≤72 hours prior to randomization	X
Coagulation	PT/INR, aPTT, fibrinogen, D-dimer	X
Serology	Serology performed as standard of care within 28 days prior to randomization are acceptable. Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are anti-HBc positive with or without anti-HBs positive); Hepatitis C: HCV antibody, HCV-RNA (for subjects who are anti-HCV positive); HIV serology (see Section 10.6)	X
Infectious disease testing	HIV, hepatitis B, hepatitis C, HTLV, and other infectious disease testing as needed for apheresis per local regulations (≤60 days prior to randomization)	X
Serum or urine pregnancy test	For women of childbearing potential with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL	10-14 days prior to start of PVd or DPd but before randomization
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. LOCAL LABORATORY ASSESSMENTS MAY BE USED TO ESTABLISH MEASURABLE DISEASE AT SCREENING, WITH LOCAL LABORATORY RESULT ≥125% OF REQUIREMENTS. HOWEVER, SUBJECTS MUST HAVE LABORATORY STUDIES FOR DISEASES ASSESSMENT RECEIVED BY CENTRAL LABORATORY PRIOR TO RANDOMIZATION.		
Serum beta-2 microglobulin	Central laboratory	X
Quantitative immunoglobulins	Includes IgG, IgA, IgM, IgD, and IgE. Central laboratory	X
SPEP	Central laboratory.	X
UPEP (24-hour urine)	Acceptable for screening if performed as part of standard of care and sent to central laboratory for analysis after signing ICF. Central laboratory	X
Serum FLC and SIFE/UIFE	Central laboratory	X
OTHER DISEASE EVALUATIONS		
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally). If a biopsy was done within 42 days before randomization, no need to repeat for morphology; however, fresh aspirate samples need to be obtained and sent to central laboratory (Section 8.1.4). For re-screened subjects who had sufficient bone marrow aspirate and biopsy done within 42 days of the first screening date, no repeat aspirate and biopsy sample are needed.	X
MRD (bone marrow aspirate)	Central laboratory	X
Imaging: Skeletal survey or whole-body MRI or	Acceptable for screening if performed as part of standard of care within 42 days before randomization	X

Table 1: Schedule of Activities for Screening Phase for All Subjects

	Notes	Screening (≤28 days before randomization)
low-dose whole body CT or PET/CT with diagnostic CT component		
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT scan is acceptable	Acceptable for screening if performed as part of standard of care within 42 days before randomization	X
ONGOING SUBJECT REVIEW		
Adverse event	Continuous from signing of ICF	X
Concomitant therapy	All concomitant therapy from signing of ICF	X

Abbreviations: anti-HBc=anti-hepatitis B core antibody; anti-HBs=anti-hepatitis B surface antibody; aPTT=activated partial thromboplastin time; COPD=chronic obstructive pulmonary disease; CT=computed tomography; DPd=daratumumab, pomalidomide, dexamethasone; ECOG=Eastern Cooperative Oncology Group; FEV1=forced expiratory volume (in 1 second); FLC=free light chain; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HTLV=human T-lymphotropic virus; ICF=informed consent form; Ig=immunoglobulin; INR=international normalized ratio; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multi-gated acquisition; PD=progressive disease; PET=positron emission tomography; PT=prothrombin time; PVd=pomalidomide, bortezomib, and dexamethasone; SIFE=serum immunofixation; SPEP=serum M-protein quantitation by electrophoresis; TTE=transthoracic echocardiogram; UIFE=urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis.

Table 2: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (PVd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk ±14 days)
STUDY PROCEDURES										
Physical examination		Symptom-directed physical examination as clinically indicated								
ECOG		On Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and Day 1 every 8 cycles thereafter								
TTE or MUGA Scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected								
12-lead ECG		As clinically indicated						X		
Weight		X				X				
Vital signs	Including oxygen saturation	X	X	X	X	X	X	X		
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY										
CBC with differential	See Section 10.2	X	C1-C3	C1-C3	C1-C3	X		X		
Full metabolic panel	See Section 10.2	X		C1 only		X		X		
HBV-DNA	Including AST/ALT; see Section 10.6	For subjects at risk for HBV reactivation, monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 6 months after the last dose of study treatment								
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL	Within 24 hours prior to the first dose of PVd, every week for the first 4 weeks, and then every 3 weeks starting from C3D1, or every 2 weeks for WOCBP with irregular menses Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide.						X (+7) days		
STUDY INTERVENTION ADMINISTRATION										
Pomalidomide	PO; see Section 6.1.4 for full dosing details.	Days 1 to 14 of each 21-day cycle								
Bortezomib	SC; see Section 6.1.2 for full dosing details At least 72 hours should elapse between consecutive doses of bortezomib.	X	X	X	X	X	X			
Dexamethasone	PO; see Section 6.1.1 for full dosing details.	Cycles 1 to 8 Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle Cycles 9 and beyond Days 1, 2, 8, and 9 of a 21-day cycle								
ACCOUNTABILITY/EXPOSURE CHECK										
Pill count	For pomalidomide and dexamethasone	X (C2 onward)				X		X		
DISEASE EVALUATIONS (SERUM AND, URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY[c]										
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening. - Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	
SPEP	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	

Table 2: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (PVd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk ±14 days)
UPEP (24-hour urine)	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	
Serum FLC and SIFE/UIFE	Central laboratory	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation (±7 days starting with Cycle 2); For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained								
OTHER DISEASE EVALUATIONS										
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally).	To confirm CR (including sCR)								
MRD (bone marrow aspirate)	Central laboratory	Sample should be collected: • At time of suspected CR or sCR.[b] • At 6, 12, 18, and 24 months[b] (±21 days) from C1D1 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after C1D1[b]								
Imaging: Skeletal survey or whole-body MRI or low-dose whole-body CT or PET/CT with diagnostic CT component		As clinically indicated to document PD								
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		For subjects with a history of plasmacytoma - For assessment by physical examination (if applicable), every 21 days (±7 days) - For assessment by radiology, ie, at C5D1 (±14 days) and then every 12 weeks (±14 days) As clinically indicated for other subjects								
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH										
EORTC QLQC30		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
MySIm-Q		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
EQ-5D-5L		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								X
PRO-CTCAE		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
PGIS		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
MRU		Collected continuously from randomization for 33 weeks including in the event of PD before 33 weeks								
ONGOING SUBJECT REVIEW										
Adverse event		Continuous from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report any adverse events/serious adverse events considered related to study treatment until EOS								
Second primary malignancy		Continuous from randomization until EOS								
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report concomitant therapy given for any adverse events/serious adverse events considered related to study treatment until EOS								

Table 2: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (PVd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk ±14 days)
Subsequent anti-myeloma therapy										X
Survival									X	X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FLC=free light chain; ICF=informed consent form; Ig=immunoglobulin; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA= multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire PD=progressive disease; PET=positron emission tomography; PGIS=Patient Global Impression of Severity; PO=oral; PRO=patient reported outcome; PVd=pomalidomide, bortezomib, and dexamethasone; SC=subcutaneous; sCR=stringent CR; SIFE=serum immunofixation; SPEP=serum M-protein quantitation by electrophoresis; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis; wk=week; WOCBP=woman of childbearing potential

a. Start of PVd should be within 7 days after randomization. Assessments and procedures on Cycle 1 Day 1 to be performed prior to administration of study intervention.

b. A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.

c. Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)

Table 3: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (DPd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
STUDY PROCEDURES											
Physical examination		Symptom-directed physical examination as clinically indicated									
ECOG		On Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter									
TTE or MUGA Scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.									
12-lead ECG		As clinically indicated							X		
Spirometry test (ie, FEV1)	Subjects with known or suspected COPD only	As clinically indicated									
Weight		X				X		X			
Vital signs	Including oxygen saturation	X	X	X	X	X	X	X	X		
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY											
Blood group and type assessment and indirect antiglobulin test (IAT) results	IAT to be done prior to first dose of daratumumab. Results placed on subject identification wallet card; See Section 10.2	X									
CBC with differential	See Section 10.2	X	X	X	X	X		X	X		
Full metabolic panel	See Section 10.2	X		C1 only		X		X	X		
HBV-DNA	Including AST/ALT; see Section 10.6	For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 6 months after the last dose of study treatment									
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL	Within 24 hrs prior to the first dose of DPd, every week for the first 4 weeks and then every 28 days or every 14 days for WOCBP with irregular menses. Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide							X (+7 days)		
STUDY INTERVENTION ADMINISTRATION											
Pre- and post-injection medications for daratumumab subjects	PO or IV: see Sections 6.5.1.4 and 6.5.1.5 for full dosing details	X	X	X	X	X	X	X			
Daratumumab	SC; see Section 6.1.3 for full dosing details	X[b]	X	X	X	X	X	X			
Pomalidomide	PO; see Section 6.1.4 for full dosing details	On Days 1 to 21 of each 28-day cycle									
Dexamethasone	PO or IV; see Section 6.1.1 for full dosing details.	Days 1, 8, 15, and 22 of each 28-day cycle									
ACCOUNTABILITY/EXPOSURE CHECK											
Pill count	For pomalidomide and dexamethasone	X (C2 onward)				X		X	X		

Table 3: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (DPd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY[d]											
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma at screening. Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
SPEP	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
UPEP (24-hour urine)	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
Serum FLC and SIFE/UIFE	Central laboratory	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation (±7 days starting with Cycle 2). For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained									
DSIFE	Central laboratory	To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results. DSIFE is not required once CR/sCR is confirmed.									
OTHER DISEASE EVALUATIONS											
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally).	To confirm CR (including sCR).									
MRD (bone marrow aspirate)	Central laboratory	Sample should be collected: • At time of suspected CR or sCR.[c] • At 6, 12, 18, and 24 months[c] (±21 days) from C1D1 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after C1D1[c]									
Imaging: Skeletal survey or whole-body MRI or low-dose whole body CT or PET/CT with diagnostic CT component		As clinically indicated to document PD									

Table 3: Schedule of Activities for Standard Therapy Treatment Arm (Arm A) (DPd): Treatment and Post-Treatment Follow-up Phases

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		For subjects with a history of plasmacytoma - For assessment by physical examination (if applicable), every 28 days (±7 days) - For assessment by radiology, ie, at C4D1 (±14 days) and then every 12 weeks (±14 days) As clinically indicated for other subjects									
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH											
EORTC-QLQ-C30		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
MySIm-Q		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
EQ-5D-5L		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									X
PRO-CTCAE		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
PGIS		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
MRU		Collected continuously from randomization for 33 weeks including in the event of PD before 33 weeks									
ONGOING SUBJECT REVIEW											
Adverse event		Continuous from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report any adverse events/serious adverse events considered related to study treatment until EOS									
Second primary malignancy		Continuous from randomization until EOS									
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report concomitant therapy given for any adverse events/serious adverse events considered related to study treatment until EOS									
Subsequent anti-myeloma therapy											X
Survival										X	X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; DPd=daratumumab, pomalidomide, and dexamethasone; DSIFE=daratumumab-specific immunofixation electrophoresis; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FCL=free light chain; FEV1=forced expiratory volume (in 1 second); FLC=free light chain; HBV=hepatitis B virus; IAT=indirect antiglobulin test; ICF=informed consent form; Ig=immunoglobulin; IV=intravenous; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA= multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PD=progressive disease; PET=positron emission tomography; PGIs=Patient Global Impression of Severity; PO=oral; PRO=patient reported outcome; SC=subcutaneous; sCR=stringent CR; SIFE=serum immunofixation; SPEP=serum M-protein quantitation by electrophoresis; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis; VGPR=very good partial response; wk=week; WOCBP=women of childbearing potential

[a] Start of DPd should be within 7 days after randomization. Assessments and procedures on Cycle 1 Day 1 to be performed prior to administration of study intervention

[b] Subjects should be observed following Cycle 1 Day 1 daratumumab administration for 6 hours at the site where daratumumab is administered.

[c] A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.

[d] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)

Table 4: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment Phase -- Apheresis and Bridging Therapy

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase			
			Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
STUDY PROCEDURES						
Physical examination	Symptom-directed exam	X (≤72 hrs prior to apheresis)	Symptom-directed as clinically indicated			
ECOG		X (≤72 hrs prior to apheresis)				
TTE or MUGA scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.				
12-lead electrocardiogram		As clinically indicated				
Spirometry test (ie, FEV1)	Subjects with known or suspected COPD only		As clinically indicated (for DPd only)			
Weight		X (dose calculation)				
Vital signs	Including oxygen saturation. If bortezomib or daratumumab administration is planned to be omitted, vital signs for the planned day can also be omitted.	X	X (prior to 1st dose)	X	X	X (only DPd)
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY						
Blood group and type assessment and indirect antiglobulin test (IAT) results	IAT to be done prior to first dose of daratumumab. Results placed on subject identification wallet card; see Section 10.2		X (only DPd)			
Complete blood count with differential	See Section 10.2. If bortezomib or daratumumab administration is planned to be omitted, CBC assessments on those days can be done locally but need to be reviewed by the Investigator.	X (≤72 hrs prior to apheresis)	X	X (only for first 2 cycles for DPd)	D11 (PVd) or D15 (DPd)	X (only DPd) (only for first 2 cycles)
Full metabolic panel	See Section 10.2. If bortezomib or daratumumab administration is planned to be omitted, chemistry assessments on those days can be done locally but need to be reviewed by the Investigator.	X (≤72 hrs prior to apheresis)	X		D11 (PVd) or D15 (DPd)	
Infectious disease testing	HIV, hepatitis B, hepatis C, HTLV, and other infectious disease testing as needed for apheresis in EU and Israel and for other countries as required per local regulations	X				
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL.	Within 72 hrs prior to apheresis	Within 10-14 days (if the first pregnancy test falls out of required 10-14 days prior to first dose of PVd or DPd) AND within 24 hours prior to the start of PVd or DPd, every week for the first 4 weeks and 28 (+7) days after the last dose of pomalidomide. Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide			
OUTPATIENT ADMINISTRATION: IN CONSULTATION WITH AND APPROVAL OF THE SPONSOR. SEE SECTION 10.16						
Evaluation for outpatient suitability	See Section 10.16	X				

Table 4: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment Phase -- Apheresis and Bridging Therapy

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase			
			Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
ASSESSMENTS PRIOR TO APHERESIS						
Criteria for apheresis	See Section 6.1.5.2	X				
STUDY INTERVENTION ADMINISTRATION: INVESTIGATOR'S CHOICE PVD (1 CYCLE)						
Pomalidomide	PO; see Section 6.1.4 for full dosing details		On Days 1 to 14 of a 21-day cycle			
Bortezomib	SC; see Section 6.1.2 for full dosing details		X	D4, D8	D11	
Dexamethasone	PO; see Section 6.1.1 for full dosing details.		Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle			
STUDY INTERVENTION ADMINISTRATION: INVESTIGATOR'S CHOICE DPD (1 CYCLE)						
Pre- and post-injection medications for daratumumab	PO or IV; see Sections 6.5.1.4 and 6.5.1.5		X	D8	D15	X
Daratumumab	SC; see Section 6.1.3 for full dosing details		X[b]	D8	D15	X
Pomalidomide	PO: see Section 6.1.4 for full dosing details		On Days 1 to 21 of a 28-day cycle			
Dexamethasone	PO or IV; see Section 6.1.1 for full dosing details		X	D8	D15	X
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY.[d]						
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening - Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
SPEP	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
UPEP (24-hour urine)	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
Serum FLC and SIFE/UIFE	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
OTHER DISEASE EVALUATIONS						
Plasmacytoma assessment by physical exam		X (≤72 hrs prior to apheresis) (if applicable)	For subjects with a history of plasmacytoma. For assessment by physical examination (if applicable), Day 1 of each bridging cycle starting from Cycle 2 (±7 days)			
Biopsy of EM plasmacytoma	If biopsy of EM plasmacytoma is clinically indicated, a sample should be sent to the central lab	The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason				
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH						
EORTC QLQ-C30		X (≤72 hour window)	X[e]			
MySIm-Q		X(≤72 hour window)	X[e]			
EQ-5D-5L		X(≤72 hour window)	X[e]			
PRO-CTCAE		X(≤72 hour window)	X[e]			

Table 4: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment Phase -- Apheresis and Bridging Therapy

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase			
			Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
PGIS		X(≤72 hour window)	X[e]			
Medical resource utilization		Collected continuously from randomization until 33 weeks regardless of PD before 33 weeks.				
PHARMACOKINETIC AND BIOMARKER SAMPLING						
Immunophenotyping (whole blood)[f]		X				
Soluble BCMA sample (serum)		X				
CyTOF/PBMC (TCRSeq)/Plasma (whole blood)[g]		X				
ONGOING SUBJECT REVIEW						
Adverse event		Continuous from the time of signing of ICF				
Second primary malignancy		Continuous from randomization				
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF[h]				

Abbreviations: BCMA=B-cell maturation antigen; COPD=chronic obstructive pulmonary disease; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CyTOF=cytometry by time of flight; D=Day; DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=EuroQol Five Dimension Questionnaire; EU=European Union; FEV1=Forced Expiratory Volume (in 1 second); FLC=free light chain; HIV=human immunosuppressant virus; IAT= indirect antiglobulin test; ICF=informed consent form; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PET=positron emission tomography; PO=oral; PRO=patient reported outcome; PVd=pomalidomide, bortezomib, and dexamethasone; SC=subcutaneous; SIFE=serum immunofixation; SPEP=serum protein electrophoresis; TCR=T-cell receptor; TTE=transthoracic echocardiogram; UIFE=urine immunofixation; UPEP=urine protein electrophoresis; WOCBP=woman of childbearing potential

[a] Bridging therapy should be started after apheresis but no more than 7 days after randomization. If more than 2 cycles of bridging therapy are indicated, daratumumab will be administered on Days 1 and 15. Safety laboratory assessments may be performed prior to initiating bridging therapy.

[b] Subjects should be observed following Cycle 1 Day 1 daratumumab administration for 6 hours at the site where daratumumab is administered.

[c] Assessments and procedures to be performed prior to apheresis

[d] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)

[e] Only to be done for the first cycle of bridging therapy given

[f] Recollect blood samples for immunophenotyping prior to the second apheresis for subjects who require a repeat apheresis.

[g] Recollect blood sample for CyTOF/PBMC (TCRSeq)/Plasma prior to the second apheresis for subjects who require a repeat apheresis.

[h] Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Appendix 10.29).

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
STUDY PROCEDURES																			
Physical examination	Complete physical exam including neurologic exam on CAR-T Day 1; symptom-directed exam thereafter		X (prior to CAR-T infusion)	Symptom-directed physical examination as clinically indicated															
ECOG		X (prior to 1st dose only)	X						X					X	Every 12 wks x 2, then every 24 wks				
TTE or MUGA		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.																	
12-lead ECG		As clinically indicated																	
ICE neurologic test			X (≤24 hrs prior to infusion)[c]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until ICANS is resolved.															
Handwriting sample			X (≤24 hrs prior to infusion)[c]	X	X	X	X	X	X	X	X	X	Perform every 28 days up to and including Day 196						
Weight		X (prior to 1st dose only)	X																
Vital signs	Including oxygen saturation	X	X (multiple times)[d]	X	X	X	X	X	X			X	X	X	Every 12 wks				
Temperature			Measure and record temperature at least twice every day[e]																
LABORATORY ASSESSMENTS: TO BE PERFORMED LOCALLY																			
CBC with differential	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X	Every 12 weeks (±7 days) x2 and then every 6 months (± 14 days) until EOS				
CD4/CD8 Lymphocyte panel[f]	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X	Every 4 weeks until 1 year after CAR-T				
CAR-T chemistry	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X					

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]										Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528															
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Coagulation	PT/INR, aPTT, fibrinogen, D-dimer		As clinically indicated, ie, for subjects who have fever or other signs of potential CRS															
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL.	Within 72 hours prior to 1st dose	As clinically indicated or as mandated by local regulations, whichever is more stringent															
HBV-DNA	Including AST/ALT, see Section 10.6		For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 1-year post-dose of JNJ-68284528.															
OUTPATIENT ADMINISTRATION: IN CONSULTATION WITH AND APPROVAL OF THE SPONSOR. SEE SECTIONS 10.16 AND 10.17																		
Evaluation for outpatient suitability	See Section 10.16		X (predose)															
Subjects with discharge on Days 10 to 13	See Section 10.16					Daily phone calls during business days from site staff, Days 10-14												
ASSESSMENTS PRIOR TO CONDITIONING REGIMEN AND ADMINISTRATION OF JNJ-68284528																		
Criteria for conditioning regimen	See Section 6.1.5	X (≤72 hours of 1st dose only)																
Criteria for JNJ-68284528 administration	See Section 6.1.5.5		X (predose)															
STUDY INTERVENTION ADMINISTRATION																		
Cyclophosphamide/ fludarabine		X																
Pre-infusion medication	See Section 6.1.5.6		X															

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
JNJ-68284528	See CPTTM and IPPI		X																
ACCOUNTABILITY/EXPOSURE CHECK																			
Pill count	For pomalidomide and dexamethasone given as part of bridging therapy	X (prior to 1st dose only)																	
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY.[f] DISEASE EVALUATION SHOULD CONTINUE TO BE PERFORMED UNTIL CONFIRMED PD, DEATH, START OF A NEW ANTI-MYELOMA TREATMENT, WITHDRAWAL OF CONSENT FOR STUDY PARTICIPATION, OR STUDY COMPLETION, WHICHEVER OCCURS FIRST.																			
Quantitative immunoglobulin[g]	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening. Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	X
SPEP	Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	X
UPEP (24-hour urine)	Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	X
Serum FLC and SIFE/UIFE	Central laboratory	X (≤7 days before 1st dose)							For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at CAR-T Day 28, 56, 84, 112 and then every 28 days. For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed when CR is suspected or maintained									

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]										Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528															
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
DSIFE	Central laboratory DSIFE is not required after bridging therapy and prior to conditioning regimen	X[h]		To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.														
OTHER DISEASE EVALUATIONS																		
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry; performed locally)												• To confirm CR (including sCR) (bone marrow biopsy and aspirate) (local lab) • At time of PD or EOS bone marrow biopsy and aspirate should be sent to the central lab (Section 8.1.4) • Bone marrow not required if PD prior to CAR-T infusion					
MRD (bone marrow aspirate)	Central laboratory											X	Sample should be collected: • At time of suspected CR or sCR • At 6 (D196), 12 (D364), 18 (D532), and 24 (D700) months[i] (±21 days) from JNJ-68284528 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after JNJ-68284528 infusion[i]					
Imaging: Skeletal survey or low-dose whole body CT or whole-body MRI or PET/CT with diagnostic CT component				Performed as clinically indicated to document PD														

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Biopsy of EM plasmacytoma	If biopsy of EM plasmacytoma is clinically indicated, a sample should be sent to the central lab		The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason.																
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		X (For assessment by physical examination, if applicable)[j]							For subjects with a history of plasmacytoma for assessment by physical examination (if applicable), ie, CAR-T Day 28, 56, 84, 112 and then every 28 days (±7 days) - for assessment by radiology, ie, CAR-T Day 84 and then every 12 weeks (±14 days) As clinically indicated for other subjects									
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH																			
EORTC QLQ-C30		X[k]							X					X	X[l]				
MySIm-Q		X[k]							X					X	X[l]				
EQ-5D-5L		X[k]							X					X	X[l]				X
PRO-CTCAE		X[k]							X					X	X[l]				
PGIS		X[k]							X					X	X[l]				
MRU		Collected continuously for 33 weeks including in the event of PD before 33 weeks																	
PHARMACOKINETIC AND BIOMARKER ASSESSMENTS																			
Cytokine profiling (serum)[n]		X (≤7 days prior to 1st dose)	Pre-dose 2 hours post-dose (±10 min)	X	X	X	X	X	X			X	X	X					
PK CAR transgene levels sample (whole blood)[m]			Pre-dose	X	X	X	X		X			X	X	X	Every 8 wks up to 1 yr			X or EOS	
Soluble BCMA sample (serum)			Pre-dose	X	X	X	X		X			X	X	X	Every 8 wks up to 1 yr			X or EOS	
Immunogenicity ADA sample for CAR-T (serum)[n]			Pre-dose				X					X		X				X or EOS	

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Immunophenotyping (whole blood)[n, m]	Samples also collected at suspected CR	X (≤7 days before 1st dose)	Pre-dose		X	X	X	X	X	X	X	X	X	X	Every 8 wks up to 1 yr			X or EOS	
Flow cytometry (bone marrow aspirate)									X	• At time of suspected CR/sCR • 6 months (D 196) after CAR-T infusion in subjects who have not had a bone marrow within the last 3 months								X or EOS	
CyTOF (bone marrow aspirate)									X	• At time of suspected CR/sCR • 6 months (D 196) after CAR-T infusion in subjects who have not had a bone marrow within the last 3 months								X or EOS	
CyTOF/PBMC (TCRSeq)/ Plasma (whole blood)			Pre-dose			X	X	X	X	X	X	X		X				X or EOS	
RCL (whole blood)			Pre-dose	At approximately 3 (Day 84), 6 (Day 196), and 12 (Day 364) months (±1 month); then yearly (±3 months) until EOS, and then yearly (±3 months) for up to 15 years after cilta-cel infusion in a separate long-term follow- up study. Yearly collection of RCL samples is not required if all assessments within the first year are negative. Sites will be notified if a subject's sample is positive for RCL; otherwise RCL is no longer required to be collected after the 12-month visit. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.																
Serum protein analysis		X (≤7 days prior to 1st dose)	Pre-dose	Additional serum protein sample will be taken at each SIFE/SPEP evaluation, as well as at each MRD sample collection															
ONGOING SUBJECT REVIEW																			
Adverse event		Continuous from the time of signing ICF until 30 days after the last dose of bridging therapy or until CAR-T Day 112, whichever is later, regardless if subjects progress before CAR-T Day 112; thereafter, continue to report all SAEs regardless of causality, and any non-serious adverse events considered related to study treatment until EOS.[o,p] Events of HBV reactivations and COVID-19 infection should be reported during the first year post-dosing of JNJ-68284528. Subjects who progress prior to CAR-T infusion and are not able to receive CAR-T infusion, adverse events/serious adverse events should still be reported until PD or until the start of subsequent anti-myeloma therapy, whichever is earlier.																
Delayed Adverse Events			Continuous from Day1 of CAR-T infusion until EOS (with the exception of second primary malignancy, which is collected from the time of randomization until EOS)[o,p,q]																
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing ICF until 30 days after the last dose of bridging therapy or until CAR-T Day 112, whichever is later; regardless if subjects progress before CAR-T Day 112, thereafter, continue to report concomitant therapy given for any non-serious adverse events considered related to study treatment or all serious adverse event regardless of causality or delayed adverse events until EOS. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Appendix 10.29).																

Table 5: Schedule of Activities for JNJ-68284528 Treatment Arm (Arm B): Treatment (Conditioning Regimen and JNJ-68284528 Infusion), Post-Infusion Follow-up, and Post-Treatment Follow-up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]										Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528															
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Subsequent anti-myeloma therapy																			X
Survival																			X

Abbreviations: ADA=anti-drug antibody; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell; CBC=complete blood count; CPTTM=Cell Therapy Product Procedures Manual; CR=complete response; CRS=cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CyTOF=cytometry by time of flight; D=Day; DPd= daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; and dexamethasone; FLC=free light chain; HBV=hepatitis B virus; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome; ICE=Immune Effector Cell-associated Encephalopathy assessment tool; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA=multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PD=progressive disease; PET=positron emission tomography; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; PRO=patient reported outcome; PT=prothrombin time; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent CR; RCL=replication competent lentivirus; SIFE=serum immunofixation; SPEP=serum protein electrophoresis; TCR=T-cell receptor; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine protein electrophoresis; VGPR=very good partial response; wks=weeks; WOCBP=woman of childbearing potential.

[a] For subjects who discontinue due to PD or withdrawal of consent before CAR-T Day 112, the Day 112 assessments should be performed prior to discontinuation, if feasible.

[b] For subjects who discontinue due to PD or withdrawal of consent after CAR-T Day 112 but before end of study should have the assessments at PD performed prior to discontinuation, unless these assessments were performed within 14 days prior to discontinuation. End of study is when approximately 250 deaths have occurred

[c] Pre-infusion ICE test and handwriting assessment should be performed before pre-medication with diphenhydramine

[d] Immediately before the start of infusion, at the end of infusion, and 0.5 hours (±5 min), 1 hours (±10 min), and 2 hours (±10 min) after end of infusion. Monitor until normalized after a CRS event. For subjects who are hospitalized, hematology and chemistry laboratory evaluations, vital signs, and oxygen saturation should be performed at least daily or more as clinically indicated.

[e] Temperature will be checked at least twice a day. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering temperature in a diary. Diary will be reviewed at each visit, then collected on CAR-T Day 28 and stored with subject source documents.

[f] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6).

[g] Additional immunoglobulin samples may be collected as clinically indicated for safety and treated according to institutional guidelines (see Section 6.1.6.6).

[h] Only for IgG kappa MM subjects who received DPd for bridging therapy and who are SIFE positive following bridging therapy.

[i] A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.

[j] Assessment to be performed as close to prior to the first dose as possible.

[k] PRO questionnaires to be completed on the first day, prior to the start of the conditioning regimen

[l] Every 12 weeks x 2 (D196 ± 3 days, D280 ± 3days), then every 24 weeks

[m] After Day 112, CAR transgene levels, and CAR+ T cell counts will be measured every 8 weeks through 1 year. After 1 year, PK CAR transgene levels and CAR+ T cell counts (immunophenotyping) will be measured at least annually until EOS or PD, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.

