Janssen Research & Development*

Clinical Protocol

A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma

CARTITUDE-1

Protocol 68284528MMY2001; Phase 1b-2
AMENDMENT 5

JNJ-68284528

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2018-000121-32

Status: Approved
Date: 15 June 2022
Prepared by: Janssen Research & Development
EDMS number: EDMS-ERI-155210182, 6.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	11 April 2018
Amendment 1	20 August 2018
Amendment 2	11 March 2019
Amendment 3	30 July 2019
Amendment 4	20 March 2020
Amendment 5	15 June 2022

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (15 June 2022)

The overall reason 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 COVID-19 prevention and mitigation. Additional guidance for HLH and additional clarifications were also incorporated.

Applicable Section(s)	Description of Change(s)
Rationale: To present all of the guidance on COVID-19 prevention, outcomes, and mitigations in the same document.	
Attachment 17: COVID-19 Guidance on Study Conduct and Vaccine Timing	Integrated the COVID-19 guidance, which was provided as a separate document, into the protocol as Attachment 17.
Rationale: To clarify the timing for COVID-19 vaccination for cilta-cel recipients, consistent with current recommendations across the cilta-cel program.	
Attachment 17: COVID-19 Guidance on Study Conduct and Vaccine Timing	Added guidance on COVID-19 vaccine timing for cilta-cel recipients.
Rationale: To provide additional prevention and mitigation guidance for COVID-19 infections in patients treated with cilta-cel.	
1.7. Potential Safety Risks and Mitigation Strategies (Table 3) 6.3.6. Infections Attachment 17: COVID-19 Guidance on Study Conduct and Vaccine Timing	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.
Rationale: To expand the reporting timeframe for COVID-19 infections.	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (Table 1) 9.2. Safety Evaluations 12.3.1. All Adverse Events Attachment 9: Time and Events Schedules for Retreatment with JNJ-68284528 (Table 12)	Added text to indicate that events of COVID-19 infection will be reported during the first-year post-infusion of cilta-cel.
Rationale: To expand the reporting timeframe for COVID-19 medications.	
Time and Events Schedule (Table 1) 8. Prestudy and Concomitant Therapy Attachment 17: COVID-19 Guidance on Study Conduct and Vaccine Timing Attachment 9: Time and Events Schedules for Retreatment with JNJ-68284528 (Table 12)	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.
Rationale: To increase awareness and provide additional guidance about the risk of HLH, consistent with health authority feedback.	
1.7. Potential Safety Risks and Mitigation Strategies (Table 3) 6.3.1. 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.
Rationale: For clarity.	
12.3.3. Adverse Events of Special Interest	Removed stated that “Grade 1 or 2 adverse events of special interest would not qualify for expedited reporting unless they meet serious adverse event criteria.”
Rationale: To ensure movement and neurocognitive toxicities (ie, parkinsonism) are communicated in an expedited fashion, consistent with health authority advice.	
12.3.3. Adverse Events of Special Interest	Added clarification of the requirement for expedited reporting (within 24 hours) of any grade movement and neurocognitive toxicity (ie, parkinsonism).
Rationale: To help ensure adverse events are collected and reported as required.	
Attachment 18: Adverse Event Reporting Guidance for Study 68284528MMY2001	Attachment was added to summarize requirements for adverse event and expedited adverse event reporting.

Applicable Section(s)	Description of Change(s)
Rationale: To be consistent with current recommendations for RCL assessment across the cilta-cel program.	
Time and Events Schedule (Table 2) Attachment 9: Time and Events Schedules for Retreatment with JNJ-68284528 (Table 13)	Clarified the timing (Study Day in addition to Month) of RCL assessment.
Time and Events Schedule (Table 2) 9.1.6.3. Long-term Follow-up 9.4. Biomarker Evaluations Attachment 9: Time and Events Schedules for Retreatment with JNJ-68284528 (Table 13)	Added that, if post-treatment assays are negative for RCL during the first year, collection of follow-up samples may be discontinued, and yearly review of medical history will be sufficient for the patient. If any post-treatment samples are positive, further analysis of the RCL, and more extensive patient follow-up should be undertaken.
Rationale: Request for clarity regarding COVID-19 antibody reporting, including timeframe.	
9.2. Safety Evaluations	Added a request to provide COVID-19 antibody titers, if available, post cilta-cel infusion for up to 1 year.

Amendment 4 (20 March 2020)

The overall reason for the amendment: The overall reason for the amendment is to add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for JNJ-68284528.

Applicable Section(s)	Description of Change(s)
Rationale: Safety information was updated to include other neurotoxicities.	
Time and Events Schedules (Table 1 and Table 12); 3.1 Overview of Study Design	Collection of a handwriting sample and frequency of testing was added to the study procedures. Updated footnote "q" (Table 1) and "n" (Table 12) to include handwriting sample.
Time and Events Schedules (Table 1 and Table 12)	Extended ICE neurologic test to be performed at least daily until **ICANS is** resolved. For adverse events, added: **Report new neurologic adverse events or exacerbation of existing neurologic adverse events up to 12 months after JNJ-68284528 infusion.**
1.5 Summary of Clinical Studies	Added a summary of data for Study 68284528MMY2001 and a description of 6 cases of other neurotoxicities. Added updated information on Legend-2 study and Study 68284528MMY2002.
1.7 Potential Safety Risks and Mitigation Strategies; Table 3	Added other neurotoxicities to Table 3 (Potential Risks and Mitigation Strategies) as a subsection of neurologic toxicities (changed from neurological adverse events). Added specific information to CRS rather than just cross reference to Section 6.3.1. Also updated guidance for cytopenias, infections, and hypogammaglobulinemia
2.1 Objectives and Endpoints	Added exploratory objective and endpoints to characterize potential early predictive markers for neurotoxicity.
6.1.4. JNJ-68284528 Administration	Added the following: Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS**) temporally associated with CRS. Hospitalization for neurotoxicity that is not temporarily associated with CRS, or any other neurologic adverse events, is at the discretion of the investigator.**
6.3.2 Neurological Adverse Events	Divided section into overall neurologic adverse events with sub-sections of CAR-T cell-related neurotoxicity (ICANS) (Section 6.3.2.1) and other neurotoxicities (Section 6.3.2.2) Added that subjects should be monitored for neurotoxicity for 1 year post JNJ-68284528 infusion.
6.3.2.1 CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [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 with CRS. Added recommendation to rule out alternative etiologies at first sign of neurotoxicity.
6.3.2.2 Other Neurotoxicities	New section with guidance to monitor for other neurotoxicities

Applicable Section(s)	Description of Change(s)
9.2 Safety Evaluations	Added the following: Added handwriting assessments to safety measures Added neurological adverse events to adverse events that are exception to 100 day reporting. New neurological adverse events or exacerbation of existing neurological adverse events will be reported during the first year post JNJ-68284528 dose. Added grading criteria to be used for neurotoxicity and changes in handwriting For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of the brain and an EEG. Added a section describing the assessment for qualitative changes in handwriting.
12.3.1. All Adverse Events	Added neurological adverse events to the exceptions from reporting until 100 days after the last administration of study treatment. Added "new neurological adverse events or exacerbation of existing neurologic adverse events" will be reported during the first year post-dosing JNJ-68284528.
Attachment 15 Handwriting Adverse Event Toxicity Grading Criteria	Table added for qualitative grading of handwriting sample.
Rationale: Change made to allow for flexibility in assessments.	
Time and Events Schedules (Table 1 and Table 12)	Added footnote "s" (Table 1) and "p" (Table 12): Local laboratory assessments may be used under specified circumstances (See Section 9.6)
9.6. Efficacy Evaluations	Added provision for local laboratory data collection
Rationale: Revised text in the protocol for clarity.	
Time and Events Schedules (Table 1 and Table 12)	Revised as conmeds for adverse events are collected beyond Day 100: Continuous from the time of signing of ICF until **at least** 100 days after last administration of any study treatment. Concomitant usage for the treatment of adverse events after 100 days should be reported.
Time and Events Schedules (Table 2 and Table 13)	Clarified timing of sample collection for MRD
1.7 Potential Safety Risks and Mitigation Strategies; Table 3	Added guidance to CRS to "Notify the sponsor if subject is experiencing Grade 2 or higher CRS". Added guidance for neurologic adverse events to "Notify the sponsor if subject is experiencing any grade ICANS". Added guidance for neurologic adverse events to "Notify the sponsor if subject is experiencing any grade ICANS".
6.3.4. Cytopenia	Added language for parvovirus B19 testing in subjects with prolonged neutropenia
6.3.5. Hypogammaglobulinemia	Added language for IVIG prophylaxis

Applicable Section(s)	Description of Change(s)
9.4. Biomarker Evaluations	Added language for collection of tumor sample for subjects with SPM, plasmacytoma sample, and cerebral spinal fluid sample. Added that if a subject dies and an autopsy is performed, specimens may be requested by the sponsor for analysis, as allowed by local regulations.
8. Prestudy and Concomitant Therapy	Added that all medications must be recorded "…until **at least** 100 days after infusion of JNJ-68284528 Added: **After 100 days, only adverse events that are considered related to study drug need to be reported until the end of the study**. This includes concomitant therapy and any medication used to treat or support adverse events or serious adverse events **(within or beyond 100 days after infusion)**.
8.1 Permitted Medications	Added that chemotherapy agents used to treat CAR-T cell-related toxicities are permitted upon consultation with the sponsor.
8.2 Prohibited Therapies	Removed exception for therapy to treat CAR-T cell-related toxicity from prohibited therapies. Added: 'or protocol-specific therapies which may be used in conjunction with JNJ-68284528.
9.4.2. Minimal Residual Disease	Added guidance for in the event that a fresh bone marrow aspirate is not collected at baseline.
12.3.1. All Adverse Events	Added "After 100 days, only adverse events that are considered related to study drug need to be reported until the end of the study." Revised as follows: "Serious adverse events, including those spontaneously reported to the investigator ~~within 100 days after the last administration of any study treatment~~ must be reported using the Serious Adverse Event Form." Clarified that all deaths not related to disease progression should be reported to the sponsor following expedited procedures.
12.3.3 Adverse Events of Special Interest	Added other neurotoxicities. Added events that must be reported to the sponsor using the serious adverse event form within 24 hours of awareness.
14.5 Drug Accountability	Added clarification that information in this section relates to study treatment that is supplied to investigational sites from the study sponsor.
6.3.6 Infections	Deleted: Consider periodic monitoring for CMV with PCR testing. If PCR is positive based on local threshold, clinical judgment and institutional guidelines should be followed to decide about initiation of CMV treatment.
Rationale: Updated information based on current clinical data.	
1.7 Potential Safety Risks and Mitigation Strategies	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. Added: 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.
Rationale: Flexibility added to bridging therapy language.	