[n] Collect additional samples when any of the following are observed or reported: 1) CRS or ICANS/neurotoxicity related to CAR-T therapy (Grade ≥3) (at onset of the event, at any increase in grade of the CRS and at time of resolution) or as clinically indicated. If these additional sampling timepoints occur on a day of a regularly scheduled sample collection, only 1 sample collection is required for that day.

[o] Delayed AEs will be collected regardless of causality from the time of JNJ-68284528 administration (with the exception of SPMs, which are collected from the time of randomization) until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of JNJ-68284528. For subjects diagnosed with second primary malignancy, a tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements

[p] Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic disorder (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥ 3 infections.

[q] For additional information, refer to Section 8.3.1.

[r] CD4/CD8 panel should be done for newly enrolled subjects. Subjects enrolled under amendment #1 that have re-consented to amendment #2 and have received cilta-cel are not required to do the CD4/CD8 lymphocyte panel.

2. INTRODUCTION

JNJ-68284528 (ciltacabtagene autoleucel [cilta-cel]) is an autologous chimeric antigen receptor T cell (CAR-T) therapy that targets B-cell maturation antigen (BCMA), a molecule expressed on the surface of mature B lymphocytes and malignant plasma cells. Results from the Phase 1b portion of Study 68284528MMY2001 indicate that JNJ-68284528 has anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

For the most comprehensive nonclinical and clinical information regarding JNJ-68284528, refer to the latest version of the Investigator's Brochure for JNJ-68284528.

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

2.1. Study Rationale

B-cell maturation antigen (BCMA) is a cell surface antigen highly expressed on cells of the B-cell lineage. Comparative studies show a lack of BCMA in most normal tissues and absence of expression on CD34-positive hematopoietic stem cells. This selective expression and the biological importance for the proliferation and survival of myeloma cells makes BCMA a promising target for CAR-T based immunotherapy. Observed response rates and the reversible adverse events for most subjects, from the Legend-2 study and the ongoing the Phase 1b/2 Study 68284528MMY2001, (described in detail in Section 2.2.5) support further investigation of this approach in the current study. As the degree of benefit of CAR-T therapy is dependent on a patient's immune response, JNJ-68284528 could have potentially increased benefit, with greater durability of response when administered to patients with multiple myeloma (MM) who have less prior exposure to immunomodulatory and cytotoxic therapy. Fraietta initially demonstrated the prevalence of an early memory T-cell phenotype (CD27+ CD45RO- CD8+) in patients with chronic lymphocytic leukemia treated with CART19 was predictive of clinical response independent of other factors.[15] The same finding has also been demonstrated with BCMA directed CAR-T.[9] Furthermore, the same group has also shown that the early memory T-cell phenotype was significantly higher in newly diagnosed subjects post-induction chemotherapy as compared to relapsed-refractory subjects.[10] Study 68284528MMY3002 aims to determine the safety and efficacy of JNJ-68284528 in myeloma subjects who have been less heavily pretreated than subjects on the Study 68284528MMY2001. For this current study subjects are required to have received 1 to 3 prior line(s) of therapy, including prior exposure to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), and who are refractory to lenalidomide.

Pomalidomide in combination with bortezomib and dexamethasone (PVd) and daratumumab in combination with pomalidomide and dexamethasone (DPd) were selected as the comparator regimens. Pomalidomide in combination with bortezomib and dexamethasone is approved in the European Union (EU) for subjects with MM, who have received at least 1 prior treatment regimen including lenalidomide. While not approved in the United States (US), PVd is recommended (National Comprehensive Cancer Network Guidelines) for subjects with relapsed/refractory multiple myeloma (RRMM) who have received 2 or more prior lines of therapy including an IMiD

and a PI. Daratumumab in combination with pomalidomide and dexamethasone is approved in the US for the treatment of subjects with MM who have received at least 2 prior therapies including lenalidomide and a PI. While multiple newer treatment options have become available for subjects with relapsed myeloma, studies in lenalidomide refractory subjects show a progression-free survival (PFS) of only 8 to 11 months even in subjects with early relapse. Study 68284528MMY3002 (CARTITUDE-4) was designed to improve outcomes in subjects with lenalidomide-refractory myeloma, by moving CAR-T therapy earlier in the treatment of relapsed myeloma and capitalizing on the less compromised immune system of subjects in early relapse. Given their proven efficacy and regulatory approvals, PVd and DPd will serve as comparators.

2.2. Background

2.2.1. Multiple Myeloma

Multiple myeloma is a malignant plasma cell disorder diagnosed annually in approximately 86,000 patients worldwide.[4] For patients with relapsed MM, the treatment is determined on an individual basis where the patient's age, prior therapy, bone marrow function, co-morbidities, patient preference and time to relapse are considered. Common standard regimens include either a PI or an IMiD in combination with dexamethasone with or without a monoclonal antibody such as daratumumab. With each successive relapse, the depth and duration of response typically decreases. After relapse from PIs or IMiDs, patients are often retreated with drugs that have the same mechanism of action to which they have been sensitive. Often, the disease becomes refractory to all available therapies. Several studies have shown the poor prognosis of these subjects. For example, subjects refractory to both a PI and an IMiD have a median overall survival (OS) of only 8 to 9 months.[21,44] For patients who are refractory to at least 3 prior lines of therapy, including PIs and IMiDs, the median OS decreases to only 5 months.[44] Further, since it has become standard to use lenalidomide as a frontline regimen, most subjects with relapsed MM have disease that has become refractory to lenalidomide-based regimens.

2.2.2. B-Cell Maturation Antigen

B-cell maturation antigen (BCMA, also known as CD269 and TNFRSF17) is a 20-kilodalton, type III membrane protein that is part of the tumor necrosis receptor superfamily.[42] BCMA is predominantly expressed in B-lineage cells and plays a critical role in B cell maturation and subsequent differentiation into plasma cells.[42] The expression characteristics of BCMA make it an ideal therapeutic target in the treatment of MM.[16,42] BCMA binds 2 ligands that induce B-cell proliferation: a proliferation inducing ligand (APRIL; CD256) and B-cell activating factor (BAFF; CD257).[2,11,32] Upon binding of BCMA monomers to the APRIL trimer, activation and phosphorylation of p38MAPK, ELK, and NF-κB are triggered through intracellular tumor necrosis factor receptor-associated factor molecules leading to pro-survival gene regulation.[5,18,20]

2.2.3. CAR-T Therapy

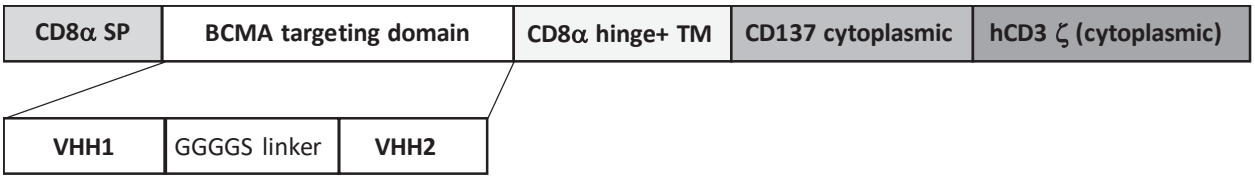
Chimeric antigen receptor T (CAR-T) cell therapy uses modified autologous T cells that are activated in an MHC-independent manner upon binding to their target. This results in lysis of the targeted cells. Kymriah® (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel), CD19-directed CAR-T based therapies, have been approved in the US for the treatment of patients with B-cell malignancy.[23,45] An ongoing Phase 1 clinical study with bb2121 (NCT02658929), a BCMA-directed CAR-T immunotherapy, demonstrated promising results for this strategy in relapsed/refractory MM.[38] Of the first 33 consecutive subjects to receive an infusion of bb2121, 76% experienced cytokine release syndrome (CRS), which was Grade 1 or 2 in 23 subjects (70%) and Grade 3 in 2 subjects (6%). Neurologic toxicity occurred in 42% of subjects. The objective response rate (partial response or better) was 85%, including 15 subjects (45%) with complete responses. A median PFS of 11.8 months was observed for the 30 subjects who received ≥150 x 10^6 CAR-positive T-cells (for the most recent information, refer to the ABECMA USPI).[1] The approval of Kymriah and Yescarta, together with preliminary study results with bb2121, suggest that administering BCMA-directed CAR-T immunotherapy may be an effective means to treat MM.

2.2.4. JNJ-68284528

Results from the Phase 1b portion of Study 68284528MMY2001 indicate that JNJ-68284528 has significant anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

The LCAR-B38M coding sequence is comprised of a human CD8 alpha signal peptide (CD8α SP), BCMA targeting domain consisting of 2 different VHH (single domain antibody, clone VHH1 and VHH2), human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain, and a human CD3 zeta cytoplasmic domain (CD3ζ) (Figure 2). The expression of LCAR-B38M is driven and controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

Figure 2: LCAR-B38M Coding Region



The JNJ-68284528 drug product used in this study and the LCAR-B38M CAR-T cell drug product used in the first-in-human Legend-2 study (See Section 2.2.5) express an identical CAR protein. The JNJ-68284528 drug product will be produced using a modified manufacturing and scale-up process. The LCAR-B38M CAR-T cell designation will be used when referring to results from the Legend-2 study. JNJ-68284528 will be used to reference the drug product in this study.

A summary of the in vitro and in vivo pharmacology, safety pharmacology, toxicology studies, and clinical studies with LCAR-B38M CAR-T cells are presented in the following sections.

2.2.5. Summary of Nonclinical and Clinical Studies

For the most comprehensive nonclinical and clinical information, refer to the latest version of the Investigator's Brochure.

Nonclinical Studies

The nonclinical pharmacology program was designed to characterize the biological activity and mechanism of action of LCAR-B38M CAR-T cells. In vitro mechanistic proof-of-principle studies have assessed target engagement with respect to:

- On-target binding (ie, binding of VHH to BCMA),
- Off-tumor target activity (ie, in human non-myeloma cell lines, including lung, liver, breast, brain, embryonic kidney and kidney expressing hERG),
- On-tumor target activity (ie, in human MM cell lines),

In vivo studies have evaluated the safety and efficacy of LCAR-B38M CAR-T cells.

The nonclinical studies support JNJ-68284528 as an effective targeted therapy against BCMA-expressing MM. Refer to the Investigator's Brochure for a complete description of the nonclinical study information.

Clinical Studies

Legend-2

Legend-2 is a first-in-human, single-arm, open-label, multicenter study to determine the safety and efficacy of LCAR-B38M CAR-T cells used to treat subjects with relapsed or refractory MM. Study enrollment was completed in November 2017; 74 subjects have been treated on this study. The clinical cutoff for the analysis presented here was 06 February 2018, with updated survival, efficacy data, and CRS grading provided as of 31 December 2018. As of the 31 December 2018 update, the median follow-up was 17.41 months (range: 0.4–32.2 months).

All subjects had relapsed or refractory MM with a median of 3 (range: 1-9) prior lines of therapy including PI therapy (73%), IMiD (87.8%), and both PI and IMiD (64.9%). Prior autologous stem cell transplantation was reported for 24.3% of subjects. The median age at study entry was 54.5 years (range: 27-74 years).

Of the 74 subjects included in the Legend-2 study, 68 (91.9%) subjects had an adverse event of CRS (median time to onset 9 days [range: 3-57 days]). Most of the CRS events were Grade 1 or Grade 2 severity. Six (8.1%) subjects experienced Grade 3 CRS and 1 (1.4%) subject experienced Grade 5 CRS. The fatal event of CRS occurred in a subject who experienced CRS and tumor lysis syndrome and died on Day 13 after receiving the LCAR-B38M CAR-T cell infusion. For most subjects, symptoms of CRS were mild and reversible. Grade 1 neurotoxicity was reported for 1 subject.

In addition to the subject who died from CRS, 1 subject had a fatal adverse event of potential acute pulmonary embolism and potential acute coronary syndrome related to treatment with LCAR-B38M CAR-T cells.

As of the 31 December 2018 update, the overall response rate (complete response [CR]+very good partial response [VGPR]+partial response [PR]) was 87.8%. Complete response was achieved by 54 (73.0%) subjects and 49 (66.2%) subjects were negative for MRD as assessed by bone marrow 8-color flow cytometry assay. The Kaplan-Meier estimate of median duration of response was 22 months (95% confidence interval [CI]: 11.79-29.14). The median PFS for the overall population was 16 months (95% CI: 10.61-28.16) and among the 49 subjects achieving MRD-negative CR, the median duration of response was 28 months. For current information, refer to the latest version of the JNJ-68284528 Investigator's Brochure.

Study 68284528MMY2001

As of the 24 June 2019 data cutoff, 25 subjects had received an infusion of JNJ-68284528 in the Phase 1b portion of Study 68284528MMY2001. The safety profile is consistent with observations from the Legend-2 study.

- Twenty-four of the 25 subjects who received JNJ-68284528 had at least 1 treatment-emergent adverse event (TEAE).
  - The most commonly reported TEAEs (>20% of subjects) were CRS (88.0%), neutropenia (80.0%), anemia (76.0%), thrombocytopenia (72.0%), leukopenia (40.0%), lymphopenia (28.0%), fatigue (24.0%), headache (24.0%), cough (24.0%), and diarrhea (20.0%)
- Grade 3 or 4 TEAEs were reported for 24 of the 25 subjects.
  - The most commonly reported Grade 3 or 4 TEAEs (>10% of subjects) were neutropenia (76.0%), anemia (48%), thrombocytopenia (60.0%), and leukopenia (40.0%), lymphopenia (16.0%) and CRS (16.0%).
- Serious adverse events were reported for 6 subjects:
  - One subject had serious TEAEs of Grade 3 CAR-T cell-related encephalopathy syndrome (CRES) and Grade 3 CRS.
  - One subject had serious TEAEs of CRS, with Grade 5 hemophagocytic lymphohistiocytosis (HLH) secondary to CRS, and Grade 4 acute kidney injury.
  - One subject had serious TEAEs of Grade 4 thrombocytopenia and Grade 3 pneumonia.
  - One subject had a serious TEAE of Grade 2 mental status change.
  - One subject had a serious TEAE of Grade 3 encephalitis.
  - One subject had serious TEAEs of Grade 1 CRS and Grade 1 confusional state.
- One subject died on Day 99 due to CRS, with Grade 5 HLH secondary to CRS.
- Twenty-two of the 25 subjects (88.0%) experienced CRS. Three subjects experienced Grade 3 CRS and 1 subject experienced Grade 5 CRS (as noted above).

- CAR-T cell-related neurotoxicity was reported in 4 subjects. One subject had Grade 3 CRES, the second subject had Grade 1 neurologic adverse events (dysarthria, slow mentation, gait disturbance, and somnolence), the third subject had Grade 1 CRES, and the fourth subject had a Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) event (difficulty in finding words). All events occurred in the setting of CRS.

The median duration of follow-up for the 21 subjects who received JNJ-68284528 and had at least 1 post-dose disease evaluation as of 24 June 2019 was 2.99 months (range: 1.3 to 9.9 months). Among these 21 subjects, 19 subjects achieved at least a partial response (PR) with an ORR (PR or better) of 90.5% (including unconfirmed responses) with 13 subjects (61.9%) having VGPR or better and 6 subjects (28.6%) having CR or better. A stringent complete response (sCR) was achieved by 4 subjects. Fifteen subjects had post-baseline bone marrow samples available for MRD assessment. All 10 subjects (100%) evaluable at the 10^{-5} sensitivity level were negative for MRD by next generation flow cytometry and/or next generation sequencing (NGS; Adaptive v 2.0). Two subjects were indeterminate at 10^{-5} due to insufficient cell counts but were MRD negative at the sensitivity threshold of 10^{-4} by NGS. No clone identification could be performed in 3 subjects by NGS. Follow-up for response continues, however these preliminary data suggest compelling efficacy in this population of heavily pre-treated subjects. For current information, refer to the latest version of the JNJ-68284528 Investigator's Brochure.

Other Neurotoxicities in Study 68284528MMY2001

CAR-T cell neurotoxicity is categorized as ICANS as well as other neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery from CRS and/or ICANS. As of the 01 September 2020 clinical cutoff, 20 participants (20.6%) in Study 68284528MMY2001 experienced a treatment-emergent CAR-T cell neurotoxicity event.

All-grade ICANS were reported for 16 participants (16.5%). Of these, 2 participants (2.1%) developed maximum Grade 3 or 4 ICANS. Median time from cilta-cel infusion to ICANS onset was 8 days (range: 3 to 12 days), and the median duration of ICANS was 4 days (range: 1 to 12 days). Fifteen participants experienced ICANS concurrent with CRS and 1 participant experienced ICANS 4 days after the recovery of CRS.

Twelve participants (12.4%) experienced other CAR-T cell neurotoxicity not defined as ICANS as assessed by the Investigator either due to symptoms or time of onset (ie, occurring after period of recovery from CRS and/or ICANS). These events included a variety of symptoms with varying severity including disturbances in consciousness, coordination and balance, movement disorders, mental impairment, cranial nerve disorders, and peripheral neuropathies.

Five of these 12 participants experienced a similar presentation of movement and neurocognitive TEAEs. These included a cluster of movement (eg, micrographia, tremors, etc), cognitive (eg, memory loss, disturbance in attention, etc) and personality change (eg, reduced facial expression, flat affect, etc) TEAEs that were observed to progress to an inability to work or care for oneself (disabling). This cluster of movement and neurocognitive TEAEs appears potentially to be associated with a combination of 2 or more factors such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.

The neurotoxicity was Grade 1 or 2 in 3 participants (3.1%), Grade 3 or 4 in 8 participants (8.2%) and Grade 5 in 1 participant (1.0%). These events had a median onset of 26.5 days from cilta-cel

infusion (range: 11 to 108 days) with a median duration of 74.5 days (range: 2 to 160 days). At the time of clinical data cutoff, 6 (50%) had resolved, 4 (33%) were ongoing at the time of death due to other causes, and 1 is ongoing in a participant still in follow-up; one case (8.3%) was fatal.

Study 68284528MMY2002

Study 68284528MMY2002 is a Phase 2, open-label, multicenter study in China (sponsored by Legend Biotech HK Limited and Janssen R&D; Investigational New Drug holder is Legend Biotech) to evaluate the efficacy and safety of LCAR-B38M CAR-T cells in adult subjects with relapsed or refractory MM. Approximately 60 subjects will be enrolled into the study. The primary objective is to evaluate the efficacy of LCAR-B38M CAR-T cells.

The first subject was dosed on 22 March 2019. As of 9 Dec 2019, 25 subjects were enrolled into the study and 13 subjects received LCAR-B38M CAR-T cells. Of the 12 subjects analyzed in the second safety evaluation team meeting, 12 subjects were reported with CRS, 1 subject had Grade 1, 5 had Grade 2, 5 had Grade 3 and 1 had Grade 4 CRS. The median onset to CAR-T infusion was 7 days (range: 2-8) and median duration of CRS was 5 days (range: 4-8). One subject received an infusion of LCAR-B38M CAR-T cells on 06 May 2019 and died on PPD 2019 due to hemorrhage secondary to thrombocytopenia. The investigator attributed the thrombocytopenia, CRS, and acute renal failure to LCAR-B38M CAR-T cell therapy. The CRS events experienced by other subjects all resolved. No neurotoxicity has been reported as of the cut-off date. For current information, refer to the latest version of the JNJ-68284528 Investigator's Brochure.

Study 68284528MMY2003

Study 68284528MMY2003 is an ongoing, multicohort, open-label, multicenter, Phase 2 study to determine whether treatment with cilta-cel results in MRD negativity in adult participants with MM. Cohorts of approximately 20 to 40 participants each, representing unique populations of patients with MM of unmet medical need, are planned. As of 23 July 2020, 18 participants have received cilta-cel infusion. Further details are provided in the most recent edition of the JNJ-68284528 Investigator’s Brochure.

2.2.6. Comparator Agents

2.2.6.1. Pomalidomide, Bortezomib, and Dexamethasone

Pomalidomide, bortezomib and low-dose dexamethasone combination was studied in the Phase 1 Study MM-005 in lenalidomide-refractory and PI-exposed relapsed or refractory MM subjects.[39] Subjects received pomalidomide (1–4 mg on Days 1–14), bortezomib (1-1.3 mg/m^2 on Days 1, 4, 8, and 11 for Cycles 1–8; Days 1 and 8 for Cycle ≥9) as well as dexamethasone 20 mg given on Days 1, 2, 4, 5, 8, 9, 11 and 12 in 21-day cycles. Subjects (n=34) received a median of 2 prior lines of therapy. With no dose-limiting toxicities, maximum tolerated dose (MTD) was defined as the maximum planned dose: pomalidomide 4 mg, bortezomib 1.3 mg/m^2. The most common Grade 3 or 4 TEAEs were neutropenia (44%) and thrombocytopenia (26%). ORR was 65% and the median duration of response was 7.4 months.

In the Phase 3 OPTIMISMM study,[40] subjects with relapsed or refractory MM with 1 to 3 prior line(s) of therapy were randomized to either PVd (n=281) or bortezomib/dexamethasone (Vd) (n=278) on the same schedule and at the defined MTD as in the Study MM-005. Seventy percent of subjects were lenalidomide-refractory. Subjects had a median of 2 prior lines of therapy. The most common Grade 3 or 4 TEAEs were neutropenia (42%), thrombocytopenia (27%) in subjects treated with PVd. In the same group, the most common Grade 3 or 4 non-hematologic toxicities were: infection (31%) with 12% of subjects having pneumonia. The febrile neutropenia rate was 3% in the PVd group. Grade 3 or 4 peripheral sensory neuropathy was reported in 8% of subjects receiving PVd. The ORR was 82 % and 50% in the PVd and Vd cohorts, respectively. VGPR or better was achieved by 53% and 18% of the subjects in the PVD and Vd cohorts, respectively. The median PFS in the entire population was 11.2 months on the PVd cohort versus 7.1 months on the Vd cohort. The median PFS was 9.5 months in lenalidomide-refractory subjects on the PVd cohort versus 5.6 months on the Vd cohort. Lenalidomide-refractory subjects with only 1 prior line of therapy had a median PFS of 17.8 months on the PVd regimen versus 9.5 months on the Vd regimen. Based on these results, PVd was approved in the EU for patients with relapsed or refractory MM and is National Comprehensive Cancer Network[29] recommended in the US for patients whose MM has relapsed after 2 or more therapies including an IMiD and a PI and is therefore being used as a comparator for this current Phase 3 study.

For further information regarding PVd refer to the current approved label for Pomalyst®/Imnovid®/pomalidomide (Pomalyst Prescribing Information; Imnovid Summary of product Characteristics)[19,33].

2.2.6.2. Daratumumab, Pomalidomide, and Dexamethasone

Daratumumab (DARZALEX®) in combination with pomalidomide and dexamethasone (DPd) has been approved in the US for the treatment of patients with MM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

The approval was based on data from the Phase I (EQUULEUS) study of DPd subjects with relapsed or refractory MM. One arm of the EQUULEUS open-label study included 103 subjects with MM who had received prior treatment with a PI and an IMiD. Subjects in the study received DPd. Subjects had a median of 4 prior lines of therapy and 89% were lenalidomide-refractory.

The ORR in the study was 59%, with 9% of subjects achieving a CR and 8% achieving a sCR. Median PFS was 8.8 months. Among the 62 responders, median duration of response was not estimable ([NE]; 95% CI: 13.6-NE).[6] Based on these results, the DPd regimen was chosen as an alternative standard therapy to be used as a comparator for this current Study 68284528MMY3002. This regimen is also being explored in the context of an ongoing randomized open-label, active-control, multicenter Phase 3 study in subjects with relapsed or refractory multiple myeloma who had received at least 1 prior treatment regimen with both lenalidomide and a PI, and had demonstrated disease progression (APOLLO; EMN14/54767414MMY3013).

A total of 304 subjects were randomized (151 DPd; 153 Pd). Subjects had a median of 2 prior lines of therapy: 79.6% of subjects were refractory to lenalidomide, 48.0% were refractory to a PI, and

42.4% were refractory to both. The median duration of treatment was 11.5 months with DPd. Results of the primary analysis demonstrated that the study met its primary endpoint of improved PFS, with a median PFS of 12.4 months, versus 6.9 months for subjects treated with Pd. With a median follow-up of 16.9 months, 99 subjects (33%) have died; the HR for OS was 0.91 (95% CI, 0.61-1.35); survival data are immature and follow-up is ongoing. The ≥CR rates for D-Pd versus Pd were 24.5% versus 3.9%; ≥VGPR rates were 51.0% vs 19.6%.

A formulation of daratumumab for subcutaneous (SC) administration was developed to shorten the time required to administer daratumumab and to lessen the rate and severity of infusion-related reactions (IRRs) observed with intravenous (IV) daratumumab. A recombinant human hyaluronidase PH20 (rHuPH20) was used to decrease the injection volume required, facilitating the subcutaneous administration of daratumumab.

The efficacy and adverse event profile of subcutaneous daratumumab are similar to those of IV daratumumab, with the exception of IRRs. Subcutaneous daratumumab has a lower rate of IRRs (16% versus 50% with IV administration). In addition, the IRRs mainly occur within 6 hours of the start of the first administration. The SC formulation of daratumumab is being evaluated in Study MMY1004, an open label, multicenter, dose escalation Phase 1b study to assess the safety, pharmacokinetics, and efficacy of subcutaneous daratumumab in participants with relapsed or refractory MM. The fixed SC dose of 1800 mg was selected based on a review of pharmacokinetics, safety, and efficacy data in Part 1 (N=53; daratumumab administered by subcutaneous infusion) and was confirmed in Part 2 (N=25; daratumumab administered by subcutaneous injection). Similar or greater maximum trough concentrations were observed following administration of SC daratumumab 1800 mg compared with standard approved dosing of IV daratumumab 16 mg/kg.[41] The IRR rate in Part 2 was 16%; events were mostly Grade 1 or 2 and included chills, dyspnea, sneezing and allergic rhinitis. Two Grade 3 events of reversible hypertension were reported. None of the IRRs led to treatment discontinuation. Injection-site reactions included reversible erythema in 24% of participants. Reversible induration at the injection site was experienced by 1 participant (4%). Subcutaneous daratumumab injections in the periumbilical area were well tolerated. The ORR in Part 2 was 52%, with 28% VGPRs and 4% CRs. Median time to response was 1 month. Median duration of response was 15.7 months and several responses deepened over time. The SC formulation currently is being tested in Study MMY3012, a Phase 3 study of IV daratumumab 16 mg/kg versus SC daratumumab 1800 mg in participants with relapsed or refractory MM; and in Study MMY2040, a Phase 2 study of SC daratumumab in combination with standard MM treatment regimens. The randomized, open-label, non-inferiority, Phase 3 Study MMY3012 of SC daratumumab 1800 mg versus IV daratumumab 16 mg/kg in subjects with RRMM (n=263 SC; n=259 IV) confirmed non-inferiority for efficacy and pharmacokinetics, a similar adverse event profile, and a significantly reduced risk of IRRs (12.7% vs. 34.5%; P<0.0001) with daratumumab SC compared with daratumumab IV.[26]

For further information regarding DPd refer to the DARZALEX® local prescribing information or Summary of Product Characteristics (SmPC).[12,13]

2.3. Benefit-Risk Assessment

The potential risks of JNJ-68284528 are identified from the following: 1) results of nonclinical studies; 2) mechanism of action; and 3) previous clinical experience with JNJ-68284528 and LCAR-B38M CAR-T cells. Longer follow-up and treatment of additional subjects, particularly subjects who have received fewer prior therapies than subjects in the Legend-2 and 68284528MMY2001 studies, may reveal additional risks.

By stimulating an inflammatory cascade, there is potential for toxicity in other tissues or organs by non-specific immune cell activation. Therefore, special attention should be given to both immunological and immunogenicity-related toxicities. Safety risks and mitigation strategies are outlined in Table 6.

Table 6: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
Cytokine release syndrome (CRS) [a]	Monitor closely for CRS and follow guidance for management in Section 6.1.6.1. Body temperature should be monitored twice daily for 28 days post infusion. At the first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation. See Table 8 for other hospitalization requirements. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. Severe thrombocytopenia, low fibrinogen, and often disseminated intravascular coagulation (DIC) may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. Section 6.1.6.1 describes measures to be taken if HLH is suspected. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever in the absence of clear infectious etiology. Early tocilizumab should be considered in subjects at high risk of severe CRS. Section 6.1.6.1 provides management guidelines for CRS. Notify the sponsor if subject is experiencing Grade 2 or higher CRS.
Neurologic toxicities [a]	**CAR-T cell-related neurotoxicity (ie, immune effector cell-associated neurotoxicity syndrome [ICANS])** Monitor closely for neurologic AEs, including CAR-T cell-related neurotoxicity (eg, ICANS) and raised intracranial pressure / cerebral edema; follow guidance for management in protocol. Participants should be advised to seek medical evaluation if they notice new onset of headache, convulsions, speech disorders, visual disorders, disturbances in consciousness, confusion and disorientation, and coordination, balance disorders, or mental status changes. Notify the sponsor if participant is experiencing any grade ICANS. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. The Immune effector Cell-associated Encephalopathy (ICE) Assessment Tool (ICE-Tool) should be performed at baseline and daily after the first symptoms of neurotoxicity are suspected and until resolution. Hospitalization is required for ≥ Grade 2 CAR-T cell-related neurotoxicity (eg, ICANS). Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities. Other cytokine-targeting therapies (for example, IL1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for participants who develop neurotoxicity that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.