Applicable Section(s)	Description of Change(s)
3.1. Overview of Study Design	Revised following guidance: **Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of CAR-T product. Investigator must contact the sponsor for approval.** Bridging therapy is now permitted for subjects receiving retreatment, with sponsor approval
Time and Events Schedule (Table 12)	Since bridging therapy is now permitted for subjects receiving retreatment, added that echocardiogram or MUGA scan should be repeated after completion of bridging therapy if it includes agents with known cardiotoxicity
Rationale: Grading column added to CRS and ICANS management tables to reflect adoption of ASBMT criteria across study protocols.	
6.3.1 Management of Cytokine Release Syndrome; Table 8	Added column for CRS grade.
6.3.2.1 CAR-T Cell-related Neurotoxicity (ICANS); Table 9	Added column for ICANS grade. Added to row 1 (ICE score 7-9) dexamethasone can be considered for Grade 1 ICANS.
Rationale: Added recommendations for extended anti-microbial usage.	
6.3.6. Infections	Added: 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 Attachment 16).
Attachment 16	Table with anti-microbial prophylaxis recommendations
Rationale: Corrected an error.	
9.3.3. Pharmacokinetic Parameters	Deleted 'for each dose level' from the following statement as all subjects will be summarized in 1 group: Pharmacokinetic parameters will be estimated for individuals, and descriptive statistics will be calculated ~~for each dose level~~.
9.10 Medical Resource Utilization	Added "**Health economics data such as** medical resource utilization data associated with medical encounters…." Added "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."
Rationale: References were updated.	
References	Added reference: MD Anderson Cancer Center. IEC Therapy Toxicity Assessment and Management. 2019. Appendix J. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf Deleted reference: Legend Biotech. Clinical Safety and Efficacy Report. Legend-2 study. LCAR-B38M-02 or NCT03090659.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 30 July 2019

The overall reason for the amendment: The overall reason for the amendment is to transition into the Phase 2 portion of the study, describe the role of the Independent Review Committee (IRC), add the Medical Resource Utilization (MRU) assessment, and to add clarity to targeted sections of the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Updated the protocol title page with the name of the study	
Title page	Updated the title of the protocol to include "**CARTITUDE-1**".
Rationale: Independent Review Committee added for evaluation of disease status	
Synopsis; 2.2 Hypothesis	Added language for the inclusion of an Independent Review Committee to evaluate disease status. Clarification added to the study hypothesis: "Treatment with JNJ-68284528 will demonstrate acceptable safety and will have significant anti-myeloma activity (ie, the lower limit of two-sided 95% confidence interval [CI] for ORR, **as assessed by the IRC,** is greater than 30%) at the targeted recommended Phase 2 dose (RP2D) level in subjects with advanced relapsed or refractory multiple myeloma."
Synopsis; 2.1 Objectives and Endpoints	Update to the Evaluations: "Disease status will be evaluated **by an Independent Review Committee (IRC)** according to **clinical judgement as guided by the IMWG consensus recommendations for multiple myeloma**.
2.2 Hypotheses	The second primary endpoint was updated as follows: ORR (at least a partial response [PR] or better) as defined by the International Myeloma Working Group (IMWG) response criteria **as assessed by the Independent Review Committee (IRC)**.
3.1 Overview of Study Design; 11.3 Efficacy Analyses	The following statement was amended to describe the role of the IRC: "Treatment with JNJ-68284528 will demonstrate acceptable safety and will have significant anti-myeloma activity (ie, the lower limit of two-sided 95% confidence interval [CI] for ORR, **as assessed by the IRC**, is greater than 30%) at the targeted recommended Phase 2 dose (RP2D) dose level in subjects with advanced relapsed or refractory multiple myeloma. "The following statement was amended to describe the role of the IRC in regard to the evaluation of the primary efficacy analysis: "~~Disease status will be evaluated according to the IMWG consensus recommendations for multiple myeloma treatment response criteria (Attachment 1)~~ [10, 11,31]~~.~~ **For the primary efficacy analysis, the disease status evaluation for each subject will be assessed by an Independent Review Committee (IRC). Disease status will be evaluated according to clinical judgement guided by the IMWG consensus recommendations for multiple myeloma treatment response criteria (Attachment 1.) [10, 11,31]. The process and convention of the IRC will be detailed in a separate charter.** ~~Response will be determined using a validated computer algorithm.~~" The following statement was added: **"For efficacy, assessment by the IRC will be used as primary."**
Rationale: Changes and corrections made for clarity	

Applicable Section(s)	Description of Change(s)
T&E Schedule (Table 1 and Table 12)	For safety criteria, added a cross reference to Section 6.1.3 (Evaluation Prior to Administration of JNJ-68284528). Added window for Hematology assessment prior to apheresis. Revised infectious disease assessment to allow for a window of testing prior to apheresis for flexibility. Revised skeletal survey evaluation to "As clinically indicated to **assess for** ~~document~~ disease progression ~~or response~~". Footnote "f" (Table 1) and footnote "e" (Table 12) updated to include: "**Serology results performed as standard of care within 28 days prior to apheresis are acceptable**.
T&E Schedule (Table 1)	Corrected PGIS post-treatment footnote: 'Xa' to 'Xo'. Footnote "b" updated to include: "For subjects who discontinue the study before Day 100, **including those who have not received an infusion of JNJ-68284528**, the Day 100 assessments should be performed prior to withdrawal if feasible."
6.1. Study Treatment Administration	Added subheading for exceptional release criteria.
Rationale: Window added to PK sampling for consistency in collections	
T&E Schedule (Table 2 and Table 13)	Additional window of "**same day as dose of JNJ-68284528 infusion**" for the PK CAR positive T cell cellular blood sample, the PK CAR transgene levels blood sample, and the soluble serum BCMA sample.
T&E Schedule (Table 2)	Clarification to footnote "a"; added "**post JNJ-68284528 infusion**".
Rationale: Medical Resource Utilization (MRU) data collection is added to evaluate the total health care resources for JNJ-68284528 CAR-T process	
T&E Schedule (Table 1 and Table 12);	Added Medical Resource Utilization requirements. Patient Reported Outcome heading updated to include **Medical Resource Utilization**. Row added to Table 1 for Medical Resource Utilization visit schedule. Added footnote "r" to define MRU data collection until Day 180 (± 7 days).
2.1 Objectives and Endpoints;	Added an exploratory objective and endpoint.
9.10 Medical Resource Utilization;	Added requirements of medical resource utilization
11.9 Medical Resource Utilization;	Added method of statistical analysis for medical resource utilization data.
Rationale: Added kanamycin to hypersensitivity reactions	

Applicable Section(s)	Description of Change(s)
1.7. Potential Safety Risks and Mitigation Strategies; 6.3.7 Hypersensitivity Reactions	Added kanamycin to list of potential hypersensitivity reactions.
Rationale: Clarification made to retreatment criteria to incorporate guidance for ongoing hematologic vs non-hematologic toxicity	
3.1 Overview of Study Design	Modified the eligibility criteria for retreatment to: • Progressive disease (PD) after best response of minimal response (MR) or better. • ~~No history of Grade 3 or higher toxicities reported~~ • **No ongoing Grade 3 or higher hematologic toxicity.** • No ongoing Grade 2 **non-hematologic toxicity (with the exception of nausea, vomiting, hair loss, and constipation).** • At least 6 months between first JNJ-68284528 infusion and detection of PD.
Rationale: Revisions made for clarity	
6.1.1 Criteria for Apheresis;	Added 24-hours prior to apheresis window for results of clinical laboratory values required for enrollment.
6.1.1 Criteria for Apheresis; 6.1.2 Criteria for Conditioning (Cyclophosphamide and Fludarabine) Dosing	Added antitumor therapy from exclusion criteria (from Section 4.2) in addition to cross reference for clarity.
6.1.2 Criteria for Conditioning (Cyclophosphamide and Fludarabine) Dosing	Clinical laboratory values required for enrollment (Section 4.1), with the following exceptions: lymphocyte count of ≥0.3 x 10^9/L. **Transfusion support is permitted to maintain a hemoglobin of ≥8.0 g/dL (≥5 mmol/L) as needed, and platelets of ≥50 x 10^9/L until 3 days before the hematology laboratory test, preceding lymphodepletion.** ~~and transfusion of platelets and administration of myeloid growth factor is permitted until 3 days before the hematology laboratory test preceding lymphodepletion.~~ Myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited.
9.2 Safety Evaluations	In clinical laboratory test subsection, updated “Blood urea nitrogen” to “Blood urea nitrogen/ urea” for countries outside of US.
Rationale: Clarification made to inclusion criteria to better define a regimen. A regimen is a line of therapy	
4.1 Inclusion criteria	Modification of inclusion criteria 4.1, 5, and 6 to replace the term “regimen” with “line of therapy”.

Applicable Section(s)	Description of Change(s)
Rationale: Contraception guidance revised in response to cyclophosphamide labeling.	
4.1 Inclusion criteria	Inclusion criterion #10: • The timeframe for which subjects must agree to practice a highly effective method of contraception has been updated from the time of signing the ICF until ~~at least 100 days~~ **1 year** after receiving a JNJ-68284528 infusion. • In addition to the highly effective method of contraception a man must also agree to use a barrier method of contraception from the time of signing the ICF until ~~at least 100 days~~ **1 year** after receiving a JNJ-68284528 infusion. • Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for ~~100 days~~ **1 year** after the last dose of study treatment.
4.2 Exclusion criteria	Exclusion criterion #20: • Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within ~~100 days~~ **1 year** after receiving study treatment. Exclusion criterion #21: • Plans to father a child while enrolled in this study or within ~~100 days~~ **1 year** after receiving study treatment.
Rationale: Clarification to safety language for consistency	
6.1.2 Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine) Dosing	To be consistent with the revisions to Section 6.1.2., text updated from: "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" to "**No signs of active infection. For subjects requiring systemic anti-microbial treatment or with temperature ≥38.0 Celsius within 7 days prior to the first dose of conditioning regimen, the investigator must receive approval to proceed from the sponsor**."
Rationale: The use of a catheter is no longer applicable	
6.1.2 Criteria for Conditioning (Cyclophosphamide and Fludarabine) Dosing	Deleted statement regarding construction of catheter.
Rationale: Modified guidance for dosing delays to ensure subject safety prior to JNJ-68284528 infusion	
6.1.3 Evaluation Prior to Administration of JNJ-68284528	<u>JNJ-68284528 Dosing Delays:</u> 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, constipation) occurs following the start of the conditioning regimen (see Section 6.1.2), the investigator should contact the sponsor prior to dosing.** Infusion of JNJ-68284528 must be delayed if any of the following events occur: • ~~Uncontrolled~~ **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 Celsius within 48 hours**

Applicable Section(s)	Description of Change(s)
	before JNJ-68284528 infusion, investigator must consult with the sponsor prior to dosing. • Grade ≥3 non-hematologic toxicities of the cyclophosphamide and fludarabine conditioning regimen (except for Grade 3 nausea, vomiting, diarrhea, or constipation). **Investigator must consult with the sponsor prior to dosing.**
Rationale: Added language to allow testing of tumor sampling in case of a report of second primary malignancies (SPM).	
6.3.8 Second Primary Malignancy; 9.1.6.3 Long-term Follow-up	Added sentence "**A tumor sample should be collected and DNA, RNA or protein analysis may be performed to investigate the presence of lentiviral elements".**
Rationale: Qualification made to prohibited therapy	
8.2 Prohibited Therapies	Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited **within the first 100 days after infusion of JNJ-68284528** (Section 6.1.2).
Rationale: Correction of errors	
9.1.6.1 Post-Infusion Period	Correction to temperature symbols for reporting fever (> updated to ≥).
Rationale: Clarification to the method of treatment response analysis	
9.6 Efficacy Evaluations	The following sentence was deleted: "Disease progression must be consistently documented across clinical study sites using the criteria in Attachment 1. ~~The sponsor will use a validated computer algorithm to analyze response to treatment~~."
Rationale: Clarification to biomarker evaluation language	
9.6.3 Bone Marrow Examination	Bone marrow aspirate or biopsy (acceptable if aspirate is not possible) will be performed for clinical assessments. **Bone marrow aspirate will be performed for** ~~and~~ biomarker evaluations.
Rationale: Clarification to Patient-Reported Outcome Assessments (Phase 2 only)	
9.8 Patient-Reported Outcome Assessments (Phase 2 only)	Language updated as follows: "Full training documentation will be provided to site coordinators before the start of data collection. PRO assessments **will be conducted beyond disease progression or subsequent anticancer therapy**. If no site visits are scheduled for additional disease evaluations, **subjects will have the option of completing the PRO assessments after disease progression or subsequent anticancer therapy via telephone**."
Rationale: Updates to the efficacy analysis	
3.1 Overview of Study Design	The sponsor will establish a data cutoff date for clinical study report (CSR) analyses. The **first** ~~primary~~ analysis will be conducted approximately 6 months after the last subject received their initial dose of JNJ-68284528. **An update of the analysis will be provided at approximately 9-12 months after the last subject received their initial dose of JNJ-68284528 and at the end of the study which is defined as 2 years after the last subject has received their initial dose of JNJ-68284528 (Section 17.9.1).** Subjects will be followed for survival after the clinical cutoff for the primary CSR. The data cutoff will be communicated to the sites. ~~Study completion/end of study will be defined as no later than 2 years after the last subject has received their initial dose of JNJ-68284528 (Section 17.9.1). However, the~~ **The** sponsor will monitor subjects treated with JNJ-68284528 for 15 years for

Applicable Section(s)	Description of Change(s)
	complications of lentiviral integration, including second primary malignancies on a long-term follow-up study.
11.3 Efficacy Analyses	An efficacy analyses end point definition was updated as follows: "Overall response rate (ORR) is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria.[10,11,31] ~~Response to treatment will be analyzed by a validated computerized algorithm.~~[9,29] The following sentence as added to the section: "**For efficacy, assessment by the IRC will be used as primary."** The timing of the primary analysis was updated as follows: "The **first** analysis for the primary endpoint, ORR (PR or better), will be conducted approximately at 6 months after the last subject has received his or her initial dose of JNJ-68284528, and will be based on the mITT analysis set. The response rate and its 95% exact confidence interval (CI) will be calculated based on binomial distribution, and the null hypothesis will be rejected if the lower bound of the confidence interval exceeds 30%. Analysis of VGPR or better response rate, DOR, PFS, and OS will be conducted at the same cutoff as the ORR, and an update of these endpoints will be provided **at approximately 9 -12 months after last subject has received his or her initial dose of JNJ-68284528 and** at the end of the study, which is defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528. Additional safety data will be collected in a long-term follow-up study." Details added regarding the type of analysis are as follows: "**A sensitivity analysis of ORR will be performed based on the subjects in the mITT analysis set who received the JNJ-68284528 product that met all of the pre-specified release criteria.** **The agreement on ORR between the determination by the IRC and the assessment by a validated computerized algorithm developed by the sponsor will be evaluated using the kappa statistic and 95% CI will also be provided."**
Rationale: Adverse event template language incorporated for clarity	
12.1.3 Severity Criteria	The following statement was added: **Any adverse event or serious adverse event not listed in the NCI CTCAE Version 5.0 will be graded according to investigator clinical judgment by using the standard grades as follows:**
Rationale: Clarification regarding reporting of Adverse Event of Special Interest	
12.3.3 Adverse Events of Special Interest	Change made to the reporting requirements for adverse events of special interest. Adverse events of special interest "**should be reported to the sponsor in a timely manner"** replaces text stating "~~will be reported to the sponsor within 24 hours of awareness, and may require enhanced data collection~~".
Rationale: Addition to list of study-specific materials	
15 Study-Specific Materials	Added "Thermal printer and barcode scanner (for sites utilizing Vineti chain of custody/chain of identity software in Phase 2)" to end of preexisting list.
Rationale: Added an attachment for anticipated adverse events to fulfil the ICSR requirement from FDA.	

Applicable Section(s)	Description of Change(s)
Attachment 14: Anticipated Adverse Events	The attachment of anticipated adverse event was added to specify the definition, reporting time of anticipated adverse events, etc.
Rationale: Updates to references	
T&E Schedule (Table 2 and Table 12); 3.3 Dose De-escalation; 9.2 Safety Evaluations; 12.1.3 Severity Criteria; Attachment 11; Attachment 13	Update to reference for ASBMT consensus grading for CRS (Lee 2018 changed to Lee 2019).
References	Reference number 9 no longer cited: "~~Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375:1319-1331.~~" Reference number 22 was updated to: "Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. **Biol Blood Marrow Transplant.2019 Apr;25(4):625-638**". Reference number 29 no longer cited: "~~Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375:754-766.~~"
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

<u>Amendment 2</u> (11 March 2019)

The overall reason for the amendment: The overall reason for the amendment is to expand the number of subjects enrolled in the Phase 1b portion of the study, update the CRS and neurotoxicity management guidelines, update the CRS and neurotoxicity grading system, and add clarity to targeted sections of the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Revisions made to allow for an expansion in the number of subjects enrolled in the Phase 1b portion of the study	
Synopsis Overview of Study Design and Dosage and Administration; 3.1. Overview of Study Design; 3.4. Dose Escalation; 11.2. Sample Size Determination	The number of subjects enrolled in the Phase 1b portion of the study was expanded from "approximately 24" to "at least 24 and up to 50 subjects".

Applicable Section(s)	Description of Change(s)
Synopsis Dosage and Administration; 3.1. Overview of Study Design	The following text was also added " Confirmation of the RP2D will be based on review of data from at least 24 subjects who were administered JNJ-68284528. Additional subjects (up to 50) will be enrolled in the Phase 1b portion of the study to generate supplemental safety and efficacy data at the RP2D."
11.2. Sample Size Determination	Addition of Table 11 to describe the probabilities of observing the adverse events under the assumed true incidence rates of the adverse events with the larger sample sizes.
Rationale: Revisions to the CRS toxicity management recommendations and to incorporate ASBMT consensus grading system for CRS	
T&E Schedule (Table 1 and Table 12); 3.3. Dose De-escalation; 9.2. Safety Evaluations; 12.1.3. Safety Criteria Attachment 11	Added that CRS will be evaluated according to the new ASBMT consensus grading (Lee et al 2018) per new Attachment 11.
6.3.1. Management of Cytokine Release Syndrome	Revisions to the guidelines for management of CRS in Table 8 to replace CRS grade with presenting symptoms. Addition of precautionary language in case of severe unresponsive CRS to evaluate for HLH/MAS and consider additional interventions. Revised section title to remove "prevention" to more accurately reflect that the section content is for management of CRS Added additional language around interventions (tocilizumab and other monoclonal antibodies targeting cytokines) for CRS.
Attachment 2	Deleted contents of Attachment 2 as CRS grading has been replaced with ASBMT consensus grading
Rationale: Revisions to update the neurotoxicity management recommendations, incorporate ASBMT consensus grading for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and include Immune Effector Cell-associated Encephalopathy (ICE) Tool.	
T&E Schedule (Table 1 and Table 12); 3.3. Dose De-escalation; 9.2. Safety Evaluations; 12.1.3. Safety Criteria; Attachment 13	Added that CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according to the ASBMT consensus grading (Attachment 13).
T&E Schedule (Table 1 and Table 12)	Assessment of ICE test added to Time and Events Schedules Table 1 and Table 11.