Table 6: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
	Movement and Neurocognitive Toxicity (ie, Parkinsonism)A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including: changes in movement (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself), cognitive impairments (eg, memory loss or forgetfulness, disturbance in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words), and personality changes (eg, reduced facial expression, flat affect, reduced ability to express emotion, less communicative, disinterest in activities). If those neurologic or psychiatric symptoms are noted, contact the medical monitor and refer the subject immediately to a neurologist for a full evaluation. Section 6.1.6.2.2 provides further details for management guidelines for neurotoxicity. If a subject is non-responsive to interventions for this neurotoxicity, consideration should be given for therapies directed at reduction or elimination of CAR-T cells. A cluster of movement and neurocognitive TEAEs were observed at a higher frequency in participants with high burden of disease and in participants experiencing higher grade CRS (Grade 2 and above) and any grade ICANS. This may be indicative that ≥Grade 2 CRS or any grade ICANS are early indicators for the development of other neurotoxicity after a period of recovery from CRS and/or ICANS. Therefore, ≥Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids) especially in patients treated with a high tumor burden, that may mitigate the risk for developing late, other neurotoxicity. Mitigation strategies for other neurotoxicity include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of study. Monitor closely for other neurotoxicities with clinical presentation for duration of study post-infusion with JNJ-68284528. If those neurologic or psychiatric symptoms are noted, contact the medical monitor, and refer the participant immediately to a neurologist for a full evaluation. Infection and sepsis were concurrently seen in many of these patients. **Cranial Nerve Palsies** Monitor patients for signs and symptoms of cranial nerve palsies (eg, facial paralysis, facial numbness). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. **Peripheral Neuropathy** Monitor patients for signs and symptoms of peripheral neuropathies (eg, sensory, motor, or sensorimotor neuropathies). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. **Guillain-Barré Syndrome** Monitor for signs and symptoms of GBS after cilta-cel infusion. Symptoms reported include those consistent with Miller-Fisher variant of GBS (encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis). Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity.
Tumor lysis syndrome (TLS)	Monitor closely for TLS with frequent monitoring of chemistry parameters and follow guidance for management in Section 6.1.6.3. Participants with high tumor burden or multiple extramedullary disease sites or plasmacytomas should be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol; and primary or secondary uricosuric agents, as indicated).
Second primary malignancies (SPM)[a]	Second primary malignancies may occur in subjects receiving JNJ-68284528. SPM should be managed per institutional standards. Second primary malignancies must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study until 15 years post

Table 6: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
	dosing of JNJ-68284528. A tumor sample should be collected and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements if an SPM develops. Section 6.1.6.4 provides management guidelines for SPMs.
Prolonged Cytopenias	Frequent monitoring of hematological parameters and provide supportive care (eg, irradiated blood, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited until Day 112. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Section 6.1.6.5 provides management guidelines for cytopenias. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.
Hypogammaglobulinemia	Monitor immunoglobulin levels after treatment and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Additional assessments of immunoglobulin levels may be done as per local standard of care. Section 6.1.6.6 provides management guidelines for hypogammaglobulinemia. Subjects with IgG < 400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or subcutaneous IgG per institutional guidelines. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy.
Serious Infections	Do not administer JNJ-68284528 to patients with active infection. Frequent monitoring for the presence of infections, with cultures or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment and institutional standards. Immunocompromised patients are at risk for opportunistic infections; prophylactic use of antibiotics, antivirals, or antifungals should be considered. Extended use of anti-microbial therapies for at least 6 month (or longer as per institutional guidelines) or consistent with post ASCT consensus guidelines after JNJ-68284528 dosing are recommended (See Section 10.28 [Appendix 28]). Perform screening for HBV, HCV, and HIV and monitor as clinically indicated, and initiate treatment as appropriate. Consider CMV serology at baseline, monitor with PCR testing as clinically indicated per institutional guidance. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in subjects treated with drugs directed against B cells such as JNJ-68284528. HBV reactivation has occurred in subjects who appear to have resolved hepatitis B infection. Prophylaxis for herpes zoster reactivation is recommended during study treatment as clinically indicated. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Section 10.6 and Table 5). Prophylaxis for participants at high risk of HBV reactivation is recommended per institutional guidance. Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in Appendix 10.29.
Hypersensitivity reactions	Allergic reactions may occur with the infusion of JNJ-68284528. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin in JNJ-68284528. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Subjects should receive premedication prior to JNJ-68284528 dosing as noted in Section 6.1.5.5.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAR-T= chimeric antigen receptor T-cell; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

a Adverse event of special interest (see Section 8.3.1)

More detailed information about the known and expected benefits and risks of JNJ-68284528 may be found in the Investigator's Brochure.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with JNJ-68284528 are justified by the anticipated benefits that may be afforded to subjects with relapsed, lenalidomide-refractory MM.

Favorable benefit and risk profiles for PVd and DPd have been demonstrated. Potential risks of PVd and DPd are described in the product labeling. Management of local injection-site reactions and injection-related reactions associated with SC administration of daratumumab are described in Section 6.1.7.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	• PFS
Secondary	
• To further compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	• Rate of CR/sCR • Overall MRD negative rate • Rate of MRD negativity in subjects with CR/sCR at 12 months ±3 months • Rate of sustained MRD negative status • OS • ORR • PFS on next line of therapy (PFS2)
• To assess the safety profile of JNJ-68284528	• Incidence and severity of adverse events
• To characterize the pharmacokinetics and pharmacodynamics of JNJ-68284528	• Pharmacokinetic and pharmacodynamic markers including but not limited, to systemic cytokine concentrations, and markers of CAR-T cells, T cell expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level.
• To assess the immunogenicity of JNJ-68284528	• Presence of anti-JNJ-68284528 antibodies
• To evaluate the impact of JNJ-68284528 treatment on the health-related quality of life of subjects compared with standard therapy, either PVd or DPd	• Time to worsening of symptoms using the MySIm-Q total symptom score • Change from baseline in health-related quality of life (HRQoL) subscale scores from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, Multiple Myeloma Symptom and

Objectives	Endpoints
	Impact Questionnaire (MySIm-Q), EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Severity (PGIS), and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items.
Exploratory	
• To further characterize the pharmacodynamics of JNJ-68284528	• Depletion of BCMA-expressing cells and circulating soluble BCMA levels
• To determine whether replication competent lentivirus is present in subjects who receive JNJ-68284528	• Screen for presence of replication competent lentivirus
• To characterize the impact of JNJ-68284528 CAR-T process on medical resource utilization compared with standard therapy, either PVd or DPd	• Number of subjects with type and length of inpatient stay and overall medical encounters
• To characterize potential early clinical, translational, and imaging markers for neurotoxicity (predictive markers)	• Qualitative changes in handwriting assessment • T_{max}, C_{max}, and phenotypic analysis of CAR-T cells • Neuroimaging (CT/MRI/PET)

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis is that JNJ-68284528 will significantly improve PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior line(s) of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, open-label, multicenter study to determine whether treatment with JNJ-68284528 will provide efficacy benefit compared to standard therapy (PVd or DPd) in subjects with relapsed and lenalidomide-refractory MM.

The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. During the Screening Phase, all subjects will provide written consent for study participation and will be screened for study eligibility within 28 days prior to randomization.

Approximately 400 subjects will be randomized 1:1 to receive either standard therapy with PVd or DPd (Arm A) or to receive JNJ-68284528 (Arm B).

Randomization will be stratified by investigator's choice of PVd or DPd, International Staging System (ISS) (I vs. II vs. III) (Section 10.5), and number of prior lines of therapy (1 vs. 2 or 3).

Data regarding subjects' health-related quality of life (HRQoL), symptoms, functioning, and general well-being will be captured using patient reported outcomes (PRO) measures. Medical resource utilization data, associated with medical encounters, will also be collected.

4.1.1. Arm A

Prior to screening, the investigator will determine if the subject will be treated with PVd or DPd, as standard therapy based on the subject's prior exposure to anti-myeloma therapies. After meeting eligibility criteria defined in Section 5.1 and Section 5.2, subjects randomized to Arm A will receive either PVd or DPd. Subjects should start PVd or DPd within 7 days after randomization.

Pomalidomide, bortezomib and dexamethasone (PVd):

Pomalidomide will be administered at a full dose of 4 mg orally (PO) on Days 1 through 14 of each 21-day cycle.

Bortezomib will be administered at a full dose of 1.3 mg/m^2 subcutaneously (SC) twice a week for 2 weeks for the first 8 Cycles and then once a week for 2 weeks from Cycle 9 onwards of each 21-day cycle. Bortezomib doses should always be administered at least 72 hours apart.

Dexamethasone will be administered PO as 20 mg/day (≤75 years of age) or 10 mg/day (>75 years of age) on Days 1, 2, 4, 5, 8, 9, 11, and 12 from Cycles 1 through 8 and on Days 1, 2, 8 and 9 from Cycle 9 onwards for each 21-day cycle.

Daratumumab, pomalidomide and dexamethasone (DPd):

Daratumumab will be given at a dose of 1800 mg SC at weekly intervals for Cycles 1 and 2, then every 2 weeks for Cycles 3 to 6, then every 4 weeks from Cycle 7 onwards of each 28-day cycle. Subjects will receive pre-treatment medications to mitigate potential IRRs.

Pomalidomide will be administered at full dose of 4 mg PO on Days 1 through 21 of each 28-day cycle.

Dexamethasone will be administered PO/IV at a total dose of 40 mg weekly (20 mg weekly for subjects >75 years of age) of each 28-day cycle (see Section 6.1.1).

Safety and efficacy will be assessed, and subjects randomized to Arm A will continue to receive PVd or DPd until confirmed progressive disease (PD), death, intolerable toxicity, withdrawal of consent, or end of the study. All subjects in Arm A will have an end-of-treatment visit. Subjects who discontinue PVd or DPd for any reason, other than PD or withdrawal of consent, will continue to be followed for response assessment until confirmed PD or the start of a subsequent anti-myeloma therapy. After confirmed PD, subjects will then be followed for survival status, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2), and the occurrence of second primary malignancies (SPMs) every 16 weeks until the end of the study (defined when approximately 250 deaths have

occurred). The occurrence of SPMs must be reported throughout study treatment and must continue to be reported until the end of the study.

4.1.2. Arm B

Eligible subjects randomized to Arm B will receive JNJ-68284528 and will undergo the following steps:

- Apheresis to collect peripheral blood mononuclear cells (PBMCs) Apheresis should be performed 3 to 6 days after randomization.
- Bridging therapy should be started after apheresis but no more than 7 days after randomization. Subjects should receive at least one cycle of bridging therapy with either PVd or DPd (determined by the investigator based on the subject's prior anti-myeloma therapy). Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of JNJ-68284528. Investigator must contact the sponsor for approval. Cycles beyond Bridging Cycle 1 may be truncated to allow for adequate washout and minimize time off therapy.
- A wash-out period must occur from the last dose of bridging therapy until prior to initiating the conditioning regimen, the length of which will depend on whether PVd or DPd was given as bridging therapy (See Section 6.1.5.4).
- Conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73 m^2.
- JNJ-68284528 will be administered with the target dose of 0.75 x 10^6 CAR-positive viable T cells/kg 5 to 7 days after the start of the conditioning regimen.
- Post-infusion Follow Up: Intensive safety, pharmacokinetics (PK), biomarkers, and efficacy monitoring during the first 112 days following JNJ-68284528 administration.
- Post-treatment Follow Up: starts once the post-infusion follow-up is complete (on Day 112) and lasts until end of study. In the post treatment follow-up phase, subjects will continue to be monitored for efficacy until confirmed PD, death, or withdrawal of consent. After confirmed PD, subjects will be followed for survival, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies, including the date of subsequent progression (PFS2), and delayed AEs (including SPMs) every 16 weeks until the end of the study (defined when approximately 250 deaths have occurred).

The occurrence of delayed AEs including SPMs must be reported during the post-infusion and post-treatment follow-up phases and continue until the end of the study. All subjects who received JNJ-68284528 will continue to be monitored for long-term safety under a separate study for up to 15 years after JNJ-68284528 administration.

Subjects in Arm B for whom apheresis or manufacturing fails may be allowed additional attempts at apheresis or manufacturing and may be allowed additional bridging therapy following discussion with the sponsor.

Efficacy and safety evaluation (Arm A and Arm B)

For both Arm A and Arm B, disease status will be evaluated according to the IMWG consensus recommendations for MM treatment response criteria (Section 10.7).[14,22,36] The primary endpoint and response-related secondary endpoints will be determined using a validated computer algorithm.

Safety evaluations will include a review of adverse events, laboratory test results, vital sign measurements, physical examination findings, (including neurological examination), assessments of cardiac function, Immune-effector Cell-associated Encephalopathy (ICE) assessment (only for Arm B), and handwriting assessments (only for Arm B), and Eastern Cooperative Oncology Group (ECOG) performance status.

Subjects who are unable to receive PVd or DPd standard therapy (Arm A), or unable to be apheresed, or receive bridging therapy, conditioning regimen or JNJ-68284528 infusion (Arm B) will be followed until confirmed PD, start of a new anti-myeloma therapy, withdrawal of consent, or end of study, whichever occurs first. Once PD is confirmed, subsequent disease assessments time points are not required. After PD subjects will then be followed for survival status, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2), and SPMs until the end of the study (see Section 8.3). Subjects who progress on Arm B prior to receiving JNJ-68284528 and who are intended to get JNJ-68284528 as part of their subsequent therapy will continue to be monitored for response evaluation via central laboratory if feasible and safety monitoring as per Table 5 (refer to Section 1.3).

One interim analysis for efficacy is planned for PFS. The interim analysis will be performed when approximately 188 PFS events, which is 75% of the total planned PFS events, are observed. The final analysis of PFS will be performed after approximately 250 PFS events are observed. The end of the study is defined as the time when approximately 250 deaths have occurred or the sponsor terminates the study, whichever occurs first.

After the end of the study, the sponsor will continue to monitor subjects treated with JNJ-68284528 for up to 15 years after administration of JNJ-68284528 on a separate long-term follow-up study (Study 68284528MMY4002) for complications of lentiviral integration, potential delayed adverse events, including SPMs.

All study evaluations will be conducted according to the Schedule of Activities (Section 1.3). A diagram of the study design is provided in Section 1.2, Schema.

Safety and efficacy data will be periodically reviewed by an Independent Data Monitoring Committee (Section 9.6 and Section 10.3).

4.2. Scientific Rationale for Study Design

Control, Study Phase/Periods, Intervention Groups

Randomization will be used to minimize bias in the assignment of subjects to intervention groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Randomization will be stratified by investigator's choice of PVd vs. DPd, ISS at screening (I vs. II vs. III), and number of prior lines of therapy (1 vs. 2 or 3).

Rationale for Pharmacokinetics (PK) and Immunogenicity Assessments

Data obtained from the JNJ-68284528 Treatment Arm (Arm B) in this study will provide information about the PK profile of JNJ-68284528 in subjects with MM. Therefore, samples will be obtained from all subjects in Arm B for PK assessments. Data may also be used for a population PK analysis to estimate additional PK parameters and provide information about the determinants of inter-subject variability in this population.

Immunogenicity to JNJ-68284528 is possible. Therefore, the presence of anti-JNJ-68284528 antibodies will be determined from PK samples collected from all subjects in the JNJ-68284528 Treatment Arm (Arm B).

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth and durability of clinical response through evaluation of MRD, using DNA sequencing of immunoglobulin genes.

Rationale for Patient-reported Outcome Evaluations

Patient-reported outcome (PRO) data complements clinical and laboratory findings to describe the subject experience, directly reported by the subject. In addition, PRO data captures inputs required for cost-effectiveness modeling and helps to communicate the value of treatment to patients, clinicians, regulators, and payers.

4.2.1. Study-Specific Ethical Design Considerations

This study is designed to provide an efficacious regimen for the treatment of subjects with lenalidomide-refractory MM. Based on the data presented in Section 2.2.4, treatment with JNJ-68284528 is anticipated to provide benefit to subjects in this study. Potential safety risks and mitigation strategies are outlined in Section 2.3. Subjects will be closely monitored.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is clinical equipoise among treatment groups. Both PVd and DPd have demonstrated durable responses in patients with MM who are refractory to lenalidomide. Based on the results of the OPTIMISMM study, in subjects with a median of 2 prior lines of therapy, PVd resulted in a median PFS of 11.2 months.[40] The median PFS in lenalidomide-refractory subjects was 9.5 months. Subjects on the EQUULEUS study had a median of 4 prior lines of therapy and treatment with DPd resulted in a median PFS of 8.8 months.[6] Results from the APOLLO study showed that in subjects with a median of 2 prior lines of therapy, treatment with DPd resulted in a median PFS of 12.4 months, versus 6.9 months for subjects treated with Pd. Experience with JNJ-68284528 in Study 68284528MMY2001 and LCAR-B38M CAR-T cells in the Legend-2 study has shown ORRs of 90.5% and 87.8%, respectively (see Section 2.2.5). While one subject died in Study 68284528MMY2002 and one in Study 68284528MMY2001, both deaths were in the setting of rapid disease progression with numerous other factors likely contributing. To mitigate this, all subjects in Study 68284528MMY3002 will receive bridging therapy that is expected, in most cases, to control the subject's myeloma while JNJ-68284528 product is being manufactured. In addition, subjects with rapidly progressing disease or ≥Grade 3 thrombocytopenia or active infection will not be allowed to proceed to conditioning regimen on this study.

Use of JNJ-68284528 is hypothesized to result in greater response rates and duration of response when used in earlier lines of therapy due to improved immune function. This study will enroll subjects who have received 1 to 3 prior lines of therapy, that includes a PI and an IMiD, and who are refractory to lenalidomide. Based on nonclinical and clinical data, JNJ-68284528 is believed to be a reasonable treatment alternative for PVd and DPd regimens.

The blood volume to be collected is an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (Section 8).

4.3. Justification for Dose

4.3.1. Rationale for PVd Dose Selection

The dose and schedule of PVd administration were selected based on the MM-005 and OPTIMISMM studies described in Section 2.2.6.1. The MTD defined in MM-005 and tested in the OPTIMISMM study is the dosing recommended by the Imnovid SmPC[19] and will be used for the current study (68284528MMY3002).

4.3.2. Rationale for DPd Dose Selection

The DPd dose selected for this study is based on the currently approved regimen of daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least 2 prior therapies including lenalidomide and a PI. The SC formulation of daratumumab will be administered in this study, based on results from the COLUMBA study indicating a significantly lower rate of IRR with daratumumab SC compared with daratumumab IV.[26]

4.3.3. Rationale for JNJ-68284528 Dose Selection

The conditioning regimen of cyclophosphamide and fludarabine will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Cyclophosphamide and fludarabine before JNJ-68284528 infusion (Day 1) is consistent with the conditioning regimen used in the marketed CAR-T products.[23,45]

JNJ-68284528 will be administered at a targeted infused dose of 0.75 x 10^6 CAR-positive viable T cells/kg. This dose was established in the Phase 1b part of Study 68284528MMY2001. As of the 24 June 2019 data cutoff, 25 subjects have been infused with JNJ-68284528 in Study 68284528MMY2001; 21 subjects were evaluable for response (postbaseline evaluation at Day 28) with a median follow-up of 3 months (range 1–10). An ORR of 90.5% was observed with 6 subjects achieving CR/sCR (28.6%), 7 subjects achieving VGPR (33.3%) and 6 subjects achieving PR (28.6%). The responses occurred rapidly, with most subjects exhibiting ≥50% myeloma protein reduction at the first disease assessment (scheduled at Day 28 after JNJ-68284528 dosing). The responses continue to deepen for all subjects who are in follow up and no disease progression has been observed as of data cutoff.

Preliminary efficacy data from Study 68284528MMY2001 showed that a dose of 0.75 x 10^6 cells/kg of JNJ-68284528 CAR-T cell is highly efficacious with acceptable safety in a patient population who had no alternative treatment option. Further discussion of the JNJ-68284528 dose selection is provided in the Investigator's Brochure.

4.4. End of Study Definition

End of Study Definition

The end of study is when approximately 250 deaths have occurred in the study.

Study Completion Definition

A subject will be considered to have completed the study if he or she has either died before the end of the study, is not lost to follow-up, has not withdrawn consent for study participation or study terminated by sponsor. All subjects who received JNJ-68284528 will be offered to participate in a long-term follow-up study (Study 68284528MMY4002). The sponsor will continue to monitor consented subjects in the long-term follow-up study at least once per year for 15 years. An appropriate transition will be arranged between this study and the long-term follow-up study to ensure no follow-up gap occurs.

5. STUDY POPULATION

Screening for eligible subjects will be performed within 28 days before randomization. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling subjects 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 subject in the study. Waivers are not allowed.

5.1. Inclusion Criteria

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

1. Be at least 18 years of age.

2. Criterion modified per Amendment 2

   2.1 Have documented diagnosis of MM as defined by the criteria below:

   - Multiple myeloma diagnosis according to the IMWG diagnostic criteria (Section 10.8).
   - Measurable disease at screening as defined by any of the following:
     - Serum monoclonal paraprotein (M-protein) level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - Light chain MM without measurable M-protein in the serum or the urine: Serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio.

   Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements. However, subjects must have laboratory studies for diseases assessment received by central laboratory prior to randomization. If central and local laboratory studies are performed on the same day, only the central laboratory results will be considered.

3. Have received 1 to 3 prior lines of therapy including a PI and IMiD. Subject must have undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy (see Section 10.9).

   Note: induction with or without hematopoietic stem cell transplant, consolidation and maintenance therapy is considered a single line of therapy.

4. Have documented evidence of PD by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.

5. Subjects with only 1 prior line of therapy must have progressed within 36 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.

6. Criterion modified per Amendment 1

   6.1. Criterion modified per Amendment 2

   6.2. Be refractory to lenalidomide per IMWG consensus guidelines (Rajkumar 2011)[36] (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than 1 prior line

of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy. However, subjects must be refractory to lenalidomide in at least one prior line.

7. Have an ECOG Performance Status score of 0 or 1 (Section 10.10).

8. Have clinical laboratory values meeting the following criteria during the Screening Phase (re-testing is allowed but the below criteria must be met in the latest test prior to randomization):

   - Hemoglobin ≥8 g/dL (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
   - Absolute neutrophil count (ANC) ≥1 × 10^9/L (without recombinant human granulocyte colony-stimulating factor [G-CSF] within 7 days and without pegylated G-CSF within 14 days of the laboratory test);
   - Platelet count ≥75 × 10^9/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom <50% of bone marrow nucleated cells are plasma cells; platelet count ≥50 x 10^9/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells;
   - Lymphocyte count ≥0.3 × 10^9/L;
   - Aspartate aminotransferase (AST) ≤3 × upper limit of normal (ULN);
   - Alanine aminotransferase (ALT) ≤3 × ULN;
   - Total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required);
   - Estimated glomerular filtration rate ≥40 mL/min per 1.73 m^2 (to be calculated using the Modification of Diet in Renal Disease (MDRD) formula, (Section 10.11).

9. Women of childbearing potential must have 2 negative pregnancy tests prior to starting PVd or DPd. The first, 10-14 days prior to the start of PVd or DPd and prior to randomization. The second pregnancy test will need to be done within 24 hours prior to the start of PVd or DPd. The investigator must verify that the results of these tests are negative prior to starting PVd or DPd. See Section 10.12 for definition of females who are not of reproductive potential.

10. When a woman is of childbearing potential, the subject must commit either to abstaining continuously from heterosexual intercourse or agree to use 2 methods of reliable birth control simultaneously. One of them a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and agree to remain on both methods from the time of signing the ICF until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of

daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B) (Section 10.12). Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Examples of highly effective contraceptives include:

- User-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner (vasectomy must be confirmed by 2 negative semen analyses);
- User-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with pomalidomide. Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Refer to Section 10.12 for further information.
- Women of childbearing potential must follow the contraception criteria outlined in the local pomalidomide pregnancy prevention program.

11. A man must commit either to abstaining continuously from heterosexual sexual intercourse or a man:

- Who is sexually active with a woman of childbearing potential or a pregnant woman must agree to use a barrier method of contraception (eg, latex or synthetic condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B), even if they have undergone a successful vasectomy;
- Should agree to practice contraception according to and for the time frame specified in the local pomalidomide pregnancy prevention program.

12. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for at least 3 months after receiving the last dose of daratumumab or bortezomib, or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B).

13. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Subjects must be willing and able

to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

14. Willing and able to adhere to the lifestyle restrictions specified in this protocol (Section 5.3)

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she has or had:

1. Prior treatment with CAR-T therapy directed at any target.

2. Any previous therapy that is targeted to BCMA.

3. Ongoing toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less; except for alopecia.

4. Subjects with Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy will not be permitted to receive PVd as standard therapy or bridging therapy; however, subject may receive DPd as standard therapy or bridging therapy.

5. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to randomization (Section 10.13).

6. Criterion modified per Amendment 2

   6.1. Was vaccinated with live attenuated vaccines within 6 weeks prior to randomization

7. Subject received any antitumor therapy as follows, prior to randomization:

   - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less;
   - Investigational vaccine within 4 weeks;
   - Monoclonal antibody treatment within 21 days;
   - Cytotoxic therapy within 14 days;
   - Proteasome inhibitor therapy within 14 days;
   - Immunomodulatory agent therapy within 7 days;
   - Radiotherapy within 14 days. However, if the radiation is given for palliative purposes and the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy. Radiotherapy within

14 days on measurable extramedullary plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management.

8. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- Malignancy that is considered cured with minimal risk of recurrence.

9. Plasma cell leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

10. Criterion modified in Amendment 1

10.1. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to JNJ-68284528 or its excipients, including dimethyl sulfoxide (refer to Investigator's Brochure), or to fludarabine, cyclophosphamide, tocilizumab, pomalidomide, dexamethasone.

- Subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to daratumumab will not be permitted to receive DPd as standard therapy or bridging therapy; however, subjects may receive PVd as standard therapy or bridging therapy. Likewise, subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to bortezomib will not be permitted to receive PVd as standard therapy or bridging therapy; but may receive DPd as standard therapy or bridging therapy.

11. Pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 3 months of receiving the last dose of daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least within 1 year after receiving JNJ-68284528 infusion or at least within 3 months after receiving the last dose of daratumumab or bortezomib or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).

12. Plans to father a child while enrolled in this study or within 3 months of receiving the last dose daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least within 1 year after receiving JNJ-68284528 infusion or at least within 3 months after receiving the last dose of daratumumab or bortezomib or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).

13. Stroke or seizure within 6 months of signing ICF.

14. Received either of the following:

- An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded.
- An autologous stem cell transplantation ≤12 weeks before apheresis.

15. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of MM.

16. Subject with chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal will not be able to receive DPd as standard therapy or bridging therapy; however, subject may receive PVd as standard therapy or bridging therapy. Note that FEV1 testing is required for subjects who are planned to receive treatment with DPd and are suspected of having COPD.

17. Criterion revised per Amendment 1

    17.1. Any of the following:

    a) Seropositive for human immunodeficiency virus (HIV)

    b) Hepatitis B infection: In the event the infection status is unclear, quantitative viral levels are necessary to determine the infection status. Subjects who are anti-HBs positive and without history of vaccination or for subjects who are anti-HBc positive with or without positive anti-HBs should have hepatitis B virus (HBV)-DNA quantification test done. Please consult Section 10.6 for further details.

c) Hepatitis C infection (defined as anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

18. Criterion revised per Amendment 1

18.1. Criterion modified per Amendment 2

18.2. Serious underlying medical or psychiatric condition or disease, that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:

- Requirement of supplemental oxygen to maintain oxygen saturation;
- Evidence of serious active viral or bacterial infection, requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection;
- Active autoimmune disease;
- Clinical evidence of dementia or altered mental status;
- Any history of Parkinson's disease or other neurodegenerative disorder
- Clinically significant cardiac disease, such as:
  - New York Heart Association Class III or IV congestive heart failure (see Section 10.14);
  - Myocardial infarction or coronary-artery-bypass graft ≤6 months prior to enrollment;
  - History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration;
  - History of severe non-ischemic cardiomyopathy;
  - Impaired cardiac function (LVEF <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan performed ≤8 weeks before randomization.

19. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study.
Note: Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question about whether a procedure is considered a major surgery, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the study.

20. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best

interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and before randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Section 5.4 (Screen Failures) describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Section 10.3 - Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

5.4. Screen Failures

Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The total screening period is 28 days. All screening tests should be performed within 28 days prior to end of screening period unless specified in the Schedule of Activities (Table 2 to Table 4).

Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreening must be discussed with and approved by the sponsor on a case-by-case

basis. Subjects who will be rescreened must sign a new ICF and will be assigned a new subject number.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

For this study, study treatment refers to PVd or DPd in Arm A and to apheresis, followed by PVd or DPd given as bridging therapy, cyclophosphamide/fludarabine conditioning regimen, and JNJ-68284528 infusion in Arm B. All dosing information must be recorded in the source documents and in the Dosage Administration page of the electronic case report form (eCRF).

JNJ-68284528 will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Subjects in Arm A will receive standard therapy (PVd or DPd) as outlined in Table 7. Subjects should start PVd or DPd within 7 days after randomization.

Table 7: Study Treatment Schedule for Standard Therapy (Arm A)

PVd[a] (21-day treatment cycles)	DPd[b] (28-day treatment cycles)
Cycles 1 to 8: Pomalidomide PO 4 mg on Days 1 to 14 Bortezomib SC 1.3 mg/m^2 on Days 1, 4, 8 and 11 Dexamethasone PO 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11 and 12	Cycles 1 and 2: Daratumumab SC 1800 mg (coformulated with rHuPH20) weekly on Days 1, 8, 15, and 22 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV: Cycle 1-2: 40 mg weekly: on Days 1, 8, 15, and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23. On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
Cycle 9 onwards: Pomalidomide PO 4 mg on Days 1-14 Bortezomib SC 1.3 mg/m^2 on Days 1 and 8 Dexamethasone PO 20 mg on Days 1, 2, 8, and 9	Cycles 3 to 6: Daratumumab SC 1800 mg (coformulated with rHuPH20) every 2 weeks on Days 1 and 15 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
	Cycle 7 onwards: Daratumumab SC 1800 mg (coformulated with rHuPH20) every 4 weeks on Day 1 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV: 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.