Applicable Section(s)	Description of Change(s)
1.7. Potential Safety Risks and Mitigation Strategies	Replaced "neurological adverse events" entry in potential risks table with Neurological adverse events including CAR-T cell-related neurotoxicity (eg, immune effector cell-associated neurotoxicity syndrome [ICANS]) Added guidance that hospitalization is required for Grade ≥2 CAR-T cell-related neurotoxicity (eg, ICANS).
6.1.4. JNJ-68284528 Administration; 6.3.2. Neurological Adverse Events	Specified that hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS) not all neurotoxicity
6.3.2. Neurological Adverse Events; 9.2. Safety Evaluations; Attachment 12	Revised section to include definition of ICANS and use of ICE assessment tool. Added a description of the neurologic examination and ICE tool to Section 9.2. Added that at first signs of seizures or raised intracranial pressure/cerebral edema that subjects should be transferred to the ICU and treated according to institutional guidelines. Revised Table 9; removed grading assessment and replaced with presenting symptoms. Management is determined by the most severe event not attributable to any other cause. Added Table 10 (Guidelines for the management of raised ICP/ cerebral edema). ICE tool added as Attachment 12
Rationale: Changes made to safety criteria for clarity	
T&E Schedule (Table 1 and Table 12)	Changed "eligibility criteria (predose)" to "safety criteria" (added as separate section) to more accurately reflect the assessment.
3.1. Overview of Study Design; 6.1.1. Criteria for Apheresis	Eligibility criteria required before apheresis now referred to as "safety criteria". Addition of Section 6.1.1 to define the safety criteria to be met before apheresis of the subject.
6.1.2. Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine) Dosing	Defined cyclophosphamide and fludarabine as conditioning regimen in the title for clarity and replaced "cyclophosphamide and fludarabine" with "conditioning regimen" for consistency throughout Section 6.1.2. Revised criterion for corticosteroids to align with changes to exclusion criterion #7. Added that the sponsor should be called for approval if a subject receives corticosteroids at a dose >10mg per day in the week prior to the start of the conditioning regimen. Added that myeloid growth factors (but not pegylated myeloid growth factors) are permitted up to 1 day prior to the start of the conditioning regimen. Added cross reference exclusion criterion #4 for washout of bridging therapy.
Rationale: Revisions made to biomarker sample collections in response to emerging data	

Applicable Section(s)	Description of Change(s)
T&E Schedule (Table 2 and Table 13)	Additional collections of immunophenotyping (whole blood) samples on Days 1 (pre-dose) ,2, 3, 7, 10, 42, 78, and every 4 weeks after Day 100 up to 1 year. Removed assessment on Day 184. Added collection for CyTOF (aspirate) (bone marrow) prior to the first dose of the conditioning regimen. Added sample collection for cytokine profiling on Day 2. Split "Prior to Subsequent Therapy or Study Completion, Whichever is First" column into "At PD" and "At Study Completion for Subjects without PD" Footnote 'c' now only applies to PK CAR positive T-cell, PK transgene levels, and ADA samples to state that additional samples are to be collected at CRS or neurotoxicity event Grade ≥2. Added additional CyTOF/PBMC/plasma (whole blood) collections on Day 7 and Day 10.
T&E Schedule (Table 2 and Table 13); 9.3.1. Evaluations	Collection of additional cytokine profiling samples at onset of CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) and then every 24 hours until event is stabilized or resolving at which point additional samples are collected at 24, 48, and 72 hours or as clinically indicated. Addition of footnote 'g' (for cytokine profiling) to Table 2 and Table 13
Rationale: Revisions made for clarity or consistency	
T&E Schedule (Table 1 and Table 12)	Removed the ≤7 day window from the disease characteristics assessment to be performed prior to the first dose of conditioning regimen Collection of serum β2-microglobulin moved from screening to prior to first dose of conditioning regimen to be consistent with collection times of other disease evaluations. Additional collection of quantitative immunoglobulins added prior to first dose of conditioning regimen. Added "and core biopsy" to "bone marrow aspirate" row title under other disease evaluations. Replaced "immunofluorescence" with "flow cytometry" as methodology to assess sCR. Revised footnote 'k' (Table 1) and 'j' (Table 12) to state that bone marrow morphology is to be assessed locally at all time points.
T&E Schedule (Table 1 and Table 12); 9.1.6.1. Post-infusion Period	Revised footnote 'h' (Table 1) and 'g' (Table 12) to indicate that subjects should record 2 temperatures including their maximum daily temperature in the diary. Clarified in footnote that temperature will be checked at least twice a day **up to Day 28**. Deleted reference to temperature collection from Section 9.1.4.1 due to redundancy.
T&E Schedule (Table 1 and Table 12); 3.1. Overview of Study Design; 3.5. Safety Evaluation Team; 6.1.4. JNJ-68284528 Administration	Added clarification that the requirement for hospitalization and **local stay** will be evaluated by the SET.

Applicable Section(s)	Description of Change(s)
T&E Schedule (Table 1); 6.1.1. Criteria for Apheresis	Screening assessments that should be collected for subjects who undergo a second apheresis were identified. Included as footnote 'a' in T&E. Clarified in footnote 'a' that the ICF must be signed before any study-related procedures are performed and remains in effect if the screening evaluation is not performed within the 28 day screening phase.
1.4. JNJ-68284528	Revised the following statement to be consistent with emerging data. "The novel design ~~of the BCMA targeting domain facilitates binding of 2 epitopes~~ **features dual targeting domains** on BCMA,…"
2.1. Objectives and Endpoints; 9.4 Biomarker Evaluations	Revisions to the secondary endpoint of objective to characterize the pharmacokinetics and pharmacodynamics of JNJ-68284528 and exploratory endpoint of objective to explore whether the infused CAR-positive T cell subsets impact pharmacodynamics, safety, and clinical activity of JNJ-68284528. Added $CD25^{+}$ to list of biomarker evaluations.
3.1. Overview of Study Design; 3.5. Safety Evaluation Team	Text added to clarify the SET meeting interval in Section 3.5. Added to Section 3.1, a cross reference to details regarding when SET meetings are to occur.
3.1. Overview of Study Design	Clarify that clinical data will be shared with the relevant health authorities **before administration of JNJ-68284528 to subjects** in the Phase 2 portion of the study
3.3. Dose De-escalation	Clarified that DLTs are those associated with JNJ-68284528
4.1. Inclusion Criteria	Added to criterion #3 that local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements
4.2. Exclusion Criteria	Revised criterion (#7) on prior corticosteroid use from daily dose to cumulative dose for clarity. Revised criterion (#3) to change to no known active disease present for ≥2 years (change from ≥3 years) to be more consistent with ASCO guidance.
6.1. Study Treatment Administration	Added that sponsor approval must be obtained to change the conditioning regimen schedule. Removed, due to redundancy, statement regarding re-assessment of eligibility criteria if cyclophosphamide and fludarabine is delayed ≥10 weeks.
6.3.7. Hypersensitivity Reactions	Added for consistency with Table 3 and the Investigator's Brochure
6.3.8. Second Primary Malignancy	Added for consistency with Table 3 and the Investigator's Brochure
8.1. Permitted Medications	Revised language around bisphosphonate recommendation: Bisphosphonates ~~should~~ **may** be initiated (if not already being administered) unless contraindicated within 1 week prior to the first dose of study treatment and continued until disease progression is established. Added therapies intended to treat CAR-T cell-related toxicity (ie, CRS). Added that myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen to be consistent with Section 6.1.2.

Applicable Section(s)	Description of Change(s)
8.2. Prohibited Therapies	Removed "Routine transfusions should not be given on the day of JNJ-68284528 administration" from list of medications prohibited during the study (ie, routine transfusions are allowed on the day of JNJ-68284528 infusion based on institutional practice). Added as an exception to prohibited therapies "part of therapy intended to treat CAR-T cell-related toxicity". Added guidance that based on the clinical judgment low-dose aspirin may be continued for thromboprophylaxis. Added that Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited to be consistent with Section 6.1.2.
9.4.2. Minimal Residual Disease	Revised the following statement "Baseline bone marrow aspirates will be used to define the myeloma clones, and post-treatment samples will be used to evaluate MRD ~~negativity in those subjects who experience at lease a CR~~. as MRD testing will be performed on all Day 28 samples, not just for subjects in which a CR has been declared.
9.6.1. Myeloma Protein Measurements in Serum and Urine	Revisions for consistency with the guidance provided in the Time and Events Schedule., Cross references added to Table 1 and Table 12.
10.3. Withdrawal from the Study	For consistency with the addition of the guidance added for risk/benefit consideration in the event that a JNJ-68284528 product does not meet pre-specified release criteria (Section 6.1), the withdrawal from study language was modified to state "**Failure to manufacture** JNJ-68284528 after 2 apheresis attempts".
12.3.1. All Adverse Events	Removal of terms for adverse events of special interest; now refers to Section 12.3.3 for complete information.
12.3.3. Adverse Events of Special Interest	Edits made for clarity and consistency with other sections of the protocol.
Attachment 6	Modification to the calculation for estimating glomerular filtration rate to standardize the calculation and remove reference to online tools.
Rationale: Deletions made due to redundancy	
4. Subject Population	Removed "NOTE" at the end of the section. As redundant with addition of Section 6.1.1
9.1.4. Cyclophosphamide and Fludarabine Conditioning Regimen 9.1.5. JNJ-68284528 Administration	Deleted text and added cross reference as content is described elsewhere in the protocol
9.1.6.1. Post-Infusion Period	Deleted text that is repetitive with other sections of the protocol, cross referenced to Table 6.

Applicable Section(s)	Description of Change(s)
Rationale: Correction made to eligibility criteria – documentation of disease progression	
4.1. Inclusion Criteria	Criterion #6 revised to state "Subject must have documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or within 12 months of their last regimen (Attachment 1). Confirmation may be from either central or local testing. Also, subjects with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of treatment afterwards.".
Rationale: Change made to exclude subjects with prior history of CNS multiple myeloma because of suspected increased risk of neurologic toxicity	
4.2. Exclusion Criteria	Revised criterion #9 to state "Known active, **or prior history of** central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma."
Rationale: Changes made to incorporate revised HBV and HCV eligibility requirements to add revised HBV monitoring criteria	
T&E schedule (Table 1 and Table 12)	Added that events of HBV reactivations should be reported during the first year post-dosing of LCAR-B38M CAR-T cells. Revised footnotes 'f' (Table 1) and 'e' (Table 12).
1.7. Potential Safety Risks and Mitigation Strategies	Added cross reference to hepatitis B virus screening guide in Attachment 8.
4.2. Exclusion Criteria; 9.2. Safety Evaluations	Removed reference to ASCO guidelines from criterion #14 as it does not represent guidance provided in Attachment 8.
Attachment 8	Revised to include guideline for prevention of HBV reactivation specific for subjects receiving immunosuppressive therapy
4.2. Exclusion Criteria	Revised criterion #15 to include "HCV-RNA quantitation positive" and added guidance for subjects with a known history of HCV infection.
6.3.6. Infections	Added warning that HBV reactivation may occur in subjects with drugs directed against B cells.
9.2. Safety Evaluations	Added HBV monitoring recommendations.
12.3.1. All Adverse Events	Added that events of HBV reactivations will be reported during the first year post-dosing of JNJ-68284528.
Attachment 8	Revised hepatitis screening guide for determining subject eligibility.
Rationale: Revision to the timing of when conditioning regimen should be re-administered upon resolution of active infection or Grade ≥3 non-hematologic toxicities of the conditioning regimen, to allow for flexibility	
6.1.3. Evaluation Prior to Administration of JNJ-68284528	Updated that the conditioning regimen should be re-administered if resolution of infection or Grade ≥3 non-hematologic toxicities of the conditioning regimen to Grade ≤1 takes more than 14 days (changed from 7 days).
Rationale: Correction to serum calcium corrected for albumin; removal of language that is no longer relevant to IMWG.	

Applicable Section(s)	Description of Change(s)
9.6.2. Serum Calcium Corrected for Albumin	Deleted the following: Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. In this study, free ionized calcium levels greater than the ULN indicate hypercalcemia.
Rationale: Additional information provided regarding subject identifiers to be included with infusion bag	
14.2. Packaging 16.2.4. Privacy of Personal Data 17.3. Subject Identification, Enrollment, and Screening Logs	For tracking and traceability of apheresis material, subject name and date of birth will be collected, as allowed by local regulations, will be collected to ensure chain of identity of the JNJ-68284528 for each subject.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (20 August 2018)

The overall reason for the amendment: The overall reason for the amendment is to collect additional safety information and add clarity to targeted sections of the protocol

Applicable Section(s)	Description of Change(s)
Rationale: Revisions made to collect additional safety information and provide an additional inclusion criterion (lower limit of lymphocyte count) that may increase potential for successful manufacture of JNJ-68284528.	
T&E Schedule (Table 1 and Table 10)	Changed window for hematology assessment on day of apheresis from ≤72 hour window to "prior to apheresis (same day)" Added hematology, chemistry, and vital signs assessments on Day 21 (to correspond with PK assessments added on Day 21).
T&E Schedule (Table 1 and Table 10); 6.1.1. Criteria for Cyclophosphamide and Fludarabine Dosing	Language added to indicate that subjects who receive bridging therapy that includes agents with known cardiac toxicity, assessment of cardiac function should be repeated within 7 days prior to the start of the conditioning regimen.
4.1. Inclusion Criteria (criterion #8); 6.1.1. Criteria for Cyclophosphamide and Fludarabine Dosing	Added lymphocyte count of $\geq 0.3 \times 10^9$/L to laboratory value criteria at screening to allow for successful apheresis.
6.1.1. Criteria for Cyclophosphamide and Fludarabine Dosing	On the day of the first dose of the conditioning regimen, subjects should be evaluated for the presence of an indwelling catheter.

Applicable Section(s)	Description of Change(s)
Rationale: Changed the baseline for efficacy assessment to more accurately reflect response to treatment	
T&E Schedule (Table 1 and Table 10)	Samples for serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) assessments will be collected to establish baseline disease characteristics prior to the first dose of the conditioning regimen.
T&E Schedule (Table 1 and Table 10); 9.6.5. Documentation of Extramedullary Plasmacytomas	Revised assessment for extramedullary plasmacytomas to be performed ≤14 days prior to the first day of the conditioning regimen instead of at screening.
Rationale: Revision made to the window in the post-treatment period to prevent out of window visits during the extended follow-up	
T&E Schedule (Table 1)	Window for post treatment visits (every 28 days after Day 100) changed from ±2 days to ±7 days
Rationale: Added infectious disease testing at apheresis to comply with local and regional donor requirements	
T&E Schedule (Table 1 and Table 10); 9.2. Study Evaluations	Added testing at the time of apheresis for HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations
Rationale: Patient reported outcomes **(**PRO) assessments and Qualitative Interviews added to obtain information on the benefit of subject's perceived health-related quality of life in the Phase 2 portion of the study	
T&E Schedule (Table 1); 2.1. Objectives and Endpoints; 9.8. Patient-Reported Outcomes; 11.8. Patient-Reported Outcome Assessments	Added the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30, EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and single items from EORTC QLQ-MY20 assessments to the Phase 2 part of the study; included as secondary endpoints.
T&E Schedule (Table 1); 2.1. Objectives and Endpoints; 9.9. Qualitative Interviews	Subjects enrolled in the Phase 2 part of the study will be given the option to participate in qualitative patient experience interviews. Exploratory objective added for qualitative interviews.
Attachment 10 (Patient Reported Outcome Measures)	Added sample PRO assessment documents
Rationale: Correction of errors	
T&E Schedule (Table 2 and Table 11)	Correction to collection for minimal residual disease (MRD) assessments in subjects with CR will occur "…up to ~~and including~~ disease progression."
T&E Schedule (Table 10)	Addition of Day 100X ECOG assessment added to be consistent with main T&E (Table 1).
Synopsis (Statistical Methods); 11.2. Sample Size Determination	Correction to the following statement: "With 60 subjects, the study will have 90% power to declare the ORR is **higher than** 30% ~~or higher~~ at the 1-sided significance level of 0.025."

Applicable Section(s)	Description of Change(s)
2.1. Objectives and Endpoints	PFS and OS added to exploratory endpoint "Correlation between MRD negative rate and duration of response, PFS, and OS", to align with corresponding exploratory objective.
3.1. Overview of Study Design	Correction to the timing of bridging therapy "(anti-plasma cell directed treatment between ~~screening~~ **apheresis** and ~~the administration of JNJ-68284528~~ **first dose of the conditioning regimen**)" consistent with what is presented in the diagram of the study design (Figure 2).
Rationale: Adjustments made to timing of pharmacokinetic and biomarker sample collections to reduce patient burden	
T&E Schedule (Table 1, Table 2, Table 10, and Table 11)	Reduced the number of bone marrow samples to be collected prior to JNJ-68284528 infusion. A single collection pre-conditioning regimen was added in place of a collection at screening and pre-dose. Collection of blood samples adjusted to align with changes in bone marrow collections. Reduced and/or change collection time points for whole blood or serum collections for immunophenotyping, CyTOF, and cytokine profiling.
Rationale: Modifications made for clarity or consistency	
T&E Schedule (Table 1 and Table 10)	Window for post-treatment assessments changed from ±2 days to ±7 days. Clarified that serum M-protein electrophoresis, urine protein electrophoresis, serum calcium corrected for albumin and serum FLC and serum/urine immunofixation will occur prior to the first dose of conditioning regimen; added ≤7 days.
T&E Schedule (Table 2 and Table 11)	To be consistent with guidance in Section 9.3.1, added footnote 'b' to ADA sample (footnote b) to indicate ADA should be collected if CRS or neurotoxicity Grade ≥2 is reported. Added footnote 'e' to CyTOF (bone marrow) and CyTOF/PBMC (whole blood) Moved placement of footnote 'd' for flow to avoid giving the impression that a sample was to be collected at end of study.
Synopsis	Revised the subject population description, for clarity, to include additional information from the inclusion criteria in Section 4.1.
Synopsis; 3.5. Safety Evaluation Team; 6.1. Study Treatment Administration	The term 'staggered enrollment' was changed to 'staggered dosing' to more correctly describe the observational period between administration of JNJ-68284528 to the first and second, second and third, and third and fourth subjects. Added that administration of the conditioning regimen and dosing with JNJ-68284528 will be paused between dosing of the sixth subject and conclusion of the first Safety Evaluation Team (SET) meeting.
T&E Schedule (Table 2 and Table 11)	Pharmacokinetic (PK) (chimeric antigen receptor [CAR]-positive T cell assessment) to be performed on bone marrow samples collected to assess PK CAR transgene levels. Row added to clarify the timing of these assessments.
3.1. Overview of Study Design	Added that subjects who receive retreatment will be monitored in the long-term follow-up study for 15 years **from the time of last treatment**.
4.1. Inclusion Criteria (criterion #4)	Added reference to definition of refractory multiple myeloma (IMWG consensus criteria).

Applicable Section(s)	Description of Change(s)
4.2. Exclusion Criteria (criterion #15)	Criterion modified as follows: "Hepatitis C (anti-hepatitis C virus [HCV] antibody positive ~~or HCV RNA quantitation positive~~) or known to have a history of hepatitis C. If **antibody** positive, further testing of quantitative levels to rule out positivity is required."
6.1. Study Treatment Administration	Clarified that if conditioning regimen must be delayed ≥10 weeks after apheresis "the subject must undergo full ~~rescreening~~ **assessment of eligibility criteria** prior to dosing **(with the exception that a repeat bone marrow collection and re-signing of the ICF are not required)**.
6.2. Pre-infusion Supportive Therapy	Clarified in Table 7 that antihistamine and antipyretic refer to diphenhydramine **or equivalent** and acetaminophen **or equivalent**, respectively.
9.1.1. Overview	Revised approximate blood volume drawn per subject (up to 2 years post treatment) to align with revisions in sample collections.
9.1.3. Apheresis	Clarification that the target number of PBMCs collected at apheresis is 6 x 10^9 PBMCs with a range of 2 to 20 x 10^9 PBMCs. The volume is no longer specified.
9.4. Biomarker Evaluations; 9.4.1. Pharmacodynamic/ Predictive Markers	Revisions made to clarify and support the biomarker evaluations to be conducted.
Rationale: Revisions to PK and Immunogenicity sections to align with assay requirements and added sampling on Day 21 to expand data collection during the first 3 weeks	
T&E Schedule (Table 2 and Table 11)	PK CAR positive T cell, CAR transgene, and soluble B cell maturation antigen (BCMA) assessments added on Day 21. Immunophenotyping, CyTOF/PBMC/plasma (whole blood), and cytokine profiling assessments added on Day 21.
T&E Schedule (Table 1 and Table 10)	Assessments for hematology, chemistry, and vital signs added on Day 21 to correspond to the visit added for PK collections.
9.3.1. Evaluations	Revisions made for clarity. Removed detail that is more appropriate for the lab manual.
9.3.2. Analytical Procedures; 9.3.4. Immunogenicity Assessment/Antibodies to JNJ-68284528	Removed statements indicating that immune response analyses (anti-drug antibody [ADA]) may be conducted on PK samples for accuracy, ADA cannot be performed on PK samples collected in this study, and are noted separately in the time and events schedules.
Rationale: Revision made to allow for red blood cell transfusion after screening maintain hemoglobin levels.	
4.1. Inclusion Criteria (criterion #8)	Added a footnote to the clinical laboratory values table stating: "For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL."
6.1.1. Criteria for Cyclophosphamide and Fludarabine Dosing	Revision made to first bulleted statement to be consistent with RBC transfusion allowance added to the inclusion criteria. "Clinical laboratory values required for enrollment (Section 4.1), with the following exceptions: lymphocyte count of ≥0.3 x 10^9/L and transfusion of ~~**red blood cells or**~~ platelets and administration of myeloid growth factor is permitted until 3 days before the hematology laboratory test."
Rationale: Guidance added for risk/benefit consideration in the event that a JNJ-68284528 product does not meet pre-specified release criteria.	