DPd=daratumumab, pomalidomide, and dexamethasone; PVd= pomalidomide, bortezomib and dexamethasone; IV=intravenous; PO=oral; SC=subcutaneous; rHuPH20=recombinant human hyaluronidase PH20

[a] Subjects >75 years of age who are receiving Cycles 1 to 8 of PVd should receive dexamethasone PO 10 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12. Subjects >75 years of age who are receiving Cycle 9 onwards of PVd should receive dexamethasone PO 10 mg on Days 1, 2, 8, and 9.

[b] Subjects >75 years of age who are receiving Cycle 1 of DPd should receive the entire dexamethasone PO/IV 20 mg weekly dose on Days 1, 8, 15, and 22. Starting with Cycle 2, dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23. See Section 6.1.1.

Subjects in Arm B will receive bridging therapy, conditioning regimen (cyclophosphamide and fludarabine), and JNJ-68284528 as outlined in Table 8.

Table 8: Study Treatment Schedule for JNJ-68284528 (Arm B)

Drug Dose		Drug Schedule (Arm B)[a]
PVd Bridging Therapy	Pomalidomide PO 4 mg/day	On Bridging Days 1-14
	Bortezomib SC 1.3 mg/m^2	On Bridging Days 1, 4, 8, and 11
	Dexamethasone PO 20 mg/day[b]	On Bridging Days 1, 2, 4, 5, 8, 9, 11, and 12
OR		
DPd Bridging Therapy	Daratumumab SC 1800 mg (co-formulated with rHuPH20) weekly	On Bridging Days 1, 8, 15, and 22
	Pomalidomide PO 4 mg/day	On Bridging Days 1 to 21
	Dexamethasone PO or IV 40 mg weekly[c]	On Bridging Days 1, 8, 15 and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23
Either DPd or PVd, followed by:		
Cyclophosphamide IV 300mg/m^2		Daily for 3 days on CAR-T Day -5, -4, -3 prior to JNJ-68284528 infusion
Fludarabine[d] IV 30mg/m^2		Daily for 3 days on CAR-T Day -5, -4, -3 prior to JNJ-68284528 infusion
JNJ-68284528 infusion 0.75 x 10^6 CAR-positive viable T cells/kg		Administered 5 to 7 days after the start of conditioning regimen

DPd=daratumumab, pomalidomide, and dexamethasone; PVd=pomalidomide, bortezomib, and dexamethasone; IV=intravenous; PO=oral; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

[a] 1 cycle of PVd or DPd consists of 21 and 28 days, respectively. A second cycle of PVd or DPd bridging therapy may be administered if clinically warranted depending on when JNJ-68284528 will be available. If more than two cycles of bridging therapy are indicated, daratumumab will be administered on Days 1 and 15.

[b] Subjects >75 years of age receiving PVd should receive dexamethasone PO 10 mg on Bridging Cycle Days 1, 2, 4, 5, 8, 9, 11, and 12.

[c] Subjects >75 years of age who are receiving DPd should receive the entire dexamethasone PO/IV 20 mg weekly dose on Bridging Days 1, 8, 15, and 22 for Cycle 1. If additional cycles are indicated, dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23. See Section 6.1.1.

[d] The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with a eGFR of 30 to 70 mL/min/1.73 m^2

6.1.1. Dexamethasone

Dexamethasone will be administered as outlined in Table 7 (Arm A) or Table 8 (Arm B).

During the weeks when the subject receives daratumumab, subjects may receive the full (40 mg) dose of dexamethasone prior to daratumumab administration or half of the dexamethasone dose (20 mg). Dexamethasone will be administered on the day of the daratumumab SC injection as the pre-injection medication (see Section 6.5.1.4) and should be given 1 to 3 hours prior to every injection. If a subject received only 20 mg dexamethasone prior to daratumumab, the remaining dose (20 mg PO) will be self-administered by the subject the following day. This applies only for subjects who are taking the full 40 mg dexamethasone dose. For subjects >75 year of age or ≤75 years of age and underweight (BMI <18.5 kg/m^2), dexamethasone may be administered at a dose of 20 mg weekly PO or IV. Subjects who are taking 20 mg of dexamethasone weekly should receive the entire 20 mg dose (PO or IV) as a pre-injection medication on the day of daratumumab SC injection during Cycle 1. Starting with Cycle 2, dexamethasone may be split over 2 consecutive days if better tolerated. For days when dexamethasone is given in the absence of daratumumab or pomalidomide, it may be given within ±2 days for each scheduled dose.

For subjects on Arm A or Arm B receiving dexamethasone as part of the standard therapy or bridging PVd, oral dexamethasone will be administered at 20 mg/day for subjects ≤75 years of age or 10 mg/day for subjects >75 year of age on the days bortezomib is administered and the next day.

Refer to local prescribing information for dexamethasone for complete information on warnings, precautions and patient management during treatment.

6.1.2. Bortezomib

For subjects on Arm A receiving bortezomib as part of the standard therapy PVd (21-day cycles), bortezomib will be administered at 1.3 mg/m^2 SC twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21) in Cycle 1 to 8. Starting with Cycle 9, bortezomib will be administered weekly on Days 1 and 8, followed by a 13-day rest period (Days 9 to 21). At least 72 hours should elapse between consecutive doses of bortezomib.

For subjects on Arm B receiving bortezomib as part of the bridging therapy PVd (21-day cycles), bortezomib will be administered at 1.3 mg/m^2 SC on Days 1, 4, 8, and 11. Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of JNJ-68284528. Investigator must contact the sponsor for approval.

Refer to local prescribing information for bortezomib for complete information on warnings, precautions and patient management during treatment.

6.1.3. Daratumumab

For subjects on Arm A receiving daratumumab as part of the standard therapy DPd (28-day cycles), daratumumab will be administered SC at a dose of 1800 mg weekly on Days 1, 8, 15, and 22 for initial 2 cycles, then every 2 weeks on Days 1 and 15 for Cycles 3 to 6, and then every 4 weeks on Day 1 starting with Cycle 7.

For subjects on Arm B receiving daratumumab as part of the bridging therapy DPd (28-day cycles), daratumumab will be administered SC at a dose of 1800 mg weekly. Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of JNJ-68284528. Investigator must contact the sponsor for approval.

Refer to the Investigational Product Preparation Instructions (IPPI) for additional guidance on administration of daratumumab SC.

Refer to local prescribing information for daratumumab for complete information on warnings, precautions and patient management during treatment.

6.1.4. Pomalidomide

For subjects on Arm A receiving pomalidomide as part of the standard therapy PVd, pomalidomide will be administered at a dose of 4 mg/day PO on Days 1 to 14 of each 21-day cycle. For subjects receiving pomalidomide as part of DPd, pomalidomide will be administered at a dose of 4 mg/day PO on Days 1 to 21 of each 28-day cycle.

For subjects on Arm B receiving pomalidomide as part of the bridging therapy PVd, pomalidomide will be administered at a dose of 4 mg/day on Days 1 to 14. For subjects on Arm B receiving pomalidomide as part of DPd, pomalidomide will be administered at a dose of 4 mg/day on Days 1 to 21.

Refer to local prescribing information for pomalidomide for complete information on warnings, precautions and patient management during treatment.

6.1.5. JNJ-68284528

6.1.5.1. Apheresis and Bridging Therapy

Subjects randomized to Arm B will undergo apheresis 3 to 6 days after randomization. If for logistical reasons apheresis cannot be performed 3-6 days after randomization, shorter timeframe will be accepted when possible. If apheresis is delayed after randomization, the sponsor should be notified. Bridging therapy with PVd or DPd, as determined by investigator's choice prior to screening, should be started after apheresis but no more than 7 days after randomization. The investigator must contact the sponsor for approval. Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of JNJ-68284528.

6.1.5.2. Criteria for Apheresis

The investigator should contact the sponsor if evidence of rapid disease progression or suspected CNS involvement is observed between randomization and apheresis. Subjects must meet the following criteria to proceed with apheresis:

- Hemoglobin ≥8 g/dL (PRBC transfusion is permitted)
- Platelet count $\geq 50 \times 10^9$/L (platelet transfusion is permitted)
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to apheresis
- No use of supplemental oxygen to maintain oxygen saturation
- ECOG performance status grade of 0 or 1
- No investigational agents and anti-myeloma therapy within the timeframe as detailed in the exclusion criteria
- No focal radiotherapy as specified in the exclusion criteria, except palliative radiotherapy for symptomatic management of bone disease
- No evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection. Subjects on anti-infective agents within 7 days prior to apheresis must receive approval to proceed from sponsor
- No major surgery as specified in the exclusion criteria
- No live, attenuated vaccines as specified in the exclusion criteria
- No new arrhythmia or other cardiac adverse events unless controlled with medical management and approved by the medical monitor

For subjects who require a repeat apheresis, the following assessments should be collected before the second apheresis: weight, hematology laboratory assessments, chemistry laboratory assessments, and echocardiogram or MUGA (if clinically indicated). Blood samples for biomarker assessments including immunophenotyping and CyTOF/PBMC (TCR Seq)/Plasma) should also be collected.

6.1.5.3. Conditioning Regimen

After completion of PVd or DPd bridging therapy, and after the site is notified in writing by the sponsor that manufacture and quality testing of JNJ-68284528 has been completed, each subject will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 for 3 doses. Sponsor approval must be obtained to change the conditioning regimen schedule. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73 m^2. Cyclophosphamide and fludarabine should be administered using administration procedures and supportive care according to the site's standard of care. JNJ-68284528 should be administered as described in the cell therapy product procedures manual (CTPPM) and IPPI. JNJ-68284528 will be administered as a single infusion 5 to 7 days after the start of the conditioning regimen (the first day of conditioning is Day -7 to Day -5, and the day of JNJ-68284528 infusion is Day 1).

Exceptional Release Criteria

In the event a JNJ-68284528 product is manufactured that does not meet pre-specified release criteria or protocol-defined maximum total cell dose, the sponsor will evaluate the risk/benefit for administration of the affected product and determine if the supply of the product to the treating physician could be considered. If required, approval from the relevant health authorities for use of the product will be obtained in compliance with local regulations regarding notification and approval. In the event the supply of the affected product is deemed appropriate by the sponsor and requested by the investigator, the investigator will discuss with the subject the potential risks and benefits of receiving the affected product and treatment alternatives. Products provided through this exceptional release or similar process that exceed the protocol maximum dose will not qualify for overdose reporting.

6.1.5.4. Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine) Dosing

The investigator should contact the sponsor if evidence of rapid disease progression or significant change in the subject's clinical status is observed after bridging therapy and before the start of the conditioning regimen. In addition, subjects must meet the following criteria to proceed with cyclophosphamide and fludarabine dosing:

- Transfusion support is permitted to maintain a hemoglobin of ≥8 g/dL as needed, and platelets of ≥50 x 10^9/L until 3 days before the hematology laboratory test, preceding lymphodepletion;
- Myeloid growth factors are permitted at investigator's discretion up to 1 day prior to the start of the conditioning regimen. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited;
- Estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2. The dose of fludarabine should be reduced according to the guidance in Section 6.1.5.3;
- The investigator must contact the sponsor if the subject has any sign of a reduction in kidney function, which may be manifested by a clinically significant increase in serum creatinine, a clinically significant decrease in eGFR, and/or a clinically significant decrease in urine output compared to baseline;

- ECOG performance status grade of 0 or 1;
- Aspartate aminotransferase (AST) ≤3 × ULN;
- Alanine aminotransferase (ALT) ≤3 × ULN;
- Total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required);
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to the first dose of the conditioning regimen;
- Subjects may not have received the following prior to the start of the conditioning regimen:
  - Daratumumab within 21 days;
  - Bortezomib within 14 days;
  - Pomalidomide within 7 days;
  - Dexamethasone within 7 days
- No active non-hematologic Grade ≥3 toxicity secondary to bridging therapy;
- No live, attenuated vaccines within 6 weeks prior to conditioning regimen;
- No signs of infection. For subjects requiring systemic anti-microbial treatment or with temperature >38.0°C/100.4°F within 7 days prior to the first dose of conditioning regimen, the investigator must receive approval to proceed from the sponsor;
- No cumulative dose of corticosteroids equivalent to ≥70 mg prednisone within the 7 days prior to conditioning regimen dosing. The sponsor should be called for approval if a subject receives corticosteroids at a dose equivalent to >10 mg prednisone per day in the week prior to the start of the conditioning regimen;
- No use of supplemental oxygen to maintain oxygen saturation;
- No new arrhythmia or other cardiac adverse events unless controlled with medical management and approved by the medical monitor.

6.1.5.5. Evaluation Prior to Administration of JNJ-68284528

JNJ-68284528 Dosing Delays:

Subjects will be evaluated for safety on the day of JNJ-68284528 infusion. If a significant health status change (eg, clinical deterioration, rapidly progressing disease) occurs following the start of the conditioning regimen (see Section 6.1.5.4), the investigator should contact sponsor prior to dosing.

Infusion of JNJ-68284528 must be delayed if any of the following events occur:

- Signs of active infection: Do not administer JNJ-68284528 to subjects with active infection. For subjects requiring systemic anti-microbial treatment, or with temperature ≥38.0°C/100.4°F within 48 hours before JNJ-68284528 infusion, investigator must consult with the sponsor prior to dosing.

- Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning (except for Grade 3 nausea, vomiting, diarrhea, or constipation). Investigator must consult with the sponsor prior to JNJ-68284528 dosing.

If resolution of these events to Grade ≤1 takes more than 14 days, the conditioning regimen should be re-administered (cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days) after a minimum of 21 days following the first dose of the first conditioning regimen (cyclophosphamide and fludarabine).

In Arm B, subjects who have confirmed PD after bridging therapy will be permitted to be infused with JNJ-68284528 if requested by the investigator and discussed with the sponsor. The investigator will discuss with the subject the potential risks and benefits of receiving the product and treatment alternatives. If the subject wishes to proceed with JNJ-68284528 infusion and the investigator determines that this is appropriate, subject may receive CAR-T cell therapy. These subjects will be determined to have a PFS event at the time of confirmed PD and will continue to be followed for subsequent progression (that is, PFS2) and overall survival (see Section 8.3 and Section 10.30 for safety monitoring and reporting procedures). Once these subjects have received JNJ-68284528 infusion, they will be monitored for continuous safety assessments and all other assessments per Table 5. For subjects with plasmacytomas at screening assessed by clinical or radiological examination repeat plasmacytoma assessment should be performed prior to conditioning.

Subjects who are unable to be apheresed or receive bridging therapy, conditioning regimen or JNJ-68284528 infusion will be followed until confirmed PD, start of a new anti-myeloma therapy, withdrawal of consent, or end of study, whichever occurs first. Once PD is confirmed, subsequent disease assessments time points are not required. After PD, subjects will then be followed for survival status, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2), and SPMs until the end of the study.

6.1.5.6. Pre-JNJ-68284528 Infusion Supportive Therapy

Prior to JNJ-68284528 infusion, subjects should receive premedication as noted below (Table 9). Corticosteroids should not be used during pre-infusion.

Table 9: Pre-JNJ-68284528 Infusion Medications

Medication	Dose	Administration
Antihistamine	diphenhydramine (50 mg) or equivalent	Oral – administer 1 hour (±15 minutes) prior to JNJ-68284528 injection Or IV – start infusion 30 minutes (±15 minutes) prior to JNJ-68284528 infusion
Antipyretic	acetaminophen (650 mg to 1,000 mg)	Oral or IV – administer 30 minutes (±15 minutes) prior to JNJ-68284528 injection

6.1.5.7. JNJ-68284528 Administration

JNJ-68284528 will be administered as summarized in Table 10.

Table 10: JNJ-68284528 Administration

Dose	JNJ-68284528 will be administered in one infusion. The target dose is 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg) as described in Section 4.3.3. The maximum total dose of cells to be administered to any subject is 1.0 x 10^8 CAR-positive viable T cells (ie, the maximum weight adjusted dose calculated for a 100-kg subject). Product will be manufactured based on weight at apheresis. If after apheresis and CAR-T cell preparation the quantity of JNJ-68284528 manufactured is not sufficient for dosing at the lower end of the dosing range, dosing for that subject may proceed, provided that a measurable quantity of JNJ-68284528 CAR-positive viable T cells that pass quality testing are generated and product is released per company exceptional release procedures (see Section 6.1.5.3). In case the quantity of cilta-cel manufactured exceeds the upper end of the dosing range, it will be evaluated similarly per company exceptional release procedures or similar process (see Section 6.1.5.3).
Route/Regimen	JNJ-68284528 IV infusion is to be administered under the supervision of site staff. Refer to the IPPI for JNJ-68284528 infusion instructions. NOTE: tocilizumab must be available on-site before the start on an infusion.
Dosing Instructions	The actual dose for study treatment administration will be based on the subject's weight (kg; to 1 decimal place) at apheresis.
Schedule of Administration	One intravenous infusion
Hospitalization Requirements	Dependent on the subject's status, medical history, concurrent comorbidities, adequate social support (full-time company of a competent adult) or potential risk factors for developing CAR-T toxicities, including CRS and neurotoxicity, it will be at the Investigator's discretion and subject's willingness whether the subject: • will be admitted for inpatient monitoring from the day of infusion (Day 1) through Day 14 of JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events), OR • will receive JNJ-68284528 infusion as an outpatient in close proximity (within 30 min) to the hospital, be monitored for outpatient follow-up and then be admitted for the required inpatient monitoring from Day 5 to Day 14 after JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events) This evaluation should occur at the time of apheresis, prior to administration of the conditioning regimen and again prior to JNJ-68284528 infusion, and in consultation and with approval from the sponsor to determine whether outpatient administration and follow-up after JNJ-68284528 infusion is suitable for a given subject and site. The patient must be clinically evaluated after JNJ-68284528 infusion for at least 6 hours before being discharged from the outpatient facility Subject to institutional guidance, local regulations, investigator discretion and sponsor approval, if outpatient JNJ-68284528 administration is being considered, please refer to Section 10.16 (JNJ-68284528 Outpatient Administration Guidelines) and Schedule of Activities (Table 5). For countries or specific hospitals which require hospitalization for all patients treated with cellular therapy, the more stringent requirements for hospitalization will prevail Subjects will be asked to remain within a 1-hour travel time of the hospital and in the company of a competent adult at all times for 1 additional week after hospital discharge, or until study Day 21, whichever is sooner. At the first sign of CRS (such as fever), subjects should be immediately hospitalized for evaluation. Further details regarding management of CRS are described in Table 11. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS) temporally associated to CRS. Further details regarding management of ICANS are described in Table 12.

Table 10: JNJ-68284528 Administration

	Hospitalization for neurotoxicity that is not temporarily associated with CRS, or any other neurologic adverse events, is at the discretion of the investigator.
Vital Sign and Clinical Safety Monitoring	Monitor vital signs as indicated in the Schedule of Activities (Table 5)

CAR=chimeric antigen receptor; CRS=cytokine release syndrome

6.1.6. Management Guidelines for Potential Risks of JNJ-68284528

6.1.6.1. Management of Cytokine Release Syndrome

In the Legend-2 study, CRS was reported in approximately 92% of subjects who received LCAR-B38M CAR-T cells. Most CRS events were Grade 1 or Grade 2. All events of CRS started with fever after the infusion of CAR-T therapy (see Section 2.2.5). Of the subjects who developed CRS, approximately 84% experienced transiently increased AST. AST increase was Grade 3 or Grade 4 in 31% and 6% of subjects with CRS, respectively. If CRS is suspected, subjects should be monitored for increased AST, and consumptive coagulopathy, indicated by an increase in D-dimers and a decrease in fibrinogen.

As of the 1 September 2020 data cutoff, CRS was reported for 92 of 97 subjects (94.8%) who received JNJ-68284528 in Study 68284528MMY2001. Most subjects (87 subjects [89.7%]) experienced CRS AEs that were Grade 1 or2, 3 (3.1%) subjects experienced Grade 3 CRS, 1 subject experienced Grade 4 CRS, and 1 subject experienced Grade 5 CRS (see Section 2.2.5).

Symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak.[24] Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation.

Laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, should be carried out in addition to daily monitoring of chemistry and hematology assessments (including ferritin and C-reactive protein [CRP]) when fever or other signs of potential CRS are present (see Table 11). In addition, pulmonary, renal and hepatic function will be monitored closely (see Table 11). Cytokine release syndrome will be captured as an adverse event of special interest (see Section 8.3.1).

Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, lactate dehydrogenase, triglycerides, soluble CD25, and cytokines (such as IFNγ and IL-6), and low serum levels of fibrinogen.[30] Severe thrombocytopenia, low fibrinogen, and often DIC may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. If HLH is suspected, anticoagulation should be avoided or modified based on institutional guidelines depending on platelet count and renal function. Subjects with HLH should have their platelet count and coagulation parameters very closely monitored and maximal support should be provided to

avoid major bleeding complications. For example, consider platelet transfusion if platelets are less than 50×10^9/L. Under these circumstances, investigators should consider treating the subject in the ICU, so that maximal monitoring and support can be carried out during this period.

Trained clinical personnel should be prepared to intervene in the event of CRS. Resources necessary for resuscitation (ie, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen, tracheostomy equipment, and a defibrillator) should be readily available. Tocilizumab must be available on-site prior to administration of JNJ-68284528. Vital signs and laboratory parameters must be monitored at regular intervals until normal. Additional specimens for pharmacokinetic and biomarker testing should be collected as per the schedule outlined in the Schedule of Activities (Table 5).

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. Cultures and imaging should be obtained: the clinical signs and symptoms should determine which tests are appropriate.

Recommendations for the clinical management of CRS are provided in Table 11. At the first sign of CRS (such as fever), subjects should be immediately hospitalized for evaluation. The use of myeloid growth factors, particularly G-CSF, should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever in the absence of clear infectious etiology. Early tocilizumab should be considered in subjects at high risk of severe CRS (for example, high baseline tumor burden, early fever onset, or persistent fever after 24 hours of symptomatic treatment). Other cytokine targeting therapies (for example, IL1 and/or anti-TNFα) may be used based on institutional practice, especially for cases of CRS which does not respond to tocilizumab and corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop high-grade CRS with laboratory findings overlapping with HLH/MAS (including hyperferritinemia) that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.

Table 11: Guidelines for the Management of Cytokine Release Syndrome

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab[b]</th><th>Corticosteroids[f]</th></tr>
<tr><td>Grade 1
Temperature ≥38°C[c]</td><td>Tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg) may be considered</td><td>NA</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.

Temperature ≥38°C[c] with:

Hypotension not requiring vasopressors,

and/or,

Hypoxia requiring oxygen via canula[e] or blow-by,</td><td>Administer tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg).

Repeat tocilizumab every 8 hours as needed if not responsive to i.v. fluids up to 1 liter or increasing supplemental oxygen.</td><td>Consider methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours).

After 2 doses of tocilizumab, consider alternative anticytokine agents.[d]</td></tr>
</table>

Table 11: Guidelines for the Management of Cytokine Release Syndrome

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
or, Grade 2 organ toxicity.	Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 3 Symptoms require and respond to aggressive intervention. Temperature ≥38°C[c] with: Hypotension requiring 1 vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal canula[e], facemask, nonrebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg i.v. every 12 hours. After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 4 Life-threatening symptoms. Requirements for ventilator support, CVVHD. Temperature ≥38°C[c] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer dexamethasone 20 mg i.v. every 6 hours.
	After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g i.v., repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (eg, other anti-T-cell therapies).	

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CVVHD=continuous veno-venous hemodialysis; i.v.=intravenous(ly); NA=not applicable.

[a] Based on ASTCT consensus grading (Lee 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details.
[c] 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 steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.
[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
[f] Continue corticosteroids use until the event is ≤Grade 1; taper steroids if total corticosteroid exposure is greater than 3 days.

Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered according to the clinical

manifestations of the subject's illness. Similarly, ancillary testing such as B-type natriuretic peptide assessment, echocardiograms, arterial blood gas, assessments of coagulation laboratory tests, liver and renal function, etc, should be performed if clinically indicated.

6.1.6.2. Neurologic Toxicities

Based on the specific mode-of-action of JNJ-68284528, severe or serious neurologic toxicities (including CAR-T cell-related neurotoxicity, ie, Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS]) may occur (Section 6.1.6.2.1). Subjects should be monitored for neurotoxicity for 1-year post JNJ-68284528 infusion (Section 6.1.6.2.2).

6.1.6.2.1. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])

Subjects should have the Immune Effector Cell-associated Encephalopathy (ICE) Assessment Tool (ICE-Tool; Section 10.15) performed within 24 hours prior to infusion of JNJ-68284528 and daily after the first symptoms of CAR-T cell related neurotoxicity (ie, ICANS) are suspected and until resolution. Consider performing ICE-Tool more frequently until neurotoxicity symptoms resolve. Consider performing neuroimaging (eg, MRI) at screening and/or neurology consultation if pre-existing disease is suspected; see Section 8.1.6, Safety Assessments.

Subjects should be monitored for neurologic toxicities including, but not restricted to, speech disorders, aphasia, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. If these or other neurologic toxicities are observed, regardless of causality, then the sponsor's medical monitor must be consulted. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (ie, ICANS) temporally associated with CRS.

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. Rule out alternative etiologies including infectious etiologies (eg, viral origin such as human herpesvirus (HHV) HHV-6, HHV-7) if clinically indicated. Subjects who have a lumbar puncture as part of their neurologic work up should have a sample of cerebral spinal fluid also sent for additional testing by the sponsor. For signs of seizures or raised intracranial pressure/cerebral edema, consider neuroimaging (computed tomography [CT]/MRI), transfer the subject to the intensive care unit and treat according to institutional guidelines or practices.

General management for CAR-T cell-related neurotoxicity (ie, ICANS) with or without concurrent CRS is summarized in Table 12. All neurologic adverse events, including CAR-T related neurotoxicity (ie, ICANS), will be captured as an adverse event of special interest (see Section 8.3.1).

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Table 11 and Table 12
- Tocilizumab according to CRS grade in Table 11
- Antiseizure medication according to neurologic toxicity in Table 12

Table 12: Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS Grade[a]	Corticosteroids
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[c] 10 mg i.v. every 6 to 12 hours for 2 to 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6[b] or depressed level of consciousness: awakens to voice	Administer dexamethasone[c] 10 mg i.v. every 6 hours for 2 to 3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2[b] (If ICE score is 0, but participant is arousable (eg, awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • nonconvulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging.[d]	Administer dexamethasone[c] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[c] dose to at least 20 mg i.v. every 6 hours; taper within 7 days, or escalate to high-dose methylprednisolone (1g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 4 ICE score-0[b] (participant is unarousable and unable to perform ICE assessment), or depressed level of consciousness, either: • participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[e]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edema, with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	Administer dexamethasone[c] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation.

Table 12: Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ASTCT=American Society for Transplantation and Cellular Therapy; EEG=electroencephalogram; i.v.=intravenous(ly).
Note: ICANS grade and management 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.

[a] Based on ASTCT consensus grading (Lee 2019).

[b] If participant is arousable and able to perform ICE assessment, assess: **Orientation** (oriented to year, month, city, hospital =4 points); **Naming** (name 3 objects, eg, point to clock, pen, button =3 points); **Following Commands** (eg, "show me 2 fingers" or "close your eyes and stick out your tongue" =1 point); **Writing** (ability to write a standard sentence =1 point); and **Attention** (count backwards from 100 by 10 =1 point) (see Section 10.15). If participant is unarousable and unable to perform ICE assessment (Grade 4 ICANS) =0 points.

[c] All references to dexamethasone administration are dexamethasone or equivalent.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.

[e] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0, but they do not influence ICANS grading.

Table 13: Guidelines for the Management of Raised Intracranial Pressure (ICP) / Cerebral Edema[a]

- Elevate head of subject's bed to an angle of 30 degrees.
- If subject has Ommaya reservoir, drain cerebral spinal fluid to target opening pressure of <20 mmHg.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28 to 30 mmHg, 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 every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and 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/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L,
  - For subjects with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 min, if needed.
- Consider IV anaesthetics for burst-suppression pattern on electroencephalography.

[a] In addition to toxicity management guidelines provided in Table 12: Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

6.1.6.2.2. Other Neurotoxicities

If other neurotoxicities characterized by movement and neurocognitive TEAEs noted below are observed, the medical monitor should be contacted, and the subject should be referred immediately to a neurologist for a full evaluation. Particular attention should be paid to the appearance of any of the following:

- movement impairments (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself),
- cognitive impairments (eg, memory loss or forgetfulness, disturbances in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words),

- personality change (eg, reduced facial expression, flat affect, reduced ability to express emotions, less communicative, disinterest in activities)

Additional monitoring and mitigation strategies include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of study.

Early detection, workup and intervention, may be important to prevent neurologic toxicity from worsening. The following is a list of potential diagnostics that should be considered in subjects with new neurologic symptoms:

- Positron emission tomography/computerized tomography (PET/CT) of the brain and/or brain MRI with perfusion and an electroencephalogram (EEG).
- Lumbar puncture to rule out infection (in particular John Cunningham virus [JCV], herpes zoster virus [HZV], herpes simplex virus [HSV]-1/2, HHV-6, HHV-7, Epstein-Barr virus [EBV], cytomegalovirus [CMV]).
- Serologic testing for HHV-6 and HHV-7 by PCR for viremia.
- CSF flow cytometry and cytology should be considered to rule out leptomeningeal disease.
- Cerebral spinal fluid (CSF) analysis to rule out paraneoplastic syndromes.
- Thiamine level (consider empiric thiamine replacement while awaiting results) (MD Anderson 2019)[28]

Other cytokine-targeting therapies (for example, IL-1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop neurotoxicity that remains unresponsive to other interventions.

Per Section 8.9 of the protocol, if cerebral spinal fluid (CSF) or other relevant biological sample analysis is clinically indicated, these samples will be requested for additional analysis by the sponsor.

6.1.6.3. Tumor Lysis Syndrome

Although tumor lysis syndrome is uncommon in subjects with MM, one subject in the Phase 1 Legend-2 Study experienced fatal tumor lysis syndrome. Subjects must be monitored closely for symptoms of tumor lysis syndrome. It is also strongly recommended that high-risk subjects, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a subject with multiple extramedullary disease sites or plasmacytomas), be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol 300 mg daily or other primary or secondary uricosuric agents, as indicated).

6.1.6.4. Second Primary Malignancy

Second primary malignancy (SPM) is a possibility due to the risk of viral insertion (DNA integration) of the lentiviral vector. SPMs should be managed per institutional standards and must be reported for the duration of the study in both treatment arms (Arm A and Arm B), irrespective of when they occur. In the JNJ-68284528 Treatment Arm (Arm B), SPMs will continue to be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528. For subjects in Arm B diagnosed with a SPM, a tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements. SPM on both arms of the study will be captured as an AE of special interest (see Section 8.3.1).

6.1.6.5. Prolonged Cytopenia

Subjects may exhibit cytopenia for several weeks following lymphodepleting chemotherapy and JNJ-68284528 infusion. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Monitor hematological parameters and provide supportive care (eg, irradiated blood products, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited within the first 112 days after infusion with JNJ-68284528. The use of myeloid growth factors, particularly G-CSF, should be avoided during CRS. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.

6.1.6.6. Hypogammaglobulinemia

Hypogammaglobulinemia may occur in subjects receiving JNJ-68284528. Monitor immunoglobulin levels after treatment as detailed in the Schedule of Activities (Table 4 and Table 5) and more frequently if clinically indicated for safety and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Subjects with IgG <400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or SC IgG as per institutional guidelines. Vaccination with live, attenuated virus vaccines is prohibited for at least 6 weeks prior to the start of the conditioning regimen and for at least 112 days after infusion of JNJ-68284528.

6.1.6.7. Serious Infections

Do not administer JNJ-68284528 to subjects with active infection. Administration of JNJ-68284528 may increase the risk of infection due to cytopenias and hypogammaglobulinemia. Subjects should be monitored frequently for infection and should have blood cultures obtained and empiric antibiotics administered per institutional standards. Immunocompromised subjects are at risk for opportunistic infections. Prophylactic use of antibiotics, antivirals, and antifungals should be considered. Extended use of anti-microbial therapies for at least 6 month (or longer as per institutional guidelines) or consistent with post ASCT consensus guidelines after CAR-T dosing are recommended (see Section 10.28, Appendix 28). Perform screening for hepatitis B virus, HCV, and HIV and monitor as clinically indicated (see HBV monitoring recommendations in Section 10.6 and Table 5), and initiate treatment as appropriate. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in subjects treated with drugs

directed against B cells such as JNJ-68284528. HBV reactivation has occurred in subjects receiving other CAR-T products who appear to have resolved hepatitis B infection. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Section 10.6 and Table 5).

Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in Appendix 10.29.

6.1.6.8. Hypersensitivity Reactions

Allergic reactions may occur with the infusion of JNJ-68284528. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide, dextran 40, residual kanamycin in JNJ-68284528. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. In the JNJ-68284528 Treatment Arm (Arm B), subjects should receive premedication prior to JNJ-68284528 dosing as noted in Section 6.1.5.5.

6.1.7. Management Guidelines for Daratumumab

6.1.7.1. Infusion-Related Reaction Management for Daratumumab SC

Subjects who receive daratumumab SC should be observed carefully during study drug administrations. Subjects should be observed for 6 hours following Cycle 1 Day 1 daratumumab administration at the site where daratumumab is administered. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks and a defibrillator) must be available at the bedside. See Section 6.5.1.4 for pre-injection medications and Section 6.5.1.5 for post-injection medications for subjects receiving daratumumab.

If an IRR develops, then daratumumab administration should be temporarily interrupted. Subjects who experience adverse events during daratumumab administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be discontinued.

Infusion-related Reactions of Grade 1 or Grade 2 for Daratumumab SC

If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the daratumumab administration should be interrupted. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion. Refer to the IPPI for further details regarding continuation of daratumumab administration.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.

Infusion-related Reactions of Grade 3 or Higher for Daratumumab SC

For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped, and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab SC administration may be restarted at the investigator's discretion. Refer to the IPPI for further details regarding continuation of daratumumab administration.

If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab administration, then the subject must be permanently discontinued from daratumumab treatment.

For IRR adverse events that are Grade 4, the daratumumab administration must be stopped, and the subject permanently discontinued from daratumumab treatment.

Recurrent Infusion-related Reactions for Daratumumab SC

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

Local Injection-site Reactions for Daratumumab SC

Injection-site reactions are localized reactions at the injection site. In daratumumab Study 54767414MMY1004 Part 1, SC administration of daratumumab in abdominal SC tissue was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection site reactions should be managed per institutional standards.

6.1.7.2. Infections

Administration of daratumumab may increase the risk of infection. Subjects should be monitored frequently for infection and should have blood cultures obtained and empiric antibiotics administered per institutional standards. For subjects with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of study treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on study treatment, suspend study treatment and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

6.2. Preparation/Handling/Storage/Accountability

Preparation, handling and Storage

Standard therapy (bortezomib, pomalidomide, daratumumab and dexamethasone)

Refer to the CTPPM for additional guidance on preparation, handling and storage information for bortezomib, pomalidomide, and dexamethasone. Refer to the IPPI for additional guidance on daratumumab SC preparation, handling and storage.

JNJ-68284528

JNJ-68284528 is provided in a single-dose unit containing CAR-positive viable T cells based on the subject weight reported at the time of apheresis.

JNJ-68284528 therapy contains human cells genetically modified with a lentiviral vector. Follow local biosafety guidelines applicable for handling and disposal of such products. The product is prepared from autologous blood collected by apheresis. JNJ-68284528 may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

Detailed instructions for storage conditions and handling will accompany clinical drug supplies to the clinical study sites. The storage conditions and expiry dates are indicated on the label. Refer to the JNJ-68284528 IPPI for additional guidance on study treatment preparation, handling, and storage.

6.2.1. Accountability

Information in this section relates to study treatment that is supplied to investigational sites from the study sponsor.

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. The study treatment administered to the subject must be documented on the drug accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

The dispensing of study treatment (eg, pomalidomide and oral dexamethasone) to the subject, and the return of study treatment from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study treatment.

Study treatment must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment, and study treatment returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment will be documented on the drug return

form. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the study treatment return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to subjects participating in the study. Returned study treatment must not be dispensed again, even to the same subject. Whenever a subject brings his or her study treatment (eg, pomalidomide or dexamethasone) to the study site for pill count, this is not seen as a return of supplies. Study treatment may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study treatment are provided in the in the SIPPM and CTPPM.

6.3. Measures to Minimize Bias: Randomization

Central randomization will be implemented in this study. Subjects will be assigned randomly to 1 of 2 arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified according to 3 baseline factors: investigator's choice of PVd vs. DPd, ISS at screening (I vs. II vs. III), and number of prior lines of therapy (1 vs. 2 or 3).

6.4. Study Intervention Compliance

Compliance with Dexamethasone and Pomalidomide (Arm A-standard therapy [PVd or DPd] and Arm B-bridging therapy [PVd or DPd])

Subjects will be asked to return containers of pomalidomide and dexamethasone at each study visit. Pill counts will be used to assess compliance. Additional details are provided in the SIPPM (CTPPM).

Compliance with Bortezomib (Arm A-standard therapy [PVd] and Arm B-bridging therapy [PVd]) and Daratumumab (Arm A-standard therapy [DPd] and Arm B-bridging therapy [DPd])

Bortezomib and daratumumab administration will be performed in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. Additional details are provided in the SIPPM.

Compliance with Apheresis, Conditioning Regimen, and JNJ-68284528 (Arm B)

Apheresis, infusion of cyclophosphamide and fludarabine, and infusion of JNJ-68284528 will be performed in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. The details of administration will be recorded in the eCRF (including date, dose of cells, start, and stop times of the IV infusion, and volume infused).

Precautions associated with the use of the study treatment and concomitant medications will be reviewed by the sponsor.

Refer to the CTPPM for a description of the chain of identity and chain of custody procedures associated with apheresis product and JNJ-68284528.

6.5. Concomitant Therapy

Throughout the study, investigators may prescribe concomitant medications or treatments (except for those listed in Section 6.5.3) deemed necessary to provide adequate supportive care. All concomitant medications will be recorded during screening. Thereafter, selected concomitant medications will be reported. Selected concomitant medications consist of any medication given for an adverse event or serious adverse event, therapeutically or prophylactically, including, but not limited to:

- Anti-cytokine or anti-cytokine receptor therapies
- Anti-seizure medications
- Any medication given for prophylaxis or treatment of tumor lysis syndrome
- Any medication given for prevention or treatment of thromboembolic events
- Medication for prevention or treatment of daratumumab IRRs
- Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.)
- Immunosuppressive agents
- Vaccinations
- Vasopressors and cardiac inotropic agents (For dose, record only maximum daily rate)
- Blood products
- Growth factors
- Systemic antimicrobials – given for prophylaxis or treatment
- Chemotherapy given for CAR-T cell related toxicity

Other:

- Bisphosphonates
- Immunoglobulin therapy
- Medications listed as prohibited in the protocol
- Palliative Radiation
- Pain medication
- Any treatment given for SPMs
- Any changes in doses from baseline or newly added concomitant medications to treat new or prior known co-morbidities

In the standard therapy Treatment Arm (Arm A), the recording period is from the signing of the ICF until 30 days after the last dose of daratumumab, pomalidomide, dexamethasone, or bortezomib, or until the start of subsequent systemic anti-myeloma treatment, if earlier. Thereafter, concomitant therapy given for adverse event/serious adverse event considered related to study treatment will be recorded until the end of the study.

In the JNJ-68284528 Treatment Arm (Arm B), the recording period is from the signing of the ICF until Day 112 after infusion of JNJ-68284528 regardless if PD occurs prior to Day 112 or subsequent anti-myeloma therapy is started prior to Day 112. After Day 112, concomitant therapy given for any non-serious adverse event considered related to study treatment or all serious adverse events regardless of causality or for delayed adverse events will be recorded until the end of the study. Exceptions include medications used to prevent (including vaccines) and treat COVID-19 and HBV reactivation, which should be reported until 1 year after cilta-cel infusion, regardless of severity or causality (Appendix 10.29).

Recorded information will include a description of the type of the drug, dosing regimen, route of administration, duration of treatment, and its indication. Medications, including details of previous anticancer treatment, should be documented in the appropriate section of the eCRF.

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

6.5.1. Recommended Medications

6.5.1.1. Prophylaxis for Thromboembolism

Pomalidomide has been associated with an increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, thromboprophylaxis is strongly recommended for all subjects on Arm A and for subjects undergoing bridging therapy on Arm B.

Subjects already on therapeutic anticoagulation may continue their prior anticoagulation regimen. All subjects should have their anticoagulation held according to institutional guidelines when subjects would be at risk of bleeding due to the combination of significant thrombocytopenia and anticoagulation. Once platelet count recovers to an acceptable level per institutional guidelines, anticoagulation should be resumed.

Refer to the pomalidomide, prescribing information for recommendations for subjects with prior history of thrombosis.

6.5.1.2. Proton Pump Inhibitor

Prophylactic use of a proton pump inhibitor (PPI) in subjects on Arm A and during bridging therapy in subjects on Arm B is recommended. If a contraindication to PPI exists or the subject is intolerant to PPIs, a histamine receptor (H_2) blocker may be substituted for the PPI.

6.5.1.3. Prophylaxis for Infections

Following JNJ-68284528 infusion, prophylaxis with antibacterial (eg, levofloxacin) and antifungal medication (eg, fluconazole) is recommended until neutrophil count returns to $\geq 1 \times 10^9$/L. Prophylaxis for herpes zoster reactivation is recommended during study treatment (Arm A) or during bridging therapy (Arm B). Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after the start of study treatment (Arm A) or the start of bridging therapy (Arm B) and continue for at least 6 months following the last dose of study treatment or bridging therapy. Acceptable antiviral therapy includes acyclovir, famciclovir, or valacyclovir (per institutional standards). Pneumocystis carinii/jirovecii prophylaxis may be considered as per institutional guidelines for Arm A and Arm B. Please refer to Appendix 10.29 for guidance on prophylaxis (eg, vaccines) and treatment of COVID-19 infection.

6.5.1.4. Pre-injection Medications for Daratumumab

For all subjects receiving daratumumab (DPd as part of standard therapy for Arm A, or as part of bridging therapy for Arm B) pre-injection medications will be administered as described in the Schedule of Activities (Table 3). On daratumumab dosing days, subjects will receive the following medications 1 to 3 hour prior to daratumumab administration:

- Dexamethasone 40 mg or 20 mg IV or PO (an equivalent of long acting corticosteroid may substitute [Section 10.13]); in this setting dexamethasone will be utilized as the treatment dose of corticosteroid for that particular day, as well as the required pre-medication prior to daratumumab dosing;
- Paracetamol (acetaminophen) 650 to 1000 mg IV or PO; and
- An antihistamine (diphenhydramine 25 to 50 mg IV or PO, or equivalent, but avoid IV use of promethazine [Section 10.18]).
- Leukotriene inhibitor (optional) on C1D1: montelukast 10 mg PO.

If necessary, oral pre- medications may be administered outside of the clinic on the day of the administration, provided they are taken within 1 to 3 hours prior to the administration.

6.5.1.5. Post-Injection Medications for Daratumumab

For subjects with a higher risk of respiratory complications (ie, subjects with COPD who have an FEV1 <80% of predicted normal, or subjects with mild asthma), the following post-injection medications should be considered:

- Antihistamine (diphenhydramine or equivalent) on the first and second days after all daratumumab administrations
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ±long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ±inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If these at-risk subjects are hospitalized, then their FEV1 should be

measured before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after the first 4 daratumumab administrations, or longer if clinically indicated. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no IRRs, then these post-injection medications may be waived after 4 doses at the investigator's discretion.

6.5.1.6. Prophylaxis for TLS

It is also recommended that subjects at high-risk of TLS, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a subject with multiple extramedullary disease sites or plasmacytomas) or high LDH be treated prophylactically for TLS in accordance with local standards (eg, hydration; diuretics; allopurinol 300 mg daily or primary or secondary uricosuric agents, as indicated).

Refer to Section 6.1.5.6 for medications subjects should receive prior to JNJ-68284528 infusion.

6.5.2. Permitted Medications

The following are examples of supportive therapies that may be used during the study for subjects randomized to either Arm A or Arm B unless otherwise stated:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H_2] antagonists or PPIs, and other medications intended to treat symptoms or signs of disease) and therapies intended to treat CAR-T cell related toxicity (ie, CRS) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Bisphosphonates may be administrated as clinically indicated, according to institutional standards. The sponsor must be notified promptly in cases where bisphosphonates are given for the management of hypercalcemia.
- Hematopoietic growth factor support and transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local standards of care. Non-pegylated myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen (Arm B only) (Section 6.1.5.4).
- Documented infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator, according to standard institutional practice.
- Chemotherapy agents used to treat CAR-T cell related toxicity are permitted upon consultation with the sponsor (see Section 6.1.6).

6.5.3. Prohibited Therapies

The following medications are prohibited during the study for subjects randomized to either Arm A or Arm B, as indicated below. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are being considered for administration (or were administered).

Arm A and Arm B

- Any chemotherapy, anticancer immunotherapy (other than JNJ-68284528), or experimental therapy, except protocol-specified conditioning agents and bridging therapy.
- Other immunosuppressant agents unless protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS).
- Orthopedic surgery or radiotherapy is generally prohibited but may be allowed in the absence of disease progression. Prior sponsor notification and approval is required. If necessary, an emergency intervention may proceed without prior approval from sponsor. In these cases, the sponsor should be notified as soon as is feasible. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues.

Arm B

- After the start of lymphodepletion and prior to Day 112, corticosteroid use should be avoided, except for the treatment of CRS or CAR-T cell-related neurotoxicity (ie, ICANS), as described in Table 11 and Table 12. Alternative therapies, if feasible, should be given prior to corticosteroids.
- Vaccination with live, attenuated vaccine in the ≤6 weeks prior to the start of conditioning regimen, and for at least 112 days after infusion of JNJ-68284528.
- The use of RANK ligand inhibitors such as denosumab is prohibited due to their potential impact on immune function.
- Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited within the first 112 days after infusion with JNJ-68284528.

Therapies to be avoided

- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential sub-clinical myeloma-related kidney disease. Based on the investigator's clinical judgement, low-dose aspirin may be continued for thromboprophylaxis.
- 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.
- For subjects receiving PVd or DPd: avoid concomitant use of pomalidomide with strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin, and fluvoxamine). If deemed medically necessary, reduce the dose of pomalidomide by 50%.

- For subjects receiving PVd, subjects should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors and caution should be exercised when bortezomib is combined with CYP3A4-or CYP2C19 substrates.

6.5.4. Subsequent Anti-myeloma Therapy

Subsequent anti-myeloma therapy administered after standard therapy PVd or DPd (Arm A) or JNJ-68284528 (Arm B) should only be administered after confirmed PD per IMWG criteria and recorded in the eCRF. The start and end date, best response and date of PD to subsequent therapy should be documented in the eCRF, if available.

6.6. Dose Modification

On the first day of each new treatment cycle and before each dose of study drug, the subject will be evaluated by the investigator for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to National Cancer Institute (NCI)-CTCAE, Version 5.0. Cycle delays will be based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

Guidelines for dose modifications are listed below. However, dose modifications decisions for pomalidomide, bortezomib, daratumumab and dexamethasone will be at the investigator's discretion per the full prescribing information and labeling in the respective current US prescribing information, EU SmPC, or equivalent document for the specific region/country. Investigators should follow the local label for the management of interactions with other medical products.

6.6.1. Dexamethasone

Dexamethasone dose reductions guidelines for subjects receiving PVd are outlined in Table 14.

Table 14: Dexamethasone Dose Reduction Steps for Subjects Receiving PVd

Dose Level	Subjects ≤ 75 years of age (Cycle 1-8: Days 1, 2, 4,5, 8, 9, 11, 12 Cycle ≥ 9: Days 1, 2, 8, 9)	Subjects >75 years of age (Cycle 1-8: Days 1, 2, 4,5, 8, 9, 11, 12 Cycle ≥ 9: Days 1, 2, 8, 9)
Starting dose	20 mg	10 mg
-1	12 mg	6 mg
-2	8 mg	4 mg

PVd=Pomalidomide, bortezomib, and dexamethasone

Dexamethasone dose reductions guidelines for subjects receiving DPd are outlined in Table 15 and Table 16.

Table 15: Dexamethasone Dose Reduction Guidelines for Subjects ≤ 75 years of Age Receiving DPd

Dose Level	Dose	May be given over 2 days as:
Starting Dose	40 mg	20 mg/ 20 mg
- 1	20 mg	12 mg/ 8 mg
- 2	10 mg	6 mg/ 4 mg

DPd=daratumumab, pomalidomide, and dexamethasone

Table 16: Dexamethasone Dose Reduction Guidelines for Subjects > 75 years of Age Receiving DPd

Dose Level	Dose	May be given over 2 days as:
Starting Dose	20 mg	12 mg/ 8 mg[a]
- 1	12 mg	8 mg/ 4 mg
- 2	8 mg	4 mg/ 4 mg

DPd=daratumumab, pomalidomide, and dexamethasone
[a] Except in Cycle 1 and Bridging Cycle 1

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of dexamethasone-related toxicities. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. For subjects whose dexamethasone treatment is discontinued may continue to receive pomalidomide/bortezomib or daratumumab/pomalidomide. Guidelines for dexamethasone-related toxicities are summarized in Table 17.

Table 17: Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
Cardiovascular	Edema >Grade 3 (anasarca or limiting function and unresponsive to therapy)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Gastrointestinal Toxicity	Dyspepsia, gastric or duodenal ulcer, or gastritis Grade 1 or 2 (requiring medical management)	Continue dexamethasone at same dose and treat with therapeutic doses of histamine 2 (H2) blockers, or proton pump inhibitor. Consider adding sucralfate or other antiulcer treatment as clinically indicated. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	Discontinue dexamethasone permanently.
General Disorders	Limb edema ≥Grade 3 (>30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living)	Hold dexamethasone until symptoms return to baseline. Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Psychiatric Disorders	Confusion or mood alteration ≥Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement. If symptoms recur, discontinue dexamethasone.
Musculoskeletal	Muscle weakness ≥Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone by 1 dose decrement. If weakness persists, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥Grade 3 (fasting glucose >250 mg/dL)	Withhold dexamethasone, treat with insulin or other hypoglycemic agents as needed until glucose is ≤Grade 2 (<250 mg/dL) then resume dexamethasone. If uncontrolled despite above measures, decrease dose by 1 dose decrement until ≤Grade 2 (<250 mg/dL).

Table 17: Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
All Other	Other toxicity ≥Grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to ≤Grade 2. If toxicity recurs, hold dexamethasone dose until toxicity has resolved to ≤Grade 2 and resume dexamethasone dose by another dose decrement. If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or sub-investigator unless an immediate safety risk appears to be present). If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by 1 dose level when the dose is restarted.

6.6.2. Pomalidomide and Bortezomib Dose Modification for Hematologic Toxicity

To initiate a new cycle of PVd, neutrophil count must be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L.

Pomalidomide and bortezomib dose modification guidelines for hematologic toxicity are summarized in Table 18. If a bortezomib dose is delayed, the next dose should still be given on the scheduled date, if there are at least 72 hours in between the two bortezomib doses.

Table 18: Pomalidomide and Bortezomib Dose Modification Guidelines for Hematologic Toxicity

Toxicity	Pomalidomide Dose Modification	Bortezomib Dose Modification
Neutropenia (any of the following): • ANC $<0.5 \times 10^9$/L • febrile neutropenia (fever ≥38.5°C and ANC $<1 \times 10^9$/L) • ANC $<1 \times 10^9$/L and infection of any grade	Interrupt pomalidomide treatment, follow CBC weekly.	Interrupt bortezomib
ANC return to $\geq 1 \times 10^9$/L	Resume pomalidomide at 1 mg less than the previous dose. For each additional occurrence, resume pomalidomide at 1 mg less than the previous dose. If pomalidomide was at 2 mg prior to interruption, consider resuming pomalidomide at 2 mg and reducing the bortezomib dose.	Resume bortezomib at the same dose as previously. For each subsequent occurrence, resume bortezomib at the same dose as previously (if pomalidomide is being reduced) or 1 dose level lower.
Thrombocytopenia Platelet count $<25 \times 10^9$/L	Interrupt pomalidomide treatment, follow CBC at least weekly.	Interrupt bortezomib
Platelet count 25-49 $\times 10^9$/L	Interrupt pomalidomide	Interrupt bortezomib
Platelet count return to $\geq 50 \times 10^9$/L	If platelet nadir was Grade 3 (platelet count 25-49 $\times 10^9$/L), then pomalidomide may be resumed at the previous dose.	If platelet nadir was Grade 3 (platelet count 25-49 $\times 10^9$/L), then bortezomib may be resumed at the previous dose.

Table 18: Pomalidomide and Bortezomib Dose Modification Guidelines for Hematologic Toxicity

Platelet count return to ≥50 x 10^9/L	For each occurrence of Grade 4 thrombocytopenia (platelet count <25 x 10^9/L), resume pomalidomide at 1 mg less than the previous dose. If pomalidomide was at 2 mg prior to interruption, consider resuming pomalidomide at 2 mg and reducing the bortezomib dose.	For each occurrence of Grade 4 thrombocytopenia (platelet count <25 x 10^9/L), resume bortezomib at the prior dose level (if pomalidomide is being reduced) or 1 dose level lower.

ANC=absolute neutrophil counts; CBC=complete blood count

Guidelines for pomalidomide dose reductions are outlined in Table 19.

Table 19: Dose Reduction Guideline for Pomalidomide Toxicity

Dose Level	Oral Pomalidomide Dose
Starting Dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg

Guidelines for bortezomib dose reductions are outlined in Table 20.

Table 20: Dose Reduction Guideline for Bortezomib Toxicity

Starting Dose (mg/m^2)	First Dose Reduction Dose -1 (mg/m^2)	Second Dose Reduction Dose -2 (mg/m^2)
1.3	1.0	0.7

Bortezomib Dose Modification Guidelines for Non-hematologic toxicities

For Grade ≥3 non-hematological toxicity (excluding neuropathy), withhold bortezomib until toxicity resolves. Bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level.

Treatment guidelines for bortezomib-related neuropathy are outlined in Table 21.

Table 21: Treatment Guidelines for Bortezomib-related Neuropathy

Toxicity[a]	Bortezomib Dose Modification
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	No action, however, changing frequency to weekly[d] may be considered based on clinical judgement and/or institutional practice
Grade 1 with pain or Grade 2 (moderate Symptoms; limiting instrumental ADL[b])	• Withhold bortezomib until toxicity resolves or returns to baseline. • Reduce bortezomib dosing by one level (maximum dose of 1.0 mg/m^2) OR • Change treatment schedule to 1.3 mg/m^2 once per week[d] (Days 1 and 8 of a 21-day cycle)
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL[c])	• Withhold bortezomib until toxicity resolves • Bortezomib therapy may be reinitiated at a reduced dose level of 0.7 mg/m^2 and change treatment schedule to once per week[d] (Days 1 and 8 of a 21-day cycle)
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Permanently discontinue study treatment

ADL=Activities of Daily Living; SmPC= Summary of Product Characteristics.

[a] Grading based on Bortezomib SmPC.

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

[c] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

[d] Weekly dosing (for example) on Days 1. 8, and 15.

6.6.3. Pomalidomide Dose Modification Guidelines for Non-hematologic Toxicities

Pomalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash and for Stevens-Johnson syndrome/toxic epidermal necrolysis related to pomalidomide and should not be resumed following discontinuation for these reactions.

Interstitial lung disease (ILD) and related events, including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of subjects with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

For subjects whose bortezomib treatment is discontinued, they may continue to receive pomalidomide/dexamethasone. For subjects whose pomalidomide/dexamethasone treatment is discontinued, bortezomib treatment may be continued.

6.6.4. Pomalidomide and Daratumumab Dose Modification for Hematologic Toxicities

Dose modification of daratumumab SC is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities. If a dose is delayed within a cycle, then the next dose should be performed at the scheduled timepoint.

Instructions for dose interruptions and reductions for daratumumab and pomalidomide related to hematological toxicities are outlined in Table 22.

In case of neutropenia, the physician should consider the use of growth factors.

To initiate a new cycle of DPd, neutrophil count must be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L.

Table 22: Pomalidomide and Daratumumab Dose Modification/Dose Delay Guideline for Hematologic Toxicities

Toxicity	Pomalidomide Dose Modification	Daratumumab Dose Delay
Neutropenia (any of the following): • ANC <0.5 x 10^9/L • febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/L) • ANC <1 x 10^9/L and infection of any grade	Interrupt pomalidomide treatment, follow CBC weekly.	Interrupt daratumumab
ANC return to ≥1 x 10^9/L	Resume pomalidomide at 1 mg less than the previous dose.	Resume daratumumab
Thrombocytopenia: Platelet count 25-49 x 10^9/L	Interrupt pomalidomide treatment.	Interrupt daratumumab
Platelet count return to ≥50 x 10^9/L	If platelet nadir was Grade 3 (platelet count 25-49 x 10^9/L), then pomalidomide may be resumed at the previous dose.	Resume daratumumab
Thrombocytopenia: Platelet count <25 x 10^9/L	Interrupt pomalidomide and monitor CBC at least weekly.	Interrupt daratumumab
Platelet count return to ≥50 x 10^9/L	For each occurrence of Grade 4 thrombocytopenia (platelet count <25 x 10^9/L), resume pomalidomide at 1 mg less than the previous dose.	Resume daratumumab

ANC=absolute neutrophil count; CBC=complete blood count

Please refer to Section 6.6.3 for pomalidomide dose modification guidelines for non-hematologic toxicities.

Daratumumab Dose Modification Guidelines for Non-hematologic Toxicities

For details on infusion-related reaction management of daratumumab SC refer to Section 6.1.7.1.

Daratumumab must be withheld for Grade 3 or 4 toxicity to allow for recovery from toxicity, regardless of relationship to study treatment with the following exceptions:

- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea (that responds within 7 days to adequate treatment of antiemetics and/or antidiarrheal agents)
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm which must be fully recovered. If daratumumab administration does not commence within the prespecified window of the scheduled administration date (Table 23), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 23: Daratumumab Administration Schedule

Cycles	Frequency	Dose Withheld	Dosing Restart
1 and 2	Weekly (q1wk)	>3 days	Next planned weekly dosing date
3 to 6	Every 2 weeks (q2wks)	>7 days	Next planned every 2 weeks dosing date
7+	Every 4 weeks (q4wks)	>14 days	Next planned every 4 weeks dosing date

qxwk=every x weeks

Any dose withholding of either daratumumab or pomalidomide for more than 28 days due to toxicity will result in permanent discontinuation of the applicable drug. Dose withholdings of more than 28 days for other reasons should be discussed with the sponsor.