Applicable Section(s)	Description of Change(s)
6.1. Study Treatment Administration	Guidance added that the sponsor will evaluate the risk/benefit for administration of a JNJ-68284528 product that did not meet pre-specified release criteria and determine if the supply of the product to the treating physician could be considered.
Rationale: Revision to allow for rescreening of subjects who do not meet all eligibility criteria	
9.1.2. Screening Phase	Revised protocol to allow subjects who did not meet all inclusion criteria or who met an exclusion criterion to be rescreened once, upon written approval from the sponsor.
Rationale: Revisions made for consistency with the current IMWG criteria	
9.6.5. Documentation of Extramedullary Plasmacytomas; Attachment 1.	Revised to be consistent with IMWG criteria as presented in Kumar 2016.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma

JNJ-68284528 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. 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 express an identical CAR protein. The JNJ-68284528 drug product will be produced using a modified manufacturing and scale-up processes. Results from the Legend-2 study indicate that LCAR-B38M CAR-T cells have significant anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

PRIMARY OBJECTIVES

Objectives	Endpoints
Primary	
• To characterize the safety of JNJ-68284528 and establish the recommended Phase 2 dose (RP2D) (Phase 1b)	• Incidence and severity of adverse events
• To evaluate the efficacy of JNJ-68284528 (Phase 2)	• Overall response rate (ORR) (partial response [PR] or better) as defined by the International Myeloma Working Group (IMWG) response criteria as assessed by the Independent Review Committee (IRC)

STUDY HYPOTHESIS

Treatment with JNJ-68284528 will demonstrate acceptable safety and will have significant anti-myeloma activity (ie, the lower limit of two-sided 95% confidence interval [CI] for ORR, as assessed by the IRC, is greater than 30%) at the targeted recommended Phase 2 dose (RP2D) level in subjects with advanced relapsed or refractory multiple myeloma.

OVERVIEW OF STUDY DESIGN

This is a Phase 1b-2, open-label, multicenter study to evaluate the safety and efficacy of JNJ-68284528 in adult subjects with relapsed or refractory multiple myeloma. At least 24 and up to approximately 50 subjects will be enrolled in the Phase 1b portion of the study in which the safety and dose of JNJ-68284528, informed by the first-in-human study with LCAR-B38M CAR-T cells (Legend-2), will be established. A staggered dosing strategy will be initially applied. The planned sample size for the Phase 2 portion of the study will be approximately 60 subjects.

Enrolled subjects will undergo apheresis to acquire peripheral blood mononuclear cells (PBMC). JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. After JNJ-68284528 production and product release, subjects will receive a conditioning regimen of cyclophosphamide and fludarabine. JNJ-68284528 will be administered 5 days to 7 days after the start of the conditioning regimen. Subjects who receive an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments. Study completion is defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528.

SUBJECT POPULATION

Eligible subjects are ≥18 years of age and have a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria and an Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0 or 1.

Subjects must satisfy all of the following criteria: 1) Measurable disease at screening as defined by any of the following: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio; 2) Received at least 3 prior lines of therapy or are double refractory to a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen), subjects will have undergone at least 1 complete cycle of treatment for each regimen (unless progressive disease [PD] was the best response); 3) Received a PI, an IMiD, and anti-CD38 antibody (prior exposure can be from different monotherapy or combination regimens); and 4) Documented disease progression during, or within 12 months, of their most recent anti-myeloma therapy.

DOSAGE AND ADMINISTRATION

A conditioning regimen consisting of cyclophosphamide 300 mg/m^2 intravenously (IV) daily and fludarabine 30 mg/m^2 (IV) daily for 3 days will be administered. JNJ-68284528 IV infusion will take place 5 to 7 days after the start of the conditioning regimen. In the Phase 1b portion of the study, 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). In the event of excess toxicity, a dose de-escalation to dose level -1 (0.3 x 10^6 CAR-positive viable T cells/kg [range: 0.1-0.5 x 10^6 CAR-positive viable T cells/kg]) for new subjects will occur. Additionally, a dose escalation to dose level 2 (target dose not to exceed a 3-fold dose escalation [2.25 x 10^6 CAR-positive viable T cells/kg, range: ± 30% of the target dose, depending on target dose chosen for dose level 2]) will be considered if specified safety criteria are met. Confirmation of the RP2D will be based on review of data from at least 24 subjects who were administered JNJ-68284528 in the Phase 1b portion of the study. Additional subjects (up to approximately 50) will be enrolled in the Phase 1b portion of the study to generate supplemental safety and efficacy data at the RP2D.

EVALUATIONS

Safety will be evaluated by adverse events, laboratory test results, vital sign measurements, physical examination findings, and assessment of ECOG performance status. Disease status will be evaluated by an IRC according to clinical judgement guided by the IMWG consensus recommendations for multiple myeloma. Blood and serum samples will be collected for assessment of JNJ-68284528 pharmacokinetics, immunogenicity (antibodies to JNJ-68284528), and predictive biomarkers of response or resistance to JNJ-68284528.

STATISTICAL METHODS

No formal statistical hypothesis testing will be performed for the Phase 1b portion of the study.

The sample size for the Phase 2 portion of the study assumes that the overall response rate for JNJ-68284528 will be 50%. With 60 subjects, the study will have 90% power to declare the ORR is higher than 30% at the 1-sided significance level of 0.025.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**									**Post-treatment (Day 101 and up to Study Completion)[b]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 28 days after day 100)[c] (± 7 days)**
Screening Assessments															
Informed consent[a]	X Before the 1st study related procedure														
Eligibility criteria	X														
Demography, Medical History	X														
Disease Characteristics[d]			X (prior to start of conditioning regimen)												
ECOG	X		Prior to 1st dose only	X								X		X	
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated												
Height	X														
12-lead ECG	X											X			
Echocardiogram or MUGA scan	X (≤8 weeks of apheresis)		For subjects who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), assessment of cardiac function should be repeated after completion of bridging therapy and prior to the start of the conditioning regimen, then again as clinically indicated if the subject develops signs/symptoms of heart failure												
ICE neurological test				X (≤24 hours prior to infusion)[q]	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.										

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [a]									**Post-treatment (Day 101 and up to Study Completion)** [b]
	≤28 days prior to apheresis [a]	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)** [b]	**(every 28 days after day 100)** [c] **(± 7 days)**
Handwriting sample				X (≤24 hours prior to infusion)[q]	X	X	X	X	X	X (also on Day 35)	X	X	X	X	up to Day 184
Safety Criteria (prior to apheresis and conditioning regimens)														
Safety criteria (See Section 6.1)		X (See Section 6.1.1)	≤72 hours of the 1st dose only (See Section 6.1.2)	X (See section 6.1.3)										
Laboratory Assessments (See Section 9.2)														
Hematology [e]	X	X (within 24 hours prior to apheresis)	Prior to 1st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	
Chemistry [e]	X	X (≤72 hour window)	Prior to 1st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	
Serology [f]	X														
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X			As clinically indicated for subjects who have fever or other signs of potential CRS										
Urinalysis	X	As clinically indicated												
Serum Pregnancy test (in subjects with childbearing potential)	X	X (≤72 hour window)	Prior to 1st dose only	As clinically indicated										

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**										**Post-treatment (Day 101 and up to Study Completion)[b]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 28 days after day 100)[c] (± 7 days)**
Infectious Disease Testing[n]	X (within 60 days of apheresis, as applicable per local regulations)														
Study Intervention Administration															
Weight	X	X (for JNJ-68284528 dose calculation)	Prior to 1st dose only	X											
Vital signs, including oxygen saturation	X	X	X	X[g]	X	X	X	X	X	X		X			
Temperature				Measure at least twice a day[h]											
Apheresis		X													
Cyclophosphamide and fludarabine			X												
Pre-infusion medication (see Section 6.2 for requirements prior to dosing with JNJ-68284528)				X											
JNJ-68284528 (See SIPPM and IPPI for administration of JNJ-68284528)				X[e]											

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [a]									Post-treatment (Day 101 and up to Study Completion) [b]
	≤28 days prior to apheresis [a]	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) [b]	(every 28 days after day 100)[c] (± 7 days)
Serum and Urine Disease Evaluations (See Section 9.6 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory.[s] Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.). Subjects with disease progression who receive retreatment with JNJ-68284528 (Table 12) must continue with disease evaluation visits.															
Serum β2-microglobulin			X (prior to first dose of conditioning regimen [≤7 days])												
Quantitative Immunoglobulins	X[i]		X (prior to first dose of conditioning regimen [≤7 days])[i]							X		X	X	X	X
Serum M-protein quantitation by electrophoresis	X		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
24-hour urine protein electrophoresis sample	X[j]		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum calcium corrected for albumin	X		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum FLC and serum/urine immunofixation	X		Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (≤7 days) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed												
Other Disease Evaluations															
Bone marrow aspirate and core biopsy [k]			X (prior to first dose of conditioning regimen [≤7 days])	To confirm CR, sCR, and at disease progression (immunohistochemistry or flow cytometry). See Table 2 for additional bone marrow collection for research.											
Skeletal Survey [l]	X		As clinically indicated to assess for disease progression												

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [a]									**Post-treatment (Day 101 and up to Study Completion)** [b]
	≤28 days prior to apheresis [a]	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)** [b]	**(every 28 days after day 100)** [c] **(± 7 days)**
Assess extramedullary Plasmacytomas [m]			X (≤14 days prior to first dose of conditioning regimen)	Measurable sites Day 28, Day 56, Day 78, Day 100 then every 4 weeks for physical examination (if applicable) and Day 78 and Day 156 then every 12 weeks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others).										
MRD and biomarker evaluations			See Biomarker Time & Events Schedule (Table 2)											
Patient Reported Outcomes (PRO), Qualitative Interviews, and Medical Resource Utilization (MRU): Phase 2 only. 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; EORTC QLQ-MY20 (4 items)	X					X				X		X	X	X	X[o]
EQ-5D-5L	X					X				X		X	X	X	X[o]
PGIS	X					X				X		X	X	X	X[o]
PGIC										X		X	X	X	
Qualitative Interviews [p]	X													X (±30 days)	Day 184 (±30 days)
Medical Resource Utilization (MRU)				X				X		X		X		X	X[r]
Ongoing Subject Review After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until study completion															
Adverse Events	Continuous from the time of signing of ICF until 100 days after last administration of any study treatment. Second primary malignancies should be followed from the time of signing of ICF signing to study completion. CRS should be evaluated according to the ASBMT consensus grading (Lee 2019)[22] (Attachment 11). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according the ASBMT consensus grading (Attachment 13). Report new neurologic adverse events or exacerbation of existing neurologic adverse events up to 12 months after JNJ-68284528 infusion. Events of HBV reactivations and COVID-19 infection should be reported during the first year post-dosing of JNJ-68284528.													

Table 1: Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [a]									**Post-treatment (Day 101 and up to Study Completion)** [b]
	≤28 days prior to apheresis [a]	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)** [b]	**(every 28 days after day 100)**[c] **(± 7 days)**
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after last administration of any study treatment. Concomitant usage for the treatment of adverse events after 100 days should be reported. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 17).														

Abbreviations: aPTT=activated partial thromboplastin time; CR=complete response; sCR=stringent complete response; CRS= cytokine release syndrome; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain; HBV=hepatitis B virus; ICANS=immune-effector cell-associated neurotoxicity syndrome; ICE=immune effector Cell-associated Encephalopathy; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA=multiple-gated acquisition; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SIPPM=site investigational product procedures manual; SOC=standard of care; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

[a] ICF must be signed before any study-related procedures are performed, and remains in effect even if the screening evaluation is not performed within the 28-day Screening Phase. Evaluations for eligibility determination performed outside the screening window may need to be repeated. For subjects who require a repeat apheresis see Section 6.1.1. for assessments should be collected before the second apheresis. If the second apheresis falls outside of the 28 day window, all screening assessments (except bone marrow collection) must be repeated.

[b] For subjects who discontinue the study before Day 100, including those who have not received an infusion of JNJ-68284528, the Day 100 assessments should be performed prior to withdrawal if feasible. Subjects who discontinue after Day 100 but before study completion should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. Study completion is defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528.

[c] Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion.

[d] Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable]), both of which may originate from prior to or during the screening period within 42 days before apheresis, or between apheresis and the conditioning regimen, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.

[e] The first 6 subjects enrolled will be hospitalized for at least 2 weeks after infusion of JNJ-68284528. The requirement for hospitalization and local stay will be evaluated by the SET for subsequent subjects. 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.

[f] Serology results performed as standard of care within 28 days prior to apheresis 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-HBs positive and anti-HBc positive); Monitor HBV-DNA, AST/ALT every 3 months for one year post-dose of JNJ-68284528. Hepatitis C**:** HCV antibody, HCV-RNA (for subjects who are anti HCV positive); HIV serology.

[g] Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion. Monitor until normalized after a CRS event.

[h] Temperature will be checked at least twice a day up to Day 28. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with subject source documents.

[i] All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.

[j] UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.

[k] Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (see Table 2).

[l] Results from skeletal survey performed as routine follow-up within 42 days before start of apheresis may be used without these tests being repeated. The skeletal survey is to be performed by either roentgenography or low-dose computed tomography (CT) scans without the use of IV contrast. If a CT is used it must be of diagnostic quality. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression).

[m] Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated prior to the first dose of the conditioning regimen, by clinical examination or radiologic imaging.

[n] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations

[o] PRO assessments to be collected every 28 days in the post-treatment Phase. For subjects with disease progression or who initiate subsequent anticancer therapy, PRO assessments should be collected every 16 weeks.

[p] Subjects enrolled in the Phase 2 portion of the study will have the option of participating in pre-treatment and post-treatment semi-structured qualitative interviews.

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

[r] Medical resource evaluation data will be collected until Day 180 (± 7 days).

[s] Local laboratory assessments may be used under specified circumstances (See Section 9.6).

Table 2: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)											At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) [b]*	Day 1 (Infusion)	Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)		
Pharmacokinetics																		
PK CAR positive T cell cellular blood sample[c]			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as dose of JNJ-68284528), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
PK CAR transgene levels blood sample[c]			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as dose of JNJ-68284528), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
Soluble serum BCMA sample			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as dose of JNJ-68284528), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
PK CAR transgene levels bone marrow sample			X (prior to first dose of conditioning regimen [≤7 days])								X		X			X		

Table 2: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)											At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) [b]*	Day 1 (Infusion)	Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	
PK CAR positive T cell bone marrow sample			X (prior to first dose of conditioning regimen [≤7 days])								X		X			X	
ADA sample (serum)[c,d]				Pre-dose					X		X		X	X	X	X	X	X
Biomarker Sampling																		
Immuno-pheno-typing (whole blood)		X	X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year	X	X	X[e]
Flow cytometry, (aspirate) (bone marrow)[e]			X (prior to first dose of conditioning regimen [≤7 days])								X		X			X	X	X
CyTOF (aspirate) (bone marrow) [e,f]			X (prior to first dose of conditioning regimen [≤7 days])													X	X	X
CyTOF/ PBMC/ Plasma (whole blood)		X					X	X	X	X	X		X		X	X	X	X[e,f]

Table 2: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments)[a] and Post-treatment (Day 101 up to study completion)**											**At PD**	**At Study Completion for subjects without PD**
	≤28 days prior to apheresis	**Upon enrollment**	**Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose)[b]***	**Day 1 (Infusion)**	**Day 2**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**Day 184 (±7 days)**	
MRD (aspirate) (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])		Sample should be collected: • For all dosed subjects at Day 28, and at 6 months, 12 months, 18 months (Day 520), and 24 months (Day 744) (± 16 days) regardless of the status of disease measured in blood and urine. • For subjects with suspected CR at the time of CR and then yearly for subjects that remain on study up to disease progression.											
Cytogenetics (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])													X	
Replication Competent Lentivirus (RCL) (whole blood)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose	At approximately 3 (Day 84), 6 (Day 168), 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 assessments within the first year are negative. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.											
Cytokine profiling[g] (serum)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose, 2hrs Post (±10 minutes)	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: ADA=anti-drug antibody; BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; PD= progressive disease; EOI=end of infusion; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; sCR=stringent complete response

[a] For subjects who discontinue the study post JNJ-68284528 infusion before Day 100, the Day 100 assessments should be performed if feasible.
[b] Window for start of conditioning regimen: Day -7 to Day -5
[c] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) Grade ≥2 (at onset of the event, and 24 and 72 hours after) or as clinically indicated; and 2) as indicated based on emerging data.
[d] ADA sample should be collected if a subject withdraws from the study after JNJ-68284528 administration but prior to disease progression or study completion.
[e] Sample should also be collected at suspected CR
[f] Sample should be collected at 12 months, relative to Day 1, for subjects that achieve CR/sCR and remain on study.
[g] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) (at onset of the event, and then every 24 hours until CRS or ICANS event has stabilized or is resolving at which time additional collections should occur at 24, 48, and 72 hours) or as clinically indicated; and 2) as indicated based on emerging data.

ABBREVIATIONS

ALL	acute lymphocytic leukemia
ANC	absolute neutrophil count
APRIL	a proliferation inducing ligand
ASBMT	American Society for Blood and Bone Marrow Transplantation
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
BNP	B-type natriuretic peptide
CAR-T	chimeric antigen receptor T (cells)
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CyTOF	cytometry by time of flight
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol Five Dimension Questionnaire
FLC	free light chain
eCRF	electronic case report form
eDC	electronic data capture
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HLH/MAS	hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HRQoL	health-related quality of life
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune-effector Cell-associated Encephalopathy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobulins
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPPI	investigational product preparation instructions
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MUGA	multiple-gated acquisition

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PQC	product quality complaint
PR	partial response
PRO	patient reported outcomes
QIg	quantitative immunoglobulin
RBC	red blood cell
RCL	replication competent lentivirus
RP2D	recommended Phase 2 dose
sBCMA	soluble BCMA
sCR	stringent complete responses
SET	safety evaluation team
SIPPM	site investigational product procedures manual
SPEP	serum protein electrophoresis
TCR	T cell receptor
TLS	tumor lysis syndrome
TNF-R	tumor necrosis factor receptor
TTR	time to response
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
VGPR	very good partial response
β-hCG	β human chorionic gonadotropin

1. INTRODUCTION

1.1. Multiple Myeloma

Multiple myeloma is characterized by the production of monoclonal immunoglobulin (Ig) proteins or protein fragments (M proteins)that have lost their function.[20,28] The proliferation of multiple myeloma cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins. Hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications.[17,28]

Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities. Therapeutic options include agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, and stem cell transplantation.

Despite these therapeutic achievements, the disease recurs and remains incurable. Thus, there is a need for novel therapeutic approaches when the disease is resistant to available therapy.