Subjects missing ≥3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the Sponsor and the review of safety and efficacy, continuation is agreed upon.

For subjects whose daratumumab treatment is discontinued, they may continue to receive pomalidomide/dexamethasone. For subjects whose pomalidomide/dexamethasone treatment is discontinued, daratumumab treatment may be continued.

6.6.5. JNJ-68284528

No dose modification of JNJ-68284528 is allowed.

6.7. Follow-up for Subsequent Myeloma Therapy and Survival (Arm A and Arm B)

Telephone contact will be made to determine the use of subsequent myeloma therapy and survival according to the Schedule of Activities (Table 2 to Table 5) until the end of the study or until the subject has died, is lost to follow-up, or has withdrawn consent. If the information on subsequent myeloma therapy and survival is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the eCRF. Investigators may contact the subject to obtain long-term follow up information regarding the subject's safety or survival status as noted in the ICF (refer to Informed Consent in Section 10.3), Regulatory, Ethical, and Study Oversight Considerations).

6.8. Intervention After the End of the Study

After the end of the study, subjects in Arm A should return to their primary physician to determine further treatment. The sponsor will ensure the subjects on Arm A will have continued access to study treatment should this not be available as part of the local standard of care.

Following completion/discontinuation or after study end, subjects in Arm B will enter a separate long-term follow-up study (Study 68284528MMY4002) in which assessments for replication competent lentivirus (RCL) and delayed AEs, including SPMs (see Section 8.3.1) will be collected yearly until 15 years after the last infusion with JNJ-68284528. For subjects diagnosed with a SPM, a tumor sample should be collected and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Discontinuation of Study Treatment for Arm A

A subject's study treatment must be discontinued if:

- The subject withdraws consent to receive study treatment
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant. Refer to Section 10.12 Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
- Noncompliance with study treatment administration or protocol requirements
- Subject received concurrent (non-protocol) anticancer treatment
- Confirmed PD per IMWG criteria

7.1.2. Discontinuation of Study Treatment for Arm B

A subject should not receive JNJ-68284528 if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject received concurrent (non-protocol) anticancer treatment (with exception of bridging therapy)
- Subject refuses further study treatment
- Noncompliance with study treatment or procedure requirements
- The subject becomes pregnant prior to infusion
- Signs of active infection or Grade ≥3 non-hematologic toxicity related to cyclophosphamide and fludarabine occurs and precludes retreatment with cyclophosphamide and fludarabine prior to JNJ-68284528 infusion per Section 6.1.5.4.

The primary reason for treatment discontinuation will be documented in the eCRF and source documents. Subjects who are unable to receive PVd or DPd standard therapy for Arm A, or unable to be apheresed, or receive bridging therapy, conditioning regimen or JNJ-68284528 infusion for Arm B, will be followed until confirmed PD, start of new anti-myeloma therapy, withdrawal of consent, or end of the study whichever occurs first. Once PD is confirmed, subsequent disease assessment time points are not required. After PD subjects will then be followed for survival status, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2), SPMs for both Arms and other delayed adverse events for Arm B until death or the end of the study.

If a subject on Arm A discontinues study treatment, then an end of treatment visit will be done. The post-treatment follow-up assessments should be obtained and scheduled assessments off study treatment should be continued. Study treatment assigned to the subject who discontinued study intervention may not be assigned to another subject. Additional subjects will not be entered to replace subjects who discontinue treatment. If a subject's study treatment is discontinued for any reason, this will not result in automatic withdrawal of the subject from the study.

A subject on Arm B who discontinues post-treatment follow-up due to progressive disease will continue to be followed for survival status, subsequent anti-myeloma therapies, and delayed AEs including SPMs. A subject on Arm B who discontinues post-infusion follow-up due to progressive disease prior to Day 112, will continue to be followed for safety (including adverse events/serious adverse events) until Day 112, and continued to be followed for survival status, subsequent anti-myeloma therapies, and delayed AEs including SPMs.

7.2. Subject Discontinuation/Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent
- The sponsor discontinued the study

The reason(s) for subject withdrawal will be recorded on the eCRF and in source documents. If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

If a subject randomized to Arm A withdraws consent following study treatment dosing, study assessments for the End-of-Treatment Visit should be completed prior to withdrawal of consent, if feasible. For a subject randomized to Arm B who withdraws consent in the post-infusion period (prior to Day 112), the Day 112 assessments should be completed, if withdrawal occurs in the post-treatment period, the assessments at PD should be completed prior to withdrawal of consent, if feasible.

Withdrawal of Consent

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

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer

needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

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

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

- The study-site personnel must attempt to contact the subject to reschedule the missed visit as soon as possible, to counsel the subject on the importance of maintaining the assigned visit schedule, to ascertain whether the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the subject (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the subject's medical records.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Table 2 to Table 5) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, safety, PROs, and medical resource utilization measurements applicable to this study.

All planned assessments, including laboratory tests, must be completed and the results reviewed prior to the start of study treatment. Treatment decisions will be based on safety assessments performed at the local laboratory and disease assessments performed at the central laboratory. Local laboratory data may be collected if central laboratory data is not available at a particular timepoint, (Section 8.1.6).

For all other assessments scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO assessments, electrocardiogram (ECG), vital signs, blood draw. Blood collections for biomarkers and pharmacokinetic assessments should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documents and the laboratory requisition form. Within 24 hours of JNJ-68284528 infusion in Arm B, if the study treatment is infused peripherally, blood samples must be drawn from a vein contralateral to the arm into which JNJ-68284528 is infused. If the study treatment is infused via a central vein line, blood samples over the subsequent 24 hours must be drawn from a vein in either arm. Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

During screening for WOCBP a pregnancy test will be performed 10-14 days prior to the start of PVd or DPd but prior to randomization. For WOCBP randomized to Arm A on the PVd standard therapy, a pregnancy test will be performed within 24 hours prior to the first dose of PVd, every week for the first 4 weeks, every 3 weeks starting from Cycle 3 Day 1, or every 2 weeks for WOCBP with irregular menses, and 28 (+7) days following the last dose of pomalidomide. For WOCBP randomized to Arm A on the DPd standard therapy, a pregnancy test will be performed within 24 hours prior to the first dose of DPd, every week for the first 4 weeks, every 28 days or every 14 days for WOCBP with irregular menses, and 28 (+7) days following the last dose of pomalidomide (see Schedule of Activities, Table 1, Table 2 and Table 3).

For WOCBP randomized to Arm B, a pregnancy test will be performed within 72 hours prior to apheresis and within 72 hours prior to initiation of conditioning regimen. During the bridging therapy, if the pregnancy test done at screening falls out of the required 10-14 days prior to starting PVd or DPd, the test will need to be repeated. A pregnancy tests will be performed within 24 hours prior to the first dose of PVd or DPd, every week for the first 4 weeks, and 28 (+7) days following the last dose of pomalidomide (Schedule of Activities, Table 1, Table 4, Table 5). 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.

The approximate blood volume to be collected from each subject in Arm A is up to 384 mL/year. For subjects in Arm B the approximate blood volume to be collected from each subject is:

- Up to 845 mL in Year 1
- Up to 238 mL in subsequent years.

Sample Collection and Handling

Refer to the Schedule of Activities (Table 2 to Table 5) for the timing and frequency of all sample collections. The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Instructions for the collection, handling, storage, and shipment of samples to the central laboratory are found in the central laboratory manual that will be provided. Collection, handling, storage, and

shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Study protocol
- Investigator's Brochure
- IPPI/SIPPM (now known as CTPPM) (includes apheresis and cell processing instructions)
- Central laboratory manual
- Interactive web response system manual
- PRO instruments and completion guidelines/training materials
- Electronic data capture (eDC) Manual
- Sample ICF
- Subject diaries and instructions/educational materials

Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. The screening phase begins when the first screening assessment is performed. Screening procedures will be performed up to 28 days before randomization. If an assessment was performed as part of the subject's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to the first dose of study treatment. The last result obtained prior to randomization will be used to determine eligibility. Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened once upon the sponsor's written approval. Subjects who are to be rescreened must sign a new informed consent before rescreening. Rescreening and subsequent activities must be conducted in accordance with protocol defined time windows.

Randomization

Following the completion of screening assessments, subjects who meet all eligibility criteria will be randomized 1:1 to either Arm A or Arm B per the IVRS.

In both Arm A and Arm B, subjects will be provided a "patient ID card" with pertinent information about the study.

Treatment Phase (Arm A)

Subjects should initiate study treatment within 7 days after randomization. Prior to initiation of study treatment, review of safety assessments should be completed per Schedule of Activities (Table 2 and Table 3). Subjects will be treated in 21-day cycles for the PVd therapy and in 28-day

cycles for the DPd therapy until disease progression, unacceptable toxicity, death, withdrawal of consent, or end of study.

Apheresis (Arm B only)

Subjects should start apheresis in 3 to 6 days after randomization. Prior to apheresis, review of safety assessments should be completed per Schedule of Activities (Table 4). Apheresis should be performed according to institutional standards. Instructions for processing and shipping apheresis product are provided in the CTPPM.

Treatment Phase-Bridging therapy, Conditioning Regimen, and JNJ-68284528 Administration (Arm B)

Bridging therapy is administered after apheresis while JNJ-68284528 is being manufactured, prior to conditioning regimen. Bridging therapy should be started after apheresis but no more than 7 days after randomization. The choice of bridging therapy, 1 cycle of PVd or DPd, will be determined by the investigator prior to screening and will be dependent on the subject's prior exposure to anti-myeloma therapies. A second cycle of bridging therapy may be administered; the investigator should contact the sponsor if a second bridging cycle is warranted due to a delay in the availability of JNJ-68284528. Cycles beyond Bridging Cycle 1 may be truncated to allow for adequate washout and minimize time off therapy.

At the completion of manufacture and quality testing of JNJ-68284528, notification will be sent to the clinical site. Prior to dosing with cyclophosphamide and fludarabine, review of safety assessments and disease characteristics should be completed per Section 6.1.5.4. Details regarding safety monitoring and study visits during this phase are included in the Schedule of Activities (Table 4 and Table 5). A conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days must be administered prior to administration of JNJ-68284528. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73 m^2. Sponsor approval must be obtained to modify the conditioning regimen schedule.

Administration of JNJ-68284528 is described in full details in Table 10. Prior to dosing with JNJ-68284528, review of safety assessments and disease characteristics should be completed per Section 6.1.5.5.

Post-treatment Follow-up Phase (Arm A)

Subjects who discontinue treatment for reasons other than documented disease progression, death or withdrawal of consent should continue to be followed for response assessments every 28 days as in Schedule of Activities Table 2 and Table 3. If a subject starts new anti-myeloma therapy prior to disease progression, every attempt should be made to perform disease evaluations until documented disease progression.

Subjects will be followed every 16 weeks, after disease progression for survival status, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2) and SPMs until the end of study.

Post-infusion Follow-up Phase and Post-treatment Follow-up Phase (Arm B)

The post-infusion follow-up phase starts after the completion of JNJ-68284528 infusion on Day 1 and lasts until Day 112. Any subject who receives an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments as per the Schedules of Activities (Table 5). During this period, subjects will be monitored closely for safety and disease assessments. Subjects will be asked to check their temperature at least twice daily (entering 2 temperatures including their maximum daily temperature on the provided diary) during the first 28 days after infusion and will be instructed to report any fever (≥38°C or ≥100.4°F) to the investigator immediately to initiate monitoring for development of CRS.

At the Investigator's discretion and patient's willingness, the subject will be admitted for inpatient monitoring from the day of infusion (Day 1) through Day 14 of JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events), OR will receive JNJ-68284528 infusion as an outpatient in close proximity (within 30 min) to the hospital, be monitored for outpatient follow-up and then be admitted for the required inpatient monitoring from Day 5 to Day 14 after JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events) (Table 10, Section 10.16, and Section 10.17).

Subjects will be asked to remain within 1 hour of the hospital and in the company of a competent adult at all times for 1 additional week after hospital discharge, or until Study Day 21, whichever is sooner.

The post-treatment follow-up phase starts once the post-infusion follow-up is complete (on Day 112) and lasts until end of study (defined until approximately 250 deaths have occurred). Assessments are to be performed per the Schedule of Activities (Table 5) and include safety and disease assessments every 28 days. In the post-treatment follow-up, subjects will continue to be monitored for efficacy until confirmed PD, death, or withdrawal of consent. After confirmed PD, subjects will be followed for survival, subsequent anti-myeloma therapies, response to subsequent anti-myeloma therapies including the date of subsequent progression (PFS2), and SPMs every 16 weeks until the end of study. The occurrence of SPMs must be reported during the post-infusion and post-treatment follow-up and continue until the end of the study. In addition, assessment for other delayed AEs will be collected until end of study and will continue to be collected yearly for up to 15 years after the JNJ-68284528 administration in a separate long-term follow-up study (Study 68284528MMY4002). Yearly collection of RCL samples is not required if all assessments within the first year are negative. Sites will be notified if a subject's sample is positive for RCL, otherwise RCL is no longer required to be collected after the 12-month visit. PRO assessments will continue to be collected in the post-treatment follow-up phase.

If a subject on Arm A or on Arm B has died, the date and cause of death will be collected and documented on the eCRF, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

Home Health Care and Telehealth Visits (Arm B)

In exceptional circumstances, home health care and telehealth visits may be implemented following the Day 364 visit, following notification from the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy and regulations. Subjects for whom there is no safety concern related to study treatment administration or any pre-existing condition(s) may have home health care and telehealth (conducted via phone or video conference) visits.

Study procedures such as ECOG assessment, vital signs, adverse event and concomitant medication reporting may be performed with home health care and telehealth visits. Protocol-specified laboratory assessments for efficacy and safety may be collected during home health care visits or at a local laboratory. At a minimum, subjects must return to the study site for bone marrow aspirate/biopsy and PRO completion as outlined in the Schedule of Activities. At these visits, a central disease evaluation sample should be collected.

If local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. Source documentation and the appropriate eCRFs must be completed.

8.1. Efficacy Assessments

Disease evaluations must be performed as specified in the Schedule of Activities (Table 2 to Table 5). Disease evaluations will be performed by a central laboratory (additional samples may be collected for analysis by the local laboratory) until PD, death, withdrawal of consent, or end of the study. Local laboratory assessments may be used under specified circumstances (Section 8.1.6). Response assessments will be based on IMWG response criteria (Section 10.7). The sponsor will use a validated computer algorithm to analyze response to treatment.

Disease progression must be confirmed by repeating central laboratory testing (See Section 8.1.6 for exceptions) at any time before the institution of any new therapy. The investigational sites are requested to notify the sponsor within 1 working day if a subject on either Arm A or Arm B has been diagnosed with disease progression (that is also confirmed with a consecutive assessment if based on M-protein/serum free light chain [FLC] levels) and provide documentation of disease progression. The sponsor's medical monitor will review the data provided to confirm that the IMWG criteria for PD have been met (see Section 10.7). Study treatment discontinuation (Arm A) or discontinuation from post-treatment follow-up (Arm B) and start of subsequent anti-myeloma therapy should occur only after sponsor confirmation of PD.

8.1.1. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory until the development of confirmed disease progression. Local laboratory assessments may be used under specified circumstances (Section 8.1.6). Assessments, listed below, will be performed as specified in the Schedule of Activities (Table 2 to Table 5).

- Serum quantitative immunoglobulin
- Serum protein electrophoresis (SPEP)

- Serum immunofixation electrophoresis
- Serum FLC assay (for subject in suspected CR/sCR and every disease assessment for subjects with serum FLC only disease)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation electrophoresis

Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine immunofixation and serum free light chain assays will be performed at screening, at C1D1 (Arm A), or prior to apheresis (Arm B) and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] is 0 or non-quantifiable). For subjects with light chain MM, serum and urine immunofixation tests will be performed routinely as per the Schedule of Activities (Table 2 to Table 5).

Daratumumab-specific Immunofixation Electrophoresis (DSIFE) for Subjects Treated with Daratumumab (Arm A on the DPd Standard Therapy or Arm B on DPd as Bridging Therapy)

Daratumumab may be detected on SPEP and SIFE assays used for monitoring disease monoclonal immunoglobulins (M-protein). This can lead to false positive SPEP and SIFE assay results for subjects with IgG kappa myeloma protein and affect assessments of responses based on modified IMWG criteria.

Therefore, a DSIFE will be performed when daratumumab interference is suspected based on SPEP and SIFE results. For subjects in Arm A, DSIFE is not required once CR/sCR is confirmed. For subjects in Arm B, DSIFE is not required after bridging therapy and prior to conditioning regimen. This reflex assay relies on the use of a daratumumab specific murine anti-idiotype antibody that binds and shifts daratumumab's migration pattern during electrophoresis, thus distinguishing daratumumab from the endogenous myeloma M protein.[27] The DSIFE will be performed at a central laboratory to confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.

8.1.2. Imaging

Imaging must be performed at screening and thereafter as clinically indicated. Imaging will be interpreted locally. Any of the following are acceptable, however, the same modality should be used for screening and if indicated to evaluate for possible PD:

- A skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease).
- Whole body MRI
- Low-dose whole body CT
- Positron emission tomography (PET)/CT with diagnostic CT component. If a CT scan is used, it must be of diagnostic quality.

Following study treatment, and before disease progression is confirmed, X-rays or CT scans should be performed locally, whenever clinically indicated based on symptoms, to document response or progression. If a subject presents with disease progression manifested by symptoms of pain due to bone changes, then disease progression may be documented by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory X-rays are necessary. If changes are equivocal, then a repeat X-ray is needed in 1 to 3 weeks.

The modality used for imaging must be indicated on the eCRF. Imaging reports must be made available to sponsor for central team review upon request.

8.1.3. Documentation of Soft Tissue Plasmacytomas

Sites of known soft tissue plasmacytomas must be documented during screening. Clinical examination or MRI may be used to document soft tissue plasmacytomas. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of soft tissue plasmacytomas. However, PET/CT scans can be used to document soft tissue plasmacytomas if the CT component of the PET/CT scan is of sufficient diagnostic quality. If PET/CT identifies soft tissue disease and CT is not of diagnostic quality, additional diagnostic quality cross-sectional imaging should be performed to obtain bi-dimensional measurements.

Soft tissue plasmacytomas should be assessed for all subjects with a history of plasmacytomas, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed, measured, and evaluated locally every 4 weeks in subjects where plasmacytoma is measurable on physical examination. Assessments will continue every 4 weeks or every 12 weeks until development of confirmed CR or confirmed disease progression as long as the soft tissue plasmacytoma remains measurable on physical or radiological examination. If assessment can only be performed radiologically, then evaluation of soft tissue plasmacytomas should be done every 12 weeks. The methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for VGPR or PR/minimal response, the sum of products of the perpendicular diameters of the existing soft tissue plasmacytomas must have decreased by over 90% or at least 50%, respectively, and new plasmacytomas must not have developed (see the disease response criteria in Section 10.7). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing soft tissue plasmacytomas must have increased by at least 50%, or the longest diameter of previous lesion >1 cm in short axis must have increased at least 50%, or a new plasmacytoma must have developed. When not all existing soft tissue plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, then the criterion for disease progression is met.

The modality used to document soft tissue plasmacytomas must be indicated on the eCRF. Imaging reports must be made available to the sponsor for central team review upon request.

8.1.4. Bone Marrow Examination

Bone marrow aspirate or biopsy (biopsy alone is acceptable if aspirate is not possible) will be performed for clinical assessments and biomarker evaluations. Clinical staging (morphology and immunohistochemistry or immunofluorescence or flow cytometry) should be done by a local laboratory; cytogenetics will be done at a central laboratory. If cytogenetic results are not available by central laboratory, local laboratory data, if available, may be entered into the eCRF. Bone marrow aspirate and biopsy will also be performed to confirm CR and sCR (both Arms) and at PD (Arm B only). For subjects in Arm B, a portion of the bone marrow aspirate at each bone marrow aspiration should be sent to the central laboratory for flow cytometry, CyTOF, and to monitor BCMA, checkpoint ligand expression in CD138-positive MM cells, and checkpoint expression on T cells. Additionally, subjects on Arm B will have bone marrow aspirate performed at 6 months post-JNJ-68284528 infusion if not performed within the past 3 months. In the event FISH analysis does not yield diagnostic results (either centrally or locally), archived bone marrow aspirate or bone marrow clot sample may be collected for FISH analysis.

8.1.5. Minimal Residual Disease Evaluations

Bone marrow aspirates will be collected to monitor MRD to define the myeloma clones as specified in the Schedule of Activities (Table 2 to Table 5). MRD negativity is being evaluated in the field as a potential surrogate for PFS and OS. MRD will be evaluated using NGS on bone marrow aspirate DNA. In the event fresh bone marrow aspirate will not be collected at Screening, or if the fresh aspirate does not yield a usable clone, non-decalcified diagnostic tissue (bone marrow aspirate slides or formalin-fixed paraffin embedded tissue) should be collected for calibration of myeloma cells to facilitate the assessment of the secondary MRD endpoints by NGS. Bone marrow aspirate should be sent to central laboratory for MRD evaluation as specified in the Schedule of Activities (Table 3, Table 4, Table 5). If a clone for MRD detection cannot be identified based on central or local material, the sponsor will notify the investigator and the subject does not need to continue with bone marrows specifically aimed at MRD detection.

8.1.6. Local Laboratory Assessments

All efforts should be made to collect efficacy data centrally. However, local laboratory data may be collected if central laboratory data is not available at a particular timepoint. If both a central and a local lab is taken on the same day, the central lab takes precedent. Documentation of the local laboratory data should be sent to the Principal Investigator and filed in the medical record. It is the Principal Investigator's responsibility to ascertain that these results are reviewed and entered into the subject's medical record and the eCRF.

8.2. Safety Assessments

Safety will be measured by adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessments of cardiac function, ICE score (Arm B only), handwriting assessments (Arm B only), and assessment of ECOG performance status grade according to the time points provided in the Schedule of Activities. Clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF. Any clinically significant abnormalities persisting at the end of the

study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. Safety monitoring assessments may be performed more frequently, if clinically indicated.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.2.1. Physical Examinations

At screening, a physical examination will be performed and will include, at a minimum, subject's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, neurologic system, and lymphatic system. Thereafter, all other exams will be symptom-directed physical examination to be conducted per the Schedule of Activities (Table 2 to Table 5) and additional examinations as clinically indicated. Abnormalities will be recorded in the appropriate section of the eCRF. In Arm B, weight will be measured prior to apheresis and prior to infusion of JNJ-68284528 (see the Schedule of Activities, Table 4 and Table 5).

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure and oxygen saturation will be assessed as specified in the Schedule of Activities. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Subjects in Arm B will be asked to check their temperature at least twice daily (entering 2 temperatures including their maximum daily temperature on the provided diary) for the first 28 days following JNJ-68284528 infusion. Subjects will be instructed to report any fever (≥38°C or ≥100.4°F) to the investigator immediately to initiate monitoring for development of CRS.

8.2.3. Electrocardiograms

Twelve-lead ECGs will be performed at screening and thereafter as clinically indicated.

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

Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. The clinical investigator will review the results, including ECG morphology, for immediate management. Abnormalities noted at screening should be included in the medical history.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology, including CD4/CD8 lymphocyte panel for Arm B, will be collected as noted in Section 10.2, Clinical Laboratory Tests. The laboratory tests

will be performed by the local laboratory. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Subjects with Grade 3 or higher toxicity or unresolved adverse events will continue to be assessed until recovery to Grade ≤1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever occurs first.

Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents. Disease-related laboratory evaluations are detailed in Section 8.1.

8.2.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be used to evaluate the effect of the disease status on the activities of daily living (Section 10.10).

8.2.6. Transthoracic Echocardiogram or MUGA Scan

Assessment of cardiac function using either transthoracic echocardiogram (TTE) or MUGA scan is required. At a minimum, this will include assessment of left ventricular ejection fraction reported as a percentage. This value should be recorded in the eCRF.

8.2.7. Neurologic Examination

Magnetic resonance imaging (MRI) at screening or neurology consultation should be considered if pre-existing CNS disease is suspected. For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of brain and an EEG. For subjects randomized to Arm B, at the first sign of neurotoxicity, neurology consultation and evaluation should be considered. CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading. Other neurological adverse events which could not be graded by ASTCT grading should be graded based on CTCAE version 5.0. Findings from neurological evaluation and testing that support CAR-T cell-related neurotoxicity (eg, ICANS) should be reported in the eCRF. Submission of neuroimaging scans may also be requested for sponsor review.

Immune-effector Cell-associated Encephalopathy (ICE) Tool Scores (Arm B)

The ICE test was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR-T products (Section 10.15).[24] The ICE tool will be collected as noted in the Schedule of Activities (Table 5) to guide management throughout the study. It will also be used to grade the severity of ICANS (Section 10.24). All ICE-Tool scores must be reported in the eCRF.

Handwriting Assessment

Qualitative changes in handwriting since baseline are being explored by the sponsor as a potential early clinical predictive marker for neurotoxicity. Currently no standardized CTCAE toxicity gradings are available in the NCI-CTCAE v5.0. for these type of changes in handwriting. Therefore, the sponsor has developed a handwriting assessment criterion to assess subjects for occurrence of the following types of changes in handwriting: micrographia, dysgraphia, or agraphia, as potential early indicators for neurotoxicity (See Section 10.27).

Handwriting assessments will be collected on a writing log according to the Schedule of Activities (Table 5) and as instructed by the sponsor. Subjects unable to write at baseline are excused from this assessment during study. The sponsor's medical monitor should immediately be notified when changes in handwriting are detected. This will prompt discussion about additional assessments to further evaluate for other neurotoxicity symptoms, further workup, as well as the potential initiation of interventions. All cases of handwriting abnormalities (ie, micrographia, dysgraphia, or agraphia) must be reported as an adverse event in the eCRF. Should a subject experience a serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious adverse event report.

8.3. Adverse Events and Serious Adverse Events

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

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study.

Anticipated events will be recorded and reported as described in Section 8.3.6.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

All Adverse Events

All adverse events (with the exception of delayed AEs [see below], and HBV reactivation and COVID-19 infection) and special reporting situations, whether serious or non-serious, will be reported as follows:

- Arm A: from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment (daratumumab, pomalidomide, dexamethasone, or bortezomib) or until the start of subsequent anti-myeloma therapy, if earlier. Beyond this adverse event reporting period, only adverse events that are considered related to study drug need to be reported until the end of the study.
- Arm B: from the time a signed and dated ICF is obtained until 30 days after the last dose of bridging therapy (daratumumab, pomalidomide, dexamethasone, or bortezomib) or until Day 112 post-infusion of JNJ-68284528 (whichever is later) and regardless if PD occurs during bridging therapy or prior to Day 112 or subsequent anti-myeloma therapy is started prior to Day 112. Beyond this adverse event reporting period, non-serious AEs that are considered related to a study drug need to be reported until the end of the study except as defined for delayed AEs below. Events of HBV reactivations and COVID-19 infection will be reported during the first-year post-infusion of JNJ-68284528.

See Section 10.30, Appendix 30 for additional guidance on AE reporting.

Adverse events and special reporting situations, whether serious or non-serious, will be collected for subjects in Arm A who are unable to receive PVd or DPd standard therapy (Arm A), or unable to be apheresed, or receive bridging therapy, conditioning regimen, or JNJ-68284528 infusion (Arm B) until PD or until the start of anti-myeloma therapy, whichever is earlier.

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 5.0, except for CRS and CAR-T cell-related neurotoxicity (eg, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Section 10.25).[24] CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASTCT consensus grading (Section 10.24). In addition to capturing ICANS and CRS adverse events (graded by ASTCT consensus grading), all individual symptoms of CRS (eg, fever, hypotension) and ICANS (eg, depressed level of consciousness, seizures) must be captured as individual adverse events and graded by CTCAE criteria. Neurotoxicity that is not temporarily associated with CRS, or any other neurologic adverse events that do not qualify as ICANS, will be graded by CTCAE criteria. Events of neurotoxicity or exacerbation of existing neurologic adverse events will be reported until the end of study.

Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Section 10.27 and reported as an adverse event in the eCRF. Should a subject experience a serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious adverse event report.

Adverse Events of Special Interest

For Arms A and B, second primary malignancies are AEs of special interest and will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality from the time of randomization to the end of study. For the purpose of reporting, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of MM (which should be reported as PD).

In addition, for Arm B, CRS, and neurotoxicity (including CAR-T cell-related neurotoxicity [ie, ICANS] and other neurotoxicities) are also AEs of special interest and will be followed as part of standard safety monitoring activities by the sponsor, from the time of JNJ-68284528 infusion and for the duration of study, regardless of severity or causality. These events will require enhanced data collection in the eCRF, be reported to the sponsor in a timely manner irrespective of seriousness, and be followed until recovery or until there is no further improvements.

In addition, for Arm B, the following must be reported to the sponsor using the Serious Adverse Event process within 24 hours of awareness of the event beginning from Day 1 cilta-cel infusion and for the duration of the study, irrespective of seriousness (eg, serious or nonserious AEs) or causality:

- ≥Grade 3 CRS
- ≥Grade 3 neurotoxicity
- Any grade movement and neurocognitive toxicity (ie, parkinsonism)
- Any grade SPMs (including recurrence of pre-existing malignancies)

Adverse events of special interest meeting the above criteria that are considered to be nonserious by the investigator are to be indicated as such on the SAE form and in the eDC tool. All AEs of special interest of any grade should be followed until recovery or until there is no further improvement.

Delayed Adverse Events

For Arm B, the following delayed AEs will be collected beginning from Day 1 JNJ-68284528 infusion (with the exception of malignancies which will be collected beginning from time of randomization) and for the duration of study regardless of causality and subsequently will be collected yearly in a long-term follow-up study for up to 15 years post-infusion of cilta-cel:

- All grade SPMs (defined as new primary malignancies or recurrence of pre-existing malignancy with the exception of MM, which should be reported as PD), must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality. In the event of malignancy, a tumor sample should be collected, and vector integration site analysis may be performed for possible insertional mutagenesis.
- New incidence or exacerbation of a pre-existing neurologic disorder (all grades). Grade 3 or higher neurotoxicity and any grade movement and neurocognitive toxicity (ie, parkinsonism) must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality.
- New incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades)
- New incidence of Grade ≥3 hematologic disorder
- New incidence of Grade ≥3 infection

Serious Adverse Events

In Arm A, serious adverse events (regardless of causality), including those spontaneously reported to the investigator within 30 days after the last dose of study treatment (daratumumab, pomalidomide, dexamethasone, or bortezomib) or until the start of subsequent anti-myeloma therapy, if earlier must be reported. Beyond this reporting period, only SAEs that are considered related to study drugs need to be reported. In Arm B, SAEs (regardless of causality and regardless of PD or subsequent anti-myeloma therapy) must be reported for the duration of the study and subsequently will be collected yearly in a long-term follow-up study (Study 68284528MMY4002) for up to 15 years post-infusion of cilta-cel. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because of the embryo-fetal risk of pomalidomide, all subjects treated with PVd or DPd must be enrolled in the pomalidomide pregnancy prevention program applicable in their region. Investigators should comply with the Global Pomalidomide Pregnancy Prevention Plan or with

the respective country-specific Pomalyst®/Imnovid® (pomalidomide) Risk Minimization Program (ie, Pregnancy prevention program) as implemented in the post-marketing setting and ensure that all subjects adhere to these programs. When no Pomalyst/Imnovid (pomalidomide) Risk Minimization Program exists, subjects must adhere to the Global Pomalidomide Pregnancy Prevention Plan.

8.3.4. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Adverse Event Definitions and Classifications in Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). Expected PD should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

All deaths not related to PD occurring at any time of the study after receiving JNJ-68284528 administration (Arm B) should be reported to the sponsor following expedited reporting procedures (see Section 10.4).

8.3.5. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.6. Anticipated Events

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (ie, disease-related) or background regimen. For the purposes of this study the following serious adverse events will be considered anticipated events:

- Hypercalcemia
- Hyperuricemia
- Bleeding
- Renal failure and insufficiency
- Bone diseases

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

Note: Some countries require reporting of all AEs to the health authorities and do not identify anticipated events for safety reporting purposes.

8.4. Treatment of Overdose

Refer to the local product prescribing information for bortezomib, pomalidomide, or dexamethasone and to the daratumumab Investigator's Brochure regarding overdose. JNJ-68284528 will be manufactured, formulated and provided by sponsor individually. Product received should be administered in a single infusion. In the event the manufactured product exceeds the protocol-defined maximum dose, the product will be evaluated per company exceptional release or similar procedures (see Section 6.1.5.3) prior to shipment to clinical site. There is no risk for overdose of JNJ-68284528.

8.5. Pharmacokinetics (Arm B Only)

Venous blood samples will be used to evaluate the PK of JNJ-68284528. Samples collected for PK 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. Subject confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples will be collected for measurement of JNJ-68284528-positive cellular concentration and transgene levels of JNJ-68284528 as specified in the Schedule of Activities (Table 4 and Table 5). Samples will also be collected at the time of onset of suspected CRS or JNJ-68284528 cell-related neurotoxicity (ie, ICANS) regardless of causality (as specified in Table 5).

Bone marrow samples will be collected for measurement of cellular concentrations of JNJ-68284528 (as specified in Table 5).

Serum samples will be collected for exploratory evaluations of soluble circulating BCMA. The data may be used for mechanistic pharmacokinetic/pharmacodynamic modeling.

The exact dates and times of sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions for the temperatures indicated in the Laboratory Manual.

8.5.2. Analytical Procedures

Post-dose blood samples will be analyzed to determine CAR-T positive cellular concentration and transgene levels of JNJ-68284528 based on the Schedule of Activities (Table 5) using a specific and sensitive assay methods that are validated by or under the supervision of the sponsor.

8.5.3. Pharmacokinetic Parameters and Evaluations

Pharmacokinetic parameters will be estimated for individuals, and descriptive statistics will be calculated. Correlation of maximum peripheral blood concentration (C_{max}) and area under the peripheral blood concentration-time curve (AUC) with dose may also be explored. Pharmacokinetic parameters include, but are not limited to, AUC from time 0 to infinity (AUC_{inf}), AUC from time 0 to t ($AUC_{[0-t]}$), C_{max}, half-life, and time to reach maximum peripheral blood concentration (T_{max}) parameters will be calculated if sufficient data are available for estimation.

8.6. Pharmacodynamics

Pharmacodynamic assessments will only be conducted in subjects who received JNJ-68284528 and are described in Section 8.9, Biomarkers.

Pharmacokinetic/pharmacodynamic modeling will be explored to understand and characterize the dose-response relationship.

8.7. Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic/pharmacodynamics modeling may be performed, including exploring the relationship between CAR-T count/transgene level and endpoints of clinical efficacy and safety. If these analyses are performed, then the details and results will be presented in a separate report.

8.8. Genetics

Pharmacogenomics are not evaluated in this study.

8.9. Biomarkers

Biomarker assessments will focus on several objectives: 1) evaluate apheresis and infused CAR-T cell subsets and activation markers including, but not limited to, CD4+, CD8+, CD25+, central memory, effector memory cells; 2) serum or plasma proteomic profiling of cytokines (such as IL-6, IL-15, and IL-10) and other immune related proteins; 3) immunophenotyping of biomarkers of response/resistance on myeloma cells (such as BCMA and PD-L1); and 4) immunophenotyping of immune cells subsets such as CD4+ and CD8+ T cells, regulatory T cells, B and NK cells. Additional biomarker samples may be collected to help understand an unexplained adverse event including but not limited to serum or PBMCs from whole blood. Additional samples for cytokines will be collected as clinically indicated (Schedule of Activates Table 5).

To monitor if RCL is generated from cilta-cel, whole blood from subjects in Arm B will be evaluated using a qPCR assay against the lentiviral vesicular stomatitis virus-G gene. If all post-infusion samples for an individual subject are negative for RCL during the first year after treatment, no additional samples will be collected and RCL assessments will be terminated. Yearly review of medical history will generally be sufficient for the subject. Sites will be notified if a subject's sample is positive for RCL, otherwise RCL is no longer required to be collected after the 12-month visit. If any post-infusion samples are positive, further RCL analysis and more extensive subject follow-up should be undertaken. Additional event triggered testing for RCL may be conducted as clinically indicated, as specified in the Schedule of Activities (SoA).

Peripheral blood mononuclear cells will be retained for exploratory analysis of the immune system which may include retroviral insertion analysis, T-cell receptor analysis (both clonality and/or diversity of T-cell receptor), functional in vitro assays, or other.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough 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 the intended utility of the data.

Based on emerging scientific evidence, the sponsor may request additional material including, but not limited to, previously collected bone marrow samples, whole blood, bone marrow aspirate or biopsy, or other tissue sample during or after study completion for a retrospective analysis. For subjects in Arm B diagnosed with a SPM, a tumor sample should be collected (See Section 6.1.6.4). Additionally, the sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason, including during screening. Subjects who have a lumbar puncture as part of their neurologic work up should have cerebral spinal fluid for additional test by the sponsor. In all cases, such analyses would be specific to research related to the study treatment(s) or diseases being investigated. If a subject dies and an autopsy is performed, specimens may be requested by the sponsor for analysis.

8.9.1. Pharmacodynamic/Predictive Markers

The baseline of the JNJ-68284528 subsets and dynamic changes/persistence and activation of the CAR-positive viable T cells may be associated with the depth and durability of response. An evaluation of these cell populations may be performed by flow cytometry or cytometry by time of flight (CyTOF) or both and correlated with response. Additional immunophenotyping may be performed on bone marrow aspirate and whole blood samples to evaluate expression of biomarkers on myeloma cells (such as BCMA and PD-L1) and immune cell populations (such as CD4+ and CD8+ T cells) by flow cytometry, CyTOF or NGS (whole exome and RNA sequencing or both). T-cell receptor sequencing may be performed to study T-cell clonality that may affect treatment response. Samples may be characterized by gene expression profiling and somatic mutation analysis by next generation sequencing (whole exome and RNA sequencing) to evaluate potential biomarkers that may correlate with response. Samples may be evaluated by other similar technologies to evaluate protein or RNA expression or for somatic DNA analysis.

Circulating serum biomarkers present following chemotherapy conditioning and following infusion of CAR-T cells have been associated with response to some CAR-T cell-based therapies. Evaluation of cytokines (such as IL-6 and IFN-γ) and other circulating proteins (such as granzymes or perforin) will be analyzed to identify potential pharmacodynamic and predictive biomarkers of response or resistance.

8.9.2. High-risk Classification by Cytogenetics

Bone marrow aspirate samples will be collected as specified in Schedule of Activities (Table 4 and Table 5) and will be utilized for translocation/mutation/genomic analysis (DNA/RNA) to assess whether specific molecular subgroups such as del17p, t(4;14), t(14;16); Gain/Amp 1q are responsive to JNJ-68284528 treatment. The clinical benefit (ORR, PFS, and OS) of JNJ-68284528 in subjects with these cytogenetic modifications or other high-risk molecular subtypes may be determined.

8.10. Immunogenicity Assessments (Arm B Only)

Antibodies to JNJ-68284528 will be evaluated in serum samples collected from all subjects in the Arm B according to the Schedule of Activities (Table 5). Samples will also be collected at the time onset of suspected CRS or CAR-T cell-related neurotoxicity (ie, ICANS) regardless of causality (as specified in Table 5).

Additionally, serum samples should also be collected at the final visit from subjects who discontinued due to PD or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions for the temperatures indicated in the Laboratory Manual.

JNJ-68284528 transgene concentration will also be determined to aide in the interpretation of immunogenicity data. These samples will be stored and evaluated if deemed necessary.

Serum samples will be screened for antibodies binding to JNJ-68284528 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to JNJ-68284528 and/or further characterize the immunogenicity of JNJ-68284528. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to JNJ-68284528 will be performed using a validated assay method by or under the supervision of the sponsor. Other analyses may be performed to characterize immunogenicity.

8.11. Patient-Reported Outcome Assessments

The subjects' HRQoL (disease-related symptoms, functioning, and general well-being) will be captured using PRO measures that will be administered using an electronic tablet (ePRO) device

at the site. These measures will be administered according to the Schedule of Activities (Table 2 to Table 5) to be completed by the subjects before any clinical tests, procedures, or other consultations that would influence subject's perceptions of their current health state. The PRO measures will be provided in the local language. If a subject requires assistance completing the PRO assessment, a study coordinator may assist but should not prompt the subject in selecting their response. Full training documentation will be provided to site coordinators before the start of data collection.

If the subject is not coming into the clinic for their scheduled visit and therefore unable to complete the PRO questionnaires in person, the PRO can be administered by interview, via the telephone.

Samples of the PRO measures are provided in Section 10.19 to Section 10.22:

- EORTC QLQ-C30
- MySIm-Q
- EQ-5D-5L
- PGIS
- PRO-CTCAE items

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) version 3 includes 30 items in 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, nausea/vomiting), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week ("past week") and responses are reported using a verbal rating scale. The item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms. The EORTC-QLQ-C30 has been widely used among patients with MM. Reliability, validity, and clinically meaningful change thresholds have been demonstrated.

The Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) is a disease-specific PRO assessment 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.

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual (values less than 0 are possible when using the UK scoring algorithm). The EQ-5D-5L asks respondents to select their response based on their current health ("today") and takes less than 5 minutes to complete. The

EQ-5D-5L questionnaire will continue to be completed after PD, in the post-treatment follow-up phase, for both Arm A and Arm B every 6 months until the end of the study. As these are not in-person visits, the PRO assessment will be done via telephone.

The PGIS is a single item to assess the subject's perception in the severity of their overall health status using a 5-point verbal rating scale. The PGIS will be used for anchor-based meaningful change analyses.

The NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is an item library of common adverse events experienced by people with cancer that are appropriate for self-reporting. Each symptom selected for inclusion can be rated by up to 3 attributes characterizing the presence/frequency, severity, and/or interference of the adverse event.[34,43] For subjects with MM the following items were selected for inclusion: nausea, vomiting, diarrhea, shortness of breath, rash, dizziness, headache, and fatigue/tiredness/lack of energy. A 5-point verbal rating scale is used for subjects to select their experience based on the last 7 days. Responses to the PRO-CTCAE will be kept separate from CTCAE data and sites will not have access to the subject's responses for real time review. Additionally, adverse event reporting will not be derived from the PRO data and safety analysis will not be performed using PRO data.

8.12. Medical Resource Utilization and Health Economics

Health economics data such as medical resource utilization data, associated with medical encounters, will be collected continuously for 33 weeks, regardless of PD prior to 33 weeks, and reported in the eCRF by the investigator and study-site personnel. Protocol-mandated procedures, tests, and encounters are excluded. Health economics data such as costs associated with the medical encounters will be collected separately from the eCRF. All health economic data will be used only in a de-identified manner.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypothesis is that JNJ-68284528 will significantly improve PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior lines of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide.

9.2. Sample Size Determination

The sample size calculation is performed on the basis of the following assumption. Based on the clinical trial OPTIMISMM data and DPd cohort in 54767414MMY1001, the median PFS for the standard therapy arm (Arm A) is assumed to be 13 months. Assuming that JNJ-68284528 can reduce the risk of the disease progression or death by 35%, ie, hazard ratio (JNJ-68284528 vs. standard therapy) of 0.65, which translates into a median PFS of 20 months for the JNJ-68284528 group, a total of 250 PFS events are needed to achieve approximately 90% power to detect this HR with a log-rank test (2-sided alpha of 0.05). With a 20-month accrual period and an additional 16-month follow-up, the total sample size needed for the study is approximately 400 (200/treatment group) subjects. The sample size calculation has taken into consideration an estimated annual dropout rate of 5%. Long-term survival follow-up will continue until approximately 250 deaths have been observed. Therefore, this study will achieve approximately 80% power to detect a 30% reduction in the risk of deaths (HR=0.7) with a log-rank test (2-sided alpha=0.05).

Details of the interim analyses are described in Section 9.5.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat (ITT)	All subjects who were randomized in the study
Safety	All randomized subjects who received any part of study treatment

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. 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.

9.4.2. Primary Endpoint

Progression-free survival is defined as the time from the date of randomization to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause,

whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

The primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups, stratified by the 3 factors: investigator's choice of PVd vs. DPd, ISS at screening (I vs. II vs. III), and number of prior lines of therapy (1 vs. 2 or 3). The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its 2-sided 95% CIs are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

9.4.3. Secondary Endpoints

Complete response (CR)/sCR is defined as the proportion of subjects who achieve a CR or sCR response according to the IMWG criteria.

Overall MRD negativity is defined as the proportion of subjects who achieve MRD negativity at any time after the date of randomization before initiation of subsequent therapy.

Rate of MRD negativity (ie, at a 10^{-5} level) in subjects with CR/sCR at 12 months ±3 months is defined as the proportion of subjects who achieve MRD-negative status and are in CR/sCR within time window.

Rate of sustained MRD negativity is defined as the proportion of subjects who achieve MRD negativity, confirmed minimum 1 year apart and without any examination showing MRD-positive status in between.

Overall survival is measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

Overall response rate (ORR) is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria. Response to treatment will be analyzed by a validated computerized algorithm.

Progression-free survival on next-line therapy (PFS2) is defined as the time interval between the date of randomization and date of event, which is defined as progressive disease as assessed by investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first. Those who are alive and for whom a second disease progression has not been observed are censored at the last date of follow up.

Time to worsening of symptoms is measured as the interval from the date of randomization to the start date of worsening in the MySIm-Q total symptom score. The criteria for worsening will be derived based on anchor-based methods using the PGIS for overall health. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening will be censored as of the last assessment date of the MySIm-Q.

The analysis methods for binary endpoints (eg, CR/sCR rate, overall MRD negativity rate, rate of negativity in subjects with CR/sCR at 12 months ±3 months, rate of sustained MRD negativity, ORR) will be conducted using stratified Cochran Mantel Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% CI and will be provided as the measure of treatment effect. For time-to-event endpoints (eg, OS, PFS2, time of worsening of symptoms), similar statistical methods will be applied as for PFS described in Section 9.4.2.

9.4.4. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities. All reported TEAEs will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized except for CRS and CAR-T cell-related neurotoxicity (eg, ICANS). Cytokine release syndrome grading will be evaluated and summarized according to the ASTCT consensus grading (Section 10.25).[24] CAR-T cell related neurotoxicity (eg, ICANS) will be graded and summarized using the ASTCT consensus grading (Section 10.24). In addition, all individual symptoms of CRS (eg, fever, hypotension) and CAR-T cell-related neurotoxicity (eg, depressed level of consciousness, seizures) captured as individual AEs and graded by CTCAE criteria will be also summarized. Neurotoxicity that is not temporally associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded and summarized by CTCAE criteria. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Worst toxicity grade during treatment will be presented according to NCI-CTCAE Version 5.0. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as cross-tabulations.

Electrocardiogram

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be summarized at scheduled time points.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be monitored and clinically relevant changes occurring during the study will be recorded on the adverse event section of the eCRF. The percentage of subjects with values beyond clinically important limits will be summarized.

9.4.5. Pharmacokinetic Analyses

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. Descriptive statistics will be used to summarize CAR-T positive cell count and transgene level at each sampling timepoint. Pharmacokinetic parameters, including, but not limited to C_{max}, AUC, and T_{max} will be summarized descriptively at each sampling timepoint.

If sufficient data are available, population-PK analysis of peripheral JNJ-68284528 cellular concentration and transgene level-time data of JNJ-68284528 may be performed. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report. Exposure-response analyses may also be performed; if performed, details will be provided in a separate analysis plan and report.

9.4.6. Biomarkers Analyses

Baseline bone marrow aspirate samples will be evaluated by an NGS assay to establish the myeloma clone (calibration), which will be used for MRD monitoring. In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at Screening and at the subsequent timepoints outlined in the Schedule of Activities. Peripheral blood sample will be collected from subjects as outlined in the Schedule of Activities and processed to plasma and PBMCs. If possible, bone marrow core biopsy sample (slides or block) from bone marrow biopsy performed at disease progression in subjects on Arm B should be sent to the central laboratory.

9.4.7. Immunogenicity Analyses

The incidence of anti-JNJ-68284528 antibodies will be summarized for all subjects who receive JNJ-68284528 and have appropriate samples for detection of antibodies to JNJ-68284528 (ie, subjects with at least 1 sample obtained after the infusion of JNJ-68284528).

Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects who developed anti-JNJ-68284528 antibodies. The effect of anti-JNJ-68284528 antibodies on pharmacokinetics, safety, and efficacy may also be evaluated.

9.4.8. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of JNJ-68284528 and endpoints of clinical efficacy or safety. Details and results of any analysis performed will be presented in a separate report.

9.4.9. Patient-Reported Outcome Analyses

The EORTC QLQ-C30, MySIm-Q, EQ-5D-5L utility and visual analog scores, and PGIS, will be descriptively summarized at each time point. Meaningful and sustained improvement in subject's HRQoL comparative to their baseline health status will be evaluated using established meaningful change thresholds as well as anchor-based methods using the PGIS.[21] Differences between treatment groups will be assessed by change from baseline (screening phase) using mixed models for repeated measures. Frequency distributions of the PRO-CTCAE items by visit will be reported.

9.4.10. Medical Resource Utilization

Medical resource utilization will be descriptively summarized by intervention group.

9.5. Interim Analysis

One interim analysis for efficacy is planned for PFS. The interim analysis will be performed after all subjects enrolled and when approximately 188 PFS events, which is approximately 75% of the total planned PFS events, have been accumulated. The significance level for PFS at this interim analysis to establish the superiority of JNJ-68284528 over standard therapy will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Assuming 188 PFS events are observed, the alpha to be spent in this interim analysis will be 0.0193 (2-sided). If the observed 2-sided p-value is smaller than this significance level, the superiority of JNJ-68284528 versus standard therapy with respect to PFS will be established. If the JNJ-68284528 Arm is numerically worse than that of the standard therapy arm in terms of PFS (observed hazard ratio >1, favoring the standard therapy arm, then the study may be terminated for futility. The final analysis of PFS will be performed after approximately 250 PFS events have been accumulated. The first and second interim analyses for OS will be performed at the same time as the interim and final analysis for PFS, respectively. In addition, the third interim analysis for OS will be performed when approximately 200 OS events have occurred. The final OS analysis will be performed at the time of approximately 250 OS events, which also defines the end of study. The alpha spending function for OS will be power spending function with parameter=2. For example, if the observed number of OS events is 114 at the time of the first interim analysis for PFS (ie, approximately 188 PFS events), the alpha to be spent for OS is 0.0104 (2-sided).

9.6. Data Monitoring Committee or Other Review Board

An Independent Data Monitoring Committee (IDMC), will be established as noted in Committees Structure in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen, CD269, TNFRSF17
CAR-T	chimeric antigen receptor T-cell
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease-2019
CR	complete response
CRES	cell-related encephalopathy syndrome
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTPPM	Cell Therapy Product Procedures Manual
CyTOF	cytometry by time of flight
DIC	disseminated intravascular coagulation
DPd	daratumumab, pomalidomide, and dexamethasone
DSIFE	daratumumab-specific immunofixation electrophoresis
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
eGRF	estimated glomerular filtration rate
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol Five Dimension Questionnaire
EU	European Union
FEV1	forced expiratory volume in 1 second
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
HTLV	human T-lymphotropic virus
IAT	Indirect Antiglobulin Test
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
ICE	Immune-effector Cell-associated Encephalopathy
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMiDs	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IPPI	investigational product preparation instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	international staging system
IV	intravenous(ly)
MDRD	Modification of Diet in Renal Disease
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
MTD	maximum tolerated dose

NCI	National Cancer Institute
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease/progression of disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	PFS on next-line therapy
PGIS	Patient Global Impression of Severity
PIs	proteasome inhibitors
PK	pharmacokinetic(s)
PO	oral(ly)
PPI	proton pump inhibitor
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PVd	pomalidomide, bortezomib, and dexamethasone
RCL	replication competent lentivirus
rHuPH20	recombinant human hyaluronidase PH20
SC	subcutaneous
sCR	stringent complete response
SIPPM	site investigational product procedures manual
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SPM	second primary malignancy
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UPEP	urine protein electrophoresis
WOPBP	women of child bearing potential

Definitions of Terms

AUC	area under the peripheral blood concentration-time curve
AUC_{inf}	AUC from time 0 to infinity
AUC(0-t)	AUC from time 0 to t
C_{max}	maximum peripheral blood concentration
T_{max}	time to reach maximum peripheral blood concentration

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
CBC with differential	Hemoglobin White Blood Cell (WBC) Platelet count	Absolute lymphocyte count Absolute neutrophil count
CD4/CD8 Lymphocyte Panel[a]	Absolute number and % CD4 Absolute number and % CD8	CD4/CD8 ratio
Coagulation	Prothrombin time/International normalized ratio Fibrinogen	Activated partial thromboplastin time D-dimer
Full Metabolic Panel	Sodium Potassium Lactic acid dehydrogenase (LDH) Blood urea nitrogen (BUN) or urea Creatinine Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Total bilirubin[b] (+ direct bilirubin for screening) Total protein Alkaline phosphatase Uric acid Albumin Phosphate Calcium eGFR[c]
CAR-T Chemistry	Sodium Potassium LDH BUN or urea Creatinine Glucose AST ALT Total bilirubin[b] (+ direct bilirubin for screening) Total protein Triglycerides	Alkaline phosphatase Uric acid Albumin Phosphate Calcium Gamma-glutamyltransferase (GGT) Ferritin Magnesium Creatine phosphokinase (CPK) C-reactive protein eGFR[d] Fibrinogen
Pregnancy Test	Serum (<25 IU/mL) β-hCG or urine	
Tests at Screening only	Serology: • Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without a history of vaccination or for subjects who are anti-HBc positive with or without anti-HBs positive) (Section 10.6) • Hepatitis C virus (HCV) infection is defined as: ○ Positive anti-HCV antibody or ○ detectable HCV-RNA or ○ history of HCV NOTE: Participants with positive anti-HCV antibody due to prior resolved disease can be enrolled only if a confirmatory HCV-RNA test is undetectable. For participants with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as undetectable HCV-RNA ≥24 weeks after completion of antiviral therapy • HIV	

Tests within 60 days prior to randomization	HIV, Hepatitis B, Hepatitis C, HCV RNA, HTLV, and other infectious disease as applicable per local regulations
Test prior to daratumumab administration	Indirect Antiglobulin Test (IAT) (see further description below)
COVID-19 antibody titer (optional)	As applicable per institutional standards, up to 1 year post cilta-cel infusion.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; CBC=complete blood count; eGFR=estimated glomerular filtration rate; HBsAg=hepatitis B surface antigen; anti-HBc=anti-hepatitis B core antibody, anti-HBs=anti-hepatitis B surface antibody; HCV=hepatitis C virus; HTLV= human T-lymphotropic virus; MDRD=Modification of Diet in Renal Disease.

a CD4/CD8 panel should be done for newly enrolled subjects. Subjects enrolled under amendment #1 that have re-consented to amendment #2 and have received cilta-cel are not required to do the CD4/CD8 lymphocyte panel.

b. Direct bilirubin if Gilbert's disease.

c. Calculated using MDRD formula (see Section 10.11) only to be included at screening.

d. Calculated using MDRD formula (see Section 10.11) only to be included prior to conditioning regimen

Indirect Antiglobulin Test (IAT)

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first study drug administration.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a subject identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first study drug administration, along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[7,8]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

b. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the daratumumab Investigator's Brochure (IB daratumumab).

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the electronic Case Report Form (eCRF) and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status]. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for

the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

Subjects who are rescreened are required to sign a new ICF.

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

DATA PROTECTION

Privacy of Personal Data

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

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

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamics, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless

required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples, including apheresis product, collected in this study and JNJ-68284528 that was manufactured but not administered to a subject may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-68284528, to understand MM, to understand differential treatment responders, and to develop tests/assays related to JNJ-68284528. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 7.2, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review efficacy and safety results at the planned interim analysis for the primary efficacy endpoint. After each interim review, the IDMC will make recommendations regarding any required modifications for the study. In addition, the IDMC will review cumulative safety data (ie, serious adverse events) after the first 20 subjects with at least 3 months follow up after randomization. Thereafter, the IDMC will review the cumulative safety data every 6 months. The details will be provided in a separate IDMC charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-68284528 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-68284528, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the

study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

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

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

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

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

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

CASE REPORT FORM COMPLETION

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

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

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

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the

protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

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

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

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

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

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

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will

be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

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

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

RECORD RETENTION

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new

custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

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

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event

must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-68284528 and daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For dexamethasone, bortezomib, and pomalidomide, with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the respective PI or SmPC.

Adverse Event Associated with the Use of the Intervention

An adverse event is considered associated with the use of the study treatment if the attribution is related by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

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

Not Related

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

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

SEVERITY CRITERIA

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 5.0, with the exception of CRS and CAR-T cell-related neurotoxicity (eg, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Section 10.25). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASTCT consensus grading (Section 10.24).[24] In addition to capturing ICANS and CRS adverse events (graded by ASTCT consensus grading), all individual symptoms of CRS (eg, fever, hypotension) and CAR-T cell-related neurotoxicity (eg, depressed level of consciousness, seizures) must be captured as individual adverse events and graded by CTCAE criteria. Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Section 10.27. Other neurotoxicities will be graded by CTCAE criteria. Any adverse events or serious adverse events not listed in the NCI-CTCAE Version 5.0 will be graded according to investigator clinical judgement 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 noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

Activities of Daily Living (ADL)

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

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

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

All Grade 3 or 4 adverse events that have not resolved by the protocol-defined adverse event collection period, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

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

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

In the event of a special reporting situation, the investigator or treating physician should contact the sponsor and closely monitor for AEs. Special reporting situations should be recorded in the eCRF. Since JNJ-68284528 will be individually manufactured and provided by the sponsor for complete administration in a single infusion, overdose with cilta-cel is not applicable for this study. Any special reporting situation that meets the criteria of an AE, including SAE, should be recorded on the AE/SAE page of the eCRF. Serious AEs should follow the 24-hour SAE reporting process (Section 8.3).

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The exceptions are CRS and JNJ-68284528-related neurotoxicity, all symptoms associated with these events will be collected in the eCRF. Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

All serious adverse events that have not resolved by the protocol-defined adverse event period, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Routine monitoring hospitalizations post-infusion required per protocol
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- The investigator may choose to hospitalize the subject per institutional standards for CAR-T therapy and in accordance to the criteria provided in Section 10.16.
- The administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.

Expected PD should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

All deaths not related to PD occurring at any time of the study after receiving JNJ-68284528, should be reported to the sponsor following expedited reporting procedures.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators,

and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: International Staging System

Stage	Criteria
I	Serum β2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Not stage I or III*
III	Serum β2-microglobulin ≥5.5 mg/L

*There are 2 categories for stage II: serum β2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

Source: Adapted from Greipp (2005)[17]

10.6. Appendix 6: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine subject eligibility for the study:

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc)**
Exclude	+	— *or* +	— *or* +
Include	—	—	—
	—	+*#	+#
	—	—	+#
	—	+*	—

* Subjects who are anti-HBs positive and without history of vaccination, should have HBV-DNA quantification test. Subjects who are anti-HBs positive and without history of vaccination, should have HBV-DNA quantification test. Subjects with positive HBV-DNA should be excluded. Subjects with negative HBV-DNA can be enrolled. If required by local country guidelines on HBV prevention, HBV-DNA and AST/ALT laboratories should be performed every 12 weeks (±14 days) until 6 months after the last dose of PVd or DPd for Arm A or every 12 weeks (±14 days) for the first 12 months after JNJ-68284528 administration for Arm B. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance.

Subjects with positive anti-HBc and either positive or negative anti-HBs should have HBV-DNA quantification test. Subjects with positive HBV-DNA should be excluded. Subjects with negative HBV-DNA can be enrolled; however, HBV-DNA and AST/ALT laboratories should be performed every 12 weeks (±14 days) until 6 months after the last dose of PVd or DPd for Arm A or every 12 weeks (±14 days) for the first 12 months after JNJ-68284528 administration for Arm B. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance.

NOTE: To minimize the number of times a subject would need to visit the clinic, the post-treatment follow-up visit (every 28 days post Day 112) can be coordinated with the AST/ALT assessment every 12 weeks (± 14 days).

10.7. Appendix 7: Criteria for Response to Multiple Myeloma Treatment

Response	Response Criteria
Stringent complete response	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry or negative 2-4 color flow cytometry
Complete response[a]	• Negative immunofixation of serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow • No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine[b]
Very good partial response[a]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours
Partial response	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to < 200 mg/24 hours • If serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is require in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response[c]	• ≥25% but ≤49% reduction of serum M-protein *and* reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for sCR, CR, VGPR, PR, MR, or progressive disease
Progressive disease[d]	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), *and/or* – Urine M-component (absolute increase must be ≥200 mg/24 hours), *and/or* – 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) – Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥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 • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Key: CR=complete response; FLC=free light chain; PC=plasma cell; PR=partial response; sCR=stringent complete response; SPD=sum of the products of the maximal perpendicular diameters of measured lesions; VGPR=very good partial response.

[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 ≥90% decrease in the difference between involved and uninvolved FLC levels. For subjects achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline.

[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] Patients with 0.5-1.0 g/dL at baseline cannot be assessed for minimal response.

[d] Clarifications to the criteria for coding progressive disease: bone marrow criteria for progressive disease 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 progressive disease) 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 progressive disease, 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)[14,22,35]

10.8. Appendix 8: International Myeloma Working Group Diagnostic Criteria

Diagnostic criteria for myeloma must be met when the subject was diagnosed. Multiple myeloma is defined as clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] and any one or more of the following myeloma-defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - **C:** Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - **R:** Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 μmol/L (>2 mg/dL)
    - **A:** Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - **B:** Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or positron emission tomography-CT (PET-CT)[c,d]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[a] ≥60%
  - Involved:uninvolved serum free light chain ratio[e] ≥100
  - >1 focal lesions on MRI studies[f]

[a] Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
[b] Measured or estimated by validated equations.
[c] If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
[d] PET-CT=^{18}F-fluorodeoxyglucose PET with CT.
[e] These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
[f] Each focal lesion must be 5 mm or more in size.

Source: Rajkumar 2014[35]

10.9. Appendix 9: Prior Multiple Myeloma Therapy Lines

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one 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 disease progression, 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.

Source: Rajkumar 2011, Rajkumar 2015[36,37]

10.10. Appendix 10: Eastern Cooperative Oncology Group Performance Status Score

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

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken 1982).[31]

10.11. Appendix 11: Formulas for Estimating Glomerular Filtration Rate

Modified Diet in Renal Disease Formula

For creatinine in mg**/dL**, the estimated glomerular filtration rate (e-GFR) for the MDRD formula is:

e-GFR (MDRD) mL/min per $1.73m^2 = 175 \times [\text{serum creatinine (mg/dL)}]^{-1\,154} \times [\text{age}]^{-0\,203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$

For creatinine in **µmol/L**, the e-GFR for the MDRD formulas is:

e-GFR (MDRD) mL/min per $1.73m^2 = 175 \text{ x } [\text{serum creatinine (µmol/L)}/88.4]^{-1\,154} \times [\text{age}]^{-0\,203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$

Source: Levey 2006[25]

10.12. Appendix 12: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.3, Pregnancy and Section 10.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman 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 24 months without an alternative medical cause. A high follicle stimulating hormone level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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

If reproductive status is questionable, additional evaluation should be considered.

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

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

Because of the embryo-fetal risk of pomalidomide, all subjects treated with PVd or DPd must be enrolled in the pomalidomide pregnancy prevention program applicable in their region. Investigators should comply with the Global Pomalidomide Pregnancy Prevention Plan or with the respective country-specific Pomalyst/Imnovid (pomalidomide) Risk Minimization Program (ie, Pregnancy prevention program) as implemented in the post-marketing setting and ensure that

all subjects adhere to these programs. When no Pomalyst/Imnovid (pomalidomide) Risk Minimization Program exists, subjects must adhere to the Global pomalidomide Pregnancy Prevention Plan.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT
Highly Effective Methods That Are User Independent *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT
Highly Effective Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - –oral
  - –injectable
- Sexual abstinence
  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide[c]
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.13. Appendix 13: Conversion Table for Glucocorticoid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Source: http://www.globalrph.com/corticocalc.htm. Accessed 14 June 2016.

10.14. Appendix 14: 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.

10.15. Appendix 15: Immune Effector Cell-associated Encephalopathy (ICE) Tool

Immune Effector Cell-Associated Encephalopathy (ICE) Tool[a]
Orientation: Orientation to year, month, city, hospital:

- **4 points**

Naming: Name 3 objects (eg, point to clock, pen, button):

- **3 points**

Following 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: Count backwards from 100 by ten:

- **1 point**

a: ICE-Tool Scoring:

- Score 10: No impairment
- Score 7-9: Grade 1 ICANS
- Score 3-6: Grade 2 ICANS
- Score 0-2: Grade 3 ICANS
- Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

10.16. Appendix 16: JNJ-68284528 Outpatient Administration Guidelines

When evaluating the suitability for outpatient administration, if allowed by local regulations and institutional guidance among other considerations, investigators should assess the subject's clinical status and the health care facility capability to safely manage outpatient logistics. General recommendations for each of these considerations are provided below:

1. Clinical consideration

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

- Not requiring packed red blood cell or platelet transfusions more frequently than every 2 days
- No presence of an indwelling central line (with the exception of a PICC line) given risk of infection in the setting of cytopenia
- No fever or active infection (bacterial, fungal, viral) since study enrollment
- No Grade 3 or higher non-hematologic toxicities of cyclophosphamide and fludarabine including nausea, vomiting, and diarrhea
- No clinically significant coagulopathy that would increase the risk of bleeding in the setting of cytopenia
- No high tumor burden defined as at least 60% plasma cell infiltration of the marrow and/or the presence of extramedullary disease
- No risk factors for developing clinically significant tumor lysis syndrome and requiring management with increased hydration, allopurinol, or rasburicase. Patients who are receiving prophylactic treatment for TLS are eligible for outpatient infusion, if deemed stable by the investigator
- No rapidly progressing disease
- 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 diphenhydramine premedication for JNJ-68284528.
- The following laboratory parameters:
  - eGFR of ≥40 mL/min/1.73 m^2
  - AST and ALT≤3 times the upper limit of normal

2. Logistical consideration for qualified healthcare facility

Outpatient administration and post-JNJ-68284528 infusion follow-up must take place at a qualified healthcare facility.

The following should be considered for outpatient administration and follow-up until Day 4 prior to inpatient admission from Day 5 to Day 14 of JNJ-68284528 infusion:

- Site must discuss with subjects how to recognize signs of CAR-T toxicities, including CRS and neurotoxicity
- Site must provide patients with educational material including but not limited to emergency contact information

- Subject will receive daily phone call follow-ups from the hospital site staff (as required by the Schedule of Activities Table 5 and Section 10.17) during typical business hours
- Subject is required to stay within 30 minutes of transportation to the hospital and remain in the company of a competent adult at all times until the time of readmission on Day 5 after JNJ-68284528 infusion
- Subject must comply with all the protocol requirement procedures, including measuring and recording of body temperature twice per day, and coming to the site for safety assessments according to the Schedule of Activities (Table 5).
- Subject must be made aware of the presenting signs and symptoms of CAR-T associated toxicities (including but not limited to CRS, neurotoxicity's, infections, etc. (as presented in the patient wallet card)
- Admission to the hospital is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity even if these occur before Day 5. Even without symptoms of CRS and/or neurotoxicity, subject will be admitted for inpatient monitoring from Day 5 to Day 14 of JNJ-68284528 infusion
- If a subject does not develop symptoms of CRS and/ or neurotoxicity or other clinically significant adverse event until Day 10 post JNJ-68284528 infusion, subject may be discharged with daily outpatient phone call follow-ups during business hours through study Day 14. Upon discharge from the hospital, the subject must stay locally within 1 hour of transportation to the hospital and remain in the company of a competent adult at all times for 1 additional week, or up to study Day 21, whichever is sooner
- Subjects that experience CRS and/or neurotoxicity, can be discharged from the hospital when they are afebrile for 24 hours and signs and symptoms of CRS and/or neurotoxicity or other clinically significant adverse event have resolved

10.17. Appendix 17: Monitoring for Subjects Receiving JNJ-68284528 as Outpatient

Subjects eligible to receive JNJ-68284528 as an outpatient (see recommendations in Section 10.16) in consultation with and approval of the sponsor.

Day 1	JNJ-68284528 infusion
Day 1 to 4	• Subject is required to stay within 30 minutes of transportation to the hospital and remain in the company of a competent adult at all times • Subject will receive daily phone call follow-ups from hospital staff during typical business hours • Admission to the hospital is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity
Day 5 to 14	• Required inpatient admission • Potential discharge on Day 10 for subjects who do not develop symptoms of CRS, neurotoxicity, or other significant adverse events – Subjects discharged on Day 10 will receive daily phone call follow-ups from the hospital staff during typical business hours through Day 14

10.18. Appendix 18: The Family of Antihistamine Medications

The following antihistamines may be used for daratumumab pre-injection medication (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

10.19. Appendix 19: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.20. Appendix 20: Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q)

MULTIPLE MYELOMA SYMPTOM AND IMPACT QUESTIONNAIRE

Instructions: The purpose of this questionnaire is to collect information about your experience with multiple myeloma. Please only consider your experiences related to your multiple myeloma when answering the following questions.

People often experience changes in the severity of their symptoms from day to day or within a single day. When answering the next 4 questions, please only think about the time within the past 7 days when each symptom was at its worst.

1. How would you rate the worst **pain in your back** within the past 7 days?

   ☐ No pain
   ☐ A little pain
   ☐ Moderate pain
   ☐ Quite a bit of pain
   ☐ Severe pain

2. How would you rate the worst **pain in your legs** within the past 7 days?

   ☐ No pain
   ☐ A little pain
   ☐ Moderate pain
   ☐ Quite a bit of pain
   ☐ Severe pain

1

3. How would you rate the worst **pain in areas other than your back or legs** within the past 7 days?

☐ No pain
☐ A little pain
☐ Moderate pain
☐ Quite a bit of pain
☐ Severe pain

4. How would you rate the worst **numbness or tingling in your hands or feet** within the past 7 days?

☐ No numbness or tingling
☐ A little numbness or tingling
☐ Moderate numbness or tingling
☐ Quite a bit of numbness or tingling
☐ Severe numbness or tingling

For each question, select only 1 answer that best describes how often you experienced each issue within the past 7 days.

5. How much did your **pain interfere** with your usual or daily activities within the past 7 days?

☐ Not at all
☐ A little bit
☐ Moderately
☐ Quite a bit
☐ Very much

2

6. How often did you have **low energy** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

7. How often did you **tire easily** (for example, needing to rest during activities) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

8. How often did you experience **muscle weakness** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

9. How often did you have **trouble with your sleep** (for example, difficulty falling asleep or staying sleep) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

10. How often did you have a **poor appetite** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

11. How often did you have **difficulty with your memory** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

12. How often did you have **difficulty concentrating** on things (for example, reading a book or following a conversation) within the <u>past 7 days</u>?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

13. How often were you **limited in doing your daily activities** within the <u>past 7 days</u> (for example, struggling or needing help with work or house chores)?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

14. How often did you have **difficulty walking** within the <u>past 7 days</u>?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

15. How often were you **limited in your social life** (for example, activities with your friends or family) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

For each question, select only 1 answer that best describes how you felt within the past 7 days.

16. How often have you felt **depressed about your multiple myeloma** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

17. How often did you **worry that your multiple myeloma could get worse** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

10.21. Appendix 21: EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

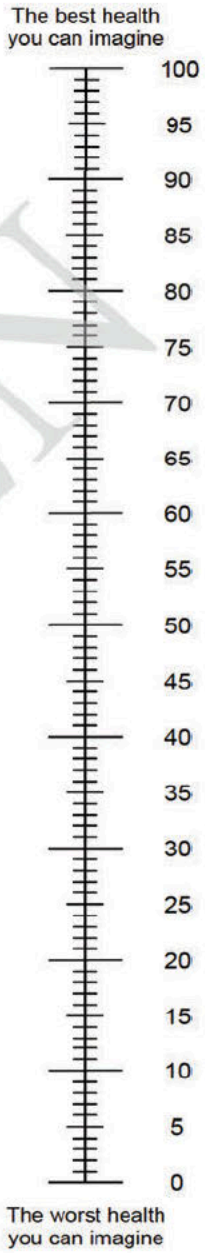
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.22. Appendix 22: Patient's Global Impression of Severity of Multiple Myeloma

Patient's Global Impression of Severity (PGIS)
of Multiple Myeloma

Overall, how would you rate the severity of your multiple myeloma disease currently? (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

PGIS_CD_v2.0

10.23. Appendix 23: NCI PRO-CTCAE ITEMS

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 6 September 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊠ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

4.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

5.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

6.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 6 September 2018

7.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.24. Appendix 24: Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) ASTCT Consensus Grading System

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) ASTCT Consensus Grading System [a,b]				
Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE).
Depressed Level of Consciousness	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulus.	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised Intracranial Pressure / Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging.	Diffuse cerebral edema on neuroimaging; or Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE=Common Terminology Criteria for Adverse Events; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome; ICE= Immune-effector Cell-associated Encephalopathy; EEG=electroencephalogram; N/A=not applicable.

[a] Toxicity grading according to Lee et al 2019[24]

[b] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure pressure/cerebral edema) not attributable to any other cause.

Note: all other neurologic adverse events (not associated with ICANS) should continue to be graded with CTCAE Version 5.0 during both phases of the study.

10.25. Appendix 25: Cytokine Release Syndrome ASTCT Consensus Grading System

Grade	Toxicity
Grade 1	Fever[a] (Temperature ≥38°C)
Grade 2	Fever[a] (Temperature ≥38°C) with either: • Hypotension not requiring vasopressors • And/or[c] hypoxia requiring low-flow nasal cannula[b] or blow-by.
Grade 3	Fever[a] (Temperature ≥38°C) with either: • Hypotension requiring a vasopressor with or without vasopressin, • And/or[c] hypoxia requiring high-flow nasal cannula[b], facemask, nonrebreather mask, or Venturi mask.
Grade 4	Fever[a] (Temperature ≥38°C) with either: • hypotension requiring multiple vasopressors (excluding vasopressin), • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).
Grade 5	Death

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP= Bilevel Positive Airway Pressure; CPAP= Continuous Positive Airway Pressure; CRS=cytokine release syndrome; CTCAE= Common Terminology Criteria for Adverse Events

[a] Fever not attributable to any other cause. In patients who have CRS then receive antipyretics 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] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

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

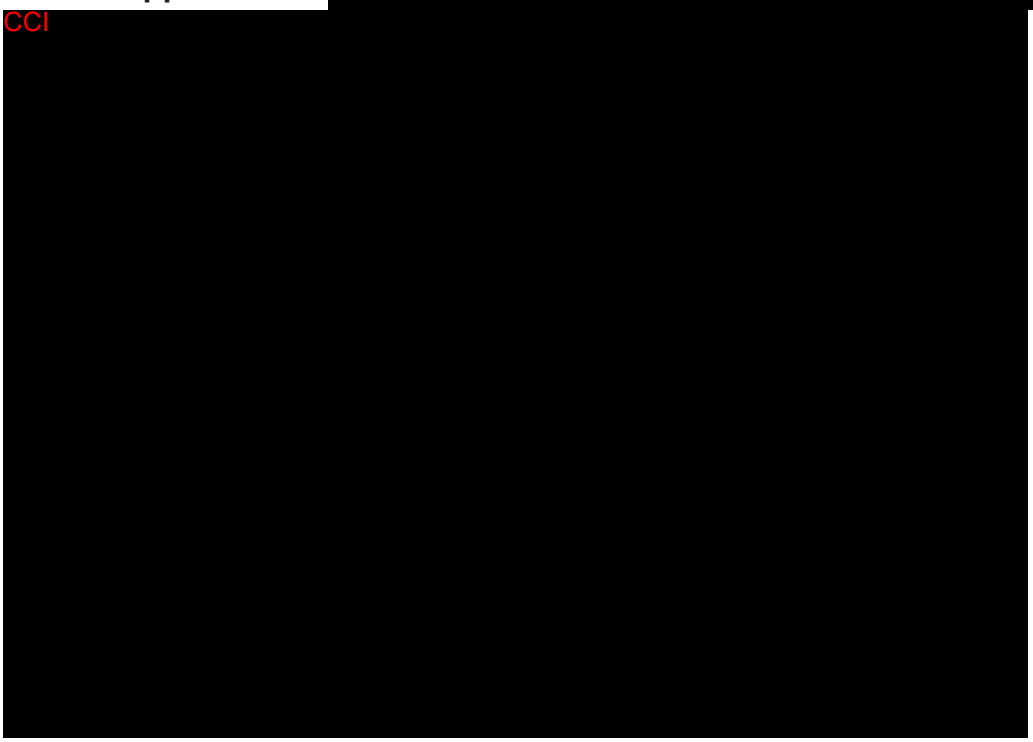
Source: Lee 2019[24]

10.26. Appendix 26: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.27. Appendix 27: CCI

CCI



10.28. Appendix 28: Anti-microbial Prophylaxis Recommendations

Subjects should receive antimicrobial prophylaxis as per recommendations below or per institutional standards.

Prophylaxis	Therapy	Start	Stop
Anti-Bacterial	Fluoroquinolones (Levofloxacin – 500 mg PO or IV daily, or equivalent) *Suggested Alternative for subjects with allergy to quinolones*: Cefpodoxime - 200 mg PO twice a day	At neutropenia onset (ANC < 500/μL) Or by Day -1	At Neutropenia resolution (for example, ANC ≥ 500/μL)
Anti-Fungal	Fluconazole - 400 mg daily (or equivalent) *Alternatives*: Caspofungin or Micafungin For prolonged neutropenia – Consider switching to Posaconazole, *or* as per institutional guidelines	At neutropenia onset (ANC < 500/μL) Or by Day -1	At Neutropenia resolution (for example, ANC ≥ 500/μL)
Anti-Viral	Acyclovir – 400 - 800 mg PO twice a day[2] (dose to be adjusted as per institutional guidelines) *Alternative*: Valacyclovir - 500 mg PO twice a day	By Day -1 of infusion	Suggested for at least 12 months post infusion
***Pneumocystis* Pneumonia (PCP)**	Pentamidine (as per institutional guidelines) followed by Trimethoprim-sulfamethoxazole – 1 DS tablet PO daily or 1 SS tablet PO daily *Alternatives*: Pentamidine (as per institutional guidelines), *or* Dapsone – 100 mg PO daily or 50 mg PO BID, *or* Atovaquone – 1500 mg PO daily	By Day -1 of infusion Pentamidine (or alternative) Day 28 (or when cytopenia recovers) Trimethoprim-sulfamethoxazole – 1 DS tablet PO daily or 1 SS tablet PO daily	Suggested duration: 6 months post-infusion OR until CD4 count ≥ 200 cells/μL, (whichever is longer)

Consider CMV serology at baseline, monitor with PCR testing as clinically indicated per institution guidance

10.29. Appendix 29: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

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

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

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 COVID-19 pandemic should be summarized in the clinical study report.

Testing for COVID-19 should be performed according to local guidance. If a subject has tested positive for COVID-19, the following should be reported in the EDC tool:

- all cases of COVID-19, regardless of severity or causality (including asymptomatic COVID-19) up to 1 year after cilta-cel infusion
- all medications given to prevent (including vaccines) or treat COVID-19 up to 1 year after cilta-cel infusion

GUIDANCE SPECIFIC TO THIS PROTOCOL:

These emergency provisions are meant to ensure subject safety on study while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

Study Visits and Assessments

- At the discretion of the investigator and with sponsor approval, study visits may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators. Blood sample collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution. Home health nursing can be done via site contract with a visiting nurse service independent of the sponsor, if not using the sponsor's home health nursing solution. Patient reported outcome questionnaires can be completed by telephone or during the home health visit.
- For subjects who are unable to come to the site for scheduled visits and/or if site capabilities are compromised by COVID-19-related restrictions, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. Normal study procedures should be followed for the applicable visits as closely as possible even if lab assessments and physical exams are performed locally. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. The remote contact with the subject (as allowable per local regulations), the local laboratory results, and the sponsor discussion should be documented in the subject source record. Similarly, at a minimum, a comment must be entered in the Comments eCRF clearly designating as "COVID-19-related" and acknowledging the discussion between the investigator and the sponsor.
- All deviations from protocol-required assessments should be documented in detail within the subject's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).
- Consenting and re-consenting of subjects will be performed as applicable for the measures taken (including also remote consenting by phone or video consultation) and according to local guidance for informed consent applicable during the COVID-19 pandemic.

The above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to ensure that subject assessments continue as outlined in the protocol without imposing health risk to subjects, their families, and site staff. Every effort should be made to complete all protocol-required assessments.

GUIDANCE ON COVID-19 VACCINE TIMING, AND COVID-19 PREVENTION AND TREATMENT FOR CILTA-CEL RECIPIENTS

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

Many vaccines against COVID-19 are being developed with different technologies and platforms and may have safety and efficacy profiles that are not fully characterized even after preliminary health authority approval. However, the benefit-risk ratio of receiving a COVID-19 vaccine among patients with multiple myeloma participating in cilta-cel studies is considered to be positive and should be considered for administration while in compliance with the cilta-cel study protocol and when not otherwise contraindicated for use in the vaccine label.

Per protocol, live attenuated vaccines must be completed at least 6 weeks prior to lymphodepletion therapy or initiated at least 112 days after cilta-cel infusion. There are no specific timing restrictions for inactivated vaccines, which include vaccines which use alternative technology like mRNA or replication-incompetent viral vectors, per protocol. Enrollment into an interventional clinical trial for an experimental vaccine is prohibited during study. Any vaccination, including COVID-19 vaccinations, must be recorded on the Concomitant Medication page of the eCRF.

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

While not specifically required per protocol, it is encouraged to complete the COVID-19 vaccine series at least 2 weeks prior to lymphodepletion, and to delay vaccination for at least 3 months after cilta-cel infusion, to maximize immune response.

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

- European Society for Blood and Marrow Transplantation (EBMT)

  https://www.ebmt.org/covid-19-and-bmt

- American Society for Transplantation and Cellular Therapy (ASTCT)

  https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients

- National Comprehensive Cancer Network (NCCN)

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

- Centers for Disease Control and Prevention (CDC)

  https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

- Nature Reviews Clinical Oncology: COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Desai A, Gainor JF, Hegde A, et al. (March 15, 2021). DOI: 10.1038/s41571-021-00487-z

  https://www.nature.com/articles/s41571-021-00487-z

Investigators should inform patients that emerging data show that patients receiving cilta-cel are possibly at higher risk of severe/fatal outcomes from COVID-19 infection compared with patients receiving standard of care therapy (Section 6.1.6.7).

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

- Subjects, particularly those who are less than 6 to 9 months from cilta-cel infusion, should be reminded that the ongoing pandemic is still putting them at risk of contracting COVID-19. Investigators should ask subjects to continue to limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention measures such as proper masking, hand hygiene, social distancing, and avoiding travel and public transportation to the extent possible.
- Investigators should discuss with subjects the importance of COVID-19 vaccines in the prevention of severe illness, hospitalization, and death from COVID-19. Subjects should assume that any vaccination administered prior to lymphodepletion and cilta-cel infusion no longer provides protection. For this reason, it is strongly recommended that all subjects receive a full COVID-19 vaccination series (eg, a primary series of 3 vaccines and a 4th booster dose for mRNA vaccines; note: mRNA vaccines are recommended), no sooner than 3 months after cilta-cel infusion, regardless of vaccination status prior to cilta-cel. In addition, if not already vaccinated, caregivers, family, and household contacts should be advised to receive COVID-19 vaccination as well.
- Investigators should consider prophylaxis (eg, Evusheld, if available in the region) to reduce subjects' risk of severe/fatal COVID during the first 6 to 9 months after cilta-cel. It is critical that subjects understand that multiple myeloma patients (even those who have not received CAR-T therapy) may not seroconvert until after the 3rd vaccine dose and as a result they may remain at a very high risk of severe COVID-19 for at least 2 to 3 months after starting vaccination.[2]
- Investigators should instruct subjects to notify them or study site staff immediately if they are diagnosed with COVID-19, even if they are asymptomatic, so that appropriate treatment measures can be determined.
- If available in the region, antivirals (eg, Paxlovid or other available agents) should be considered early after COVID-19 diagnosis. Subjects may remain asymptomatic or have minimal symptoms for a period of time prior to deteriorating. Investigators should make subjects aware that these drugs may potentially significantly lower their risk of severe COVID-19.

10.30. Appendix 30: Adverse Event Reporting Guidance for Study 68284528MMY3002

Reporting Guidelines for Adverse Events for ARM A in MMY3002 Study in eCRF:

Duration of MMY3002 Study			
Signing of ICF	**Day 1 Randomization**	**30 Days After Last Dose of Any Study Drug or until the start of subsequent anti-myeloma therapy, whichever is earlier**	**End of Study**
All AEs/SAEs, regardless of causality			Related AEs/SAEs, per investigator
	SPMs (all grades, regardless of causality or seriousness)[a]		

[a] For reporting purposes, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of recurrent multiple myeloma (ie, disease progression).

Reporting Guidelines for Adverse Events for <u>ARM B</u> in MMY3002 Study in <u>eCRF</u>:

Duration of MMY3002 Study						LTFU Study[c]: Up to 15 Years after Cilta-Cel
Signing of ICF	**Day 1 Rand.**	**Day 1 Cilta-Cel**	**Day 112 Post Cilta-Cel**	**1 Year Post Cilta-Cel**	**End of Study**	
All AEs, regardless of causality				Related AEs, per investigator		
All SAEs, regardless of causality						
	SPMs (all grades, regardless of causality or seriousness)[a,b]					
		HBV Reactivation (all grades, regardless of causality or seriousness)			≥Grade 3 HBV Reactivation (regardless of causality or seriousness)	
		COVID-19 Infection, all grades (including asymptomatic COVID-19)			≥Grade 3 COVID-19 Infection (regardless of causality or seriousness)	
		New or Exacerbation of Neurologic Disorder (all grades, regardless of causality or seriousness)				
		New or Exacerbation of Autoimmune Disorder (all grades, regardless of causality or seriousness)				
		≥Grade 3 Hematologic Disorder (regardless of causality or seriousness)				
		≥Grade 3 Infection (regardless of causality or seriousness)				

[a] For reporting purposes, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of recurrent multiple myeloma (ie, disease progression).

[b] In the event of malignancy, a tumor sample should be collected and vector integration site analysis may be performed for possible insertional mutagenesis.

[c] Refer to the Study 68284528MMY4002 for specific details.

Note: Adverse events and special reporting situations, whether serious or non-serious, will be collected for subjects in Arm A who are unable to receive PVd or DPd standard therapy (Arm A), or unable to be apheresed, or receive bridging therapy, conditioning regimen, or JNJ 68284528 infusion (Arm B) until PD or until the start of anti-myeloma therapy, whichever is earlier.

Expedited Reporting Guidelines <u>for MMY3002 Study</u> to Sponsor <u>GMS</u>:

Duration of MMY3002 Study		
Signing of ICF	**Day 1 Cilta-Cel**	**End of Study**
Arm A: Expedited Reporting[a] of all SAEs and SPMs (regardless of causality) for duration of study.		
Arm B: Expedited Reporting[a] of all	**<u>Arm B</u>**: Expedited Reporting[a] of all SAEs, and following AESIs (regardless of causality or seriousness):	

SAEs (regardless of causality) for duration of study.	• ≥Grade 3 CRS • ≥Grade 3 Neurotoxicity • Any grade movement and neurocognitive toxicity (ie, parkinsonism) • SPMs (any grade)

[a] Expedited reporting includes reporting to Sponsor Global Medical Safety within 24 hours via SAE Fax Form or other defined SAE reporting process per protocol.

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INVESTIGATOR AGREEMENT

JNJ-68284528 (ciltacabtagene autoleucel)
Clinical Protocol 68284528MMY3002 Amendment 4

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: 18 Aug 2022
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 205
Status: Approved, Date: 18 August 2022