1.2. BCMA

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.[31] BCMA is predominantly expressed in B-lineage cells and plays a critical role in B cell maturation and subsequent differentiation into plasma cells.[31] BCMA binds 2 ligands that induce B cell proliferation: a proliferation inducing ligand (APRIL; CD256) and B-cell activating factor (BAFF; CD257).[3,9,29] 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 (TNF-R)-associated factor (TRAF) molecules leading to pro-survival gene regulation.[5,14,16]

In multiple myeloma cell lines and patient samples, BCMA is more stably expressed specifically on the B cell lineage than CD138, a key plasma cell marker which is also expressed on normal fibroblasts and epithelial cells.[27] The expression characteristics of BCMA make it an ideal therapeutic target in the treatment of multiple myeloma.[13,31]

1.3. 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), a CD19 directed CAR-T cell-based immunotherapy, is approved in the US for the treatment of pre-B acute lymphocytic leukemia (ALL) that is refractory or in second or later relapse for patients up to 25 years of age. Yescarta™ (axicabtagene ciloleucel), another CD19 directed CAR-T based therapy, is approved in the US for the treatment of adult patients with relapsed or refractory large B-cell lymphoma. An ongoing Phase 1 clinical study with bb2121, a BCMA-directed CAR-T immunotherapy, demonstrated promising results for

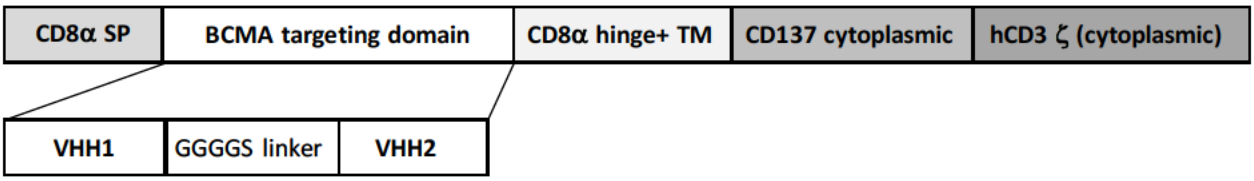
this strategy in relapsed/refractory multiple myeloma. Of 21 subjects who were infused with bb2121, 71% experienced cytokine release syndrome (CRS) that was generally mild. The ORR was 89% and increased to 100% for subjects treated with 15 x 10^7 CAR-positive T cells or higher.[4] The approval of Kymriah® and Yescarta™, taken with preliminary study results with bb2121, suggest that administering BCMA-directed CAR-T immunotherapy may be an effective means to treat multiple myeloma.

1.4. JNJ-68284528

The investigational agent, JNJ-68284528, consists of autologous CAR-T cells designed to treat subjects with relapsed or refractory multiple myeloma. The target antigen is BCMA. The novel design features dual targeting domains on BCMA, enabling tight binding of LCAR-B38M to the BCMA-expressing cells.

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 1). The expression of LCAR-B38M is driven and controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

Figure 1: 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 1.5 and Section 3.2) express an identical CAR protein. The JNJ-68284528 drug product will be produced using a modified manufacturing and scale-up processes. 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. For the most comprehensive nonclinical and clinical information, refer to the latest version of the Investigator's Brochure. 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.

1.5. Summary of Clinical 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 multiple myeloma cell lines)

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

Refer to the Investigator's Brochure for a complete description of the nonclinical study information.

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 multiple myeloma. The study was conducted in China by Legend Biotech. 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 multiple myeloma 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 transplant (ASCT) was reported for 24.3% of subjects. The median age at study entry was 54.5 years (range: 27-74 years). The median follow-up was 6.31 months (range: 0.4 – 20.7 months). The median number of LCAR-B38M CAR-positive viable T cells administered was 0.513 x 10^6 CAR-positive viable T cells/kg (range: 0.07-2.10 x 10^6 CAR-positive viable T cells/kg).

Of the 74 subjects included in the Legend 2 study, 68 (91.8%) subjects had an adverse event of CRS (median time to onset 9 days [range: 1-19 days]), including Grade 1 for 37 subjects, Grade 2 for 25 subjects, Grade 3 for 5 subjects, and Grade 5 for 1 subject. The fatal event of CRS occurred in a 40-year-old female who experienced CRS and tumor lysis syndrome (TLS) 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.

Cytopenias (thrombocytopenia and neutropenia) were common, however, prolonged Grade 4 cytopenias with duration exceeding 35 days were infrequent. Infection events were reported in 7 (9.5%) subjects; however, the rate did not appear to exceed that expected for subjects with multiple myeloma.

In addition to the subject who died from CRS, 1 subject had a fatal adverse event related to treatment with LCAR-B38M CAR-T cells. A 54-year old male with a history of coronary artery disease and extensive anthracycline therapy who experienced CRS with a maximum Grade of 2, and died on Day 22 after LCAR-B38M CAR-T infusion due to a potential acute pulmonary embolism and potential acute coronary syndrome.

Although the Legend-2 study was conducted in China, one 56-year old male, Caucasian subject from the United States was treated. The subject received similar prior therapy (5 prior lines of therapy including PI, IMiD, and anti-CD38 antibody treatment) as is required on this study. He experienced Grade 3 CRS after LCAR-B38M CAR-T cell infusion. The CRS resolved after treatment with anti-IL-6 receptor antibody and TNFα inhibitor. The subject achieved a stringent complete response (sCR).

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. Administering the CAR-T cells as a split dose did not appear to have a different safety or efficacy profile compared with administering it as a single dose (See Section 3.2). There was no apparent association between response and the number of total viable T cells or CAR-positive viable T cells infused.

Study 68284528MMY2001 (study data generated following initiation of the conduct of this protocol)

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%), 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.

Other Neurotoxicities

As of 06 March 2020, neurotoxicity with symptoms suggestive of Parkinsonian features that occurred after a period of recovery from CRS and/or ICANS have been observed in 6 subjects from Study 68284528MMY2001 (n=97). Among 6 subjects, 3 subjects had confirmed Parkinsonian-like symptoms with some shared features in their clinical presentation have been observed, with initial presentation between Day 19 and Day 101 after JNJ-68284528 infusion. Symptoms include altered mental status, feeling or appearing agitated, personality changes (such as being more withdrawn, expressing little emotion), lack of facial expression, being less communicative (answering questions with 1-word), difficulty with short term memory, slowing of movements, difficulty performing simple tasks (such as buttoning a shirt), difficulty swallowing, joint or muscle stiffness or inflexibility, shuffling gait (walking very slowly with small steps and heavy feet), restlessness, impaired balance, bradykinesia, slight cogwheeling/rigidity in extremities, micrographia (small handwriting) and impaired ability to perform activities of daily living (ADLs). On exam, all 3 subjects presented with symptoms described as Parkinsonian. The

brain MRI showed no acute abnormalities in these subjects. The remaining 3 subjects had a mixed presentation of neurotoxicities (including some Parkinsonian-like symptoms) which presented with complicating comorbidities. All 6 subjects referenced above had previously experienced CRS (4 Grade 2, 2 Grade 3 all of which resolved) and 5 out of 6 subjects had ICANS (3 Grade 1, 1 Grade 2, 1 Grade 3). Three subjects referenced above have died. Although these subjects also experienced other adverse events which may have contributed to the cause of death, such as infection and sepsis, the role of neurotoxicity cannot be ruled out.

Study 68284528MMY2002 (study data generated following initiation of the conduct of the protocol)

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 multiple myeloma. 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 12 May 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 cutoff date. Further details are provided in the most recent edition of the Investigator's Brochure.

1.6. Overall Rationale for the Study

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.[7,15] 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, JNJ-68284528. Results in 74 subjects from the Legend-2 study indicate an ORR of 87.8% with a CR rate of 64.9%. The observed response rates and the reversible adverse events for most subjects, support further investigation of this approach in the current study.

1.7. Potential Safety Risks and Mitigation Strategies

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 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. Potential safety risks and mitigation strategies are outlined in Table 3.

Table 3: Potential Risks and Mitigation Strategies

Potential Risk	Mitigation Strategies
Cytokine release syndrome (CRS) [a, b]	Monitor closely for CRS and follow guidance for management in Section 6.3.1. 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 6 for other hospitalization requirements. 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 6.3.1 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. Notify the sponsor if subject is experiencing Grade 2 or higher CRS.
Tumor lysis syndrome (TLS) [a]	Monitor closely for TLS with frequent monitoring of chemistry parameters and follow guidance for management in Section 6.3.3.
Cytopenias	Frequent monitoring of hematological parameters and provide supportive care (eg, irradiated blood and thrombocyte concentrates, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.
Infections	Do not administer JNJ-68284528 to subjects 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. 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 Attachment 16). 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 subject with risk of HBV reactivation (Attachment 8). 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 Attachment 17.
Hypogammaglobulinemia	Monitor immunoglobulin levels after treatment and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Subjects with IgG < 400 mg/dL and recurrent infections may receive prophylactic IVIG as per institutional guidelines.
Neurologic toxicities [a,b]	**CAR-T cell-related neurotoxicity (ie, immune effector cell-associated neurotoxicity syndrome [ICANS])[a]** Early recognition of neurologic adverse events is critical to management. Subjects 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 subject is experiencing any grade ICANS.

Table 3: Potential Risks and Mitigation Strategies

Potential Risk	Mitigation Strategies
	At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. Hospitalization is required for Grade ≥2 CAR-T cell-related neurotoxicity (eg, ICANS). Section 6.3.2 provides management guidelines for neurotoxicity.
	Other Neurotoxicities Monitor closely for other neurotoxicities with clinical presentation for 1-year post-infusion with JNJ-68284528. Symptoms include difficulty sleeping, feeling or appearing agitated, personality changes (such as being more withdrawn, expressing little emotion), lack of facial expression, being less communicative (answering questions with 1-word), difficulty with short term memory, slowing of movements, difficulty performing simple tasks (such as buttoning a shirt), difficulty swallowing, joint or muscle stiffness or inflexibility, shuffling gait (walking very slowly with small steps and heavy feet), restlessness, micrographia (small handwriting), and impaired ability to perform ADLs. 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 6.3.2 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. Subjects with Parkinsonian-like neurotoxicities were observed at a higher frequency in subjects with high burden of disease and in subjects 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 an early indication of risk of other neurotoxicity that may develop 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 subjects treated with high tumor burden, may mitigate the risk of developing neurotoxicity later, after resolution of CRS. Infection and sepsis were concurrently seen in many of these subjects.
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 ampicillin or kanamycin in JNJ-68284528. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible.
Second primary malignancies (SPM)[a]	Second primary malignancies may occur in subjects receiving JNJ-68284528. 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 yearly until 15 years post dosing of JNJ-68284528.

a Adverse event of special interest (see Section 12.3.3)
b Identified Risk

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety of JNJ-68284528 and establish the dose (RP2D) (Phase 1b)	• Incidence and severity of adverse events.
• To evaluate the efficacy of JNJ-68284528 (Phase 2)	• ORR (at least a partial response [PR] or better) as defined by the International Myeloma Working Group (IMWG) response criteria as assessed by the Independent Review Committee (IRC).
Secondary	
• To characterize the safety of JNJ-68284528 (Phase 2)	• Incidence and severity of adverse events.

Objectives	Endpoints
• To characterize the pharmacokinetics and pharmacodynamics of JNJ-68284528	• Pharmacokinetic and pharmacodynamic markers including but not limited depletion of BCMA expressing cells, circulating soluble BCMA, 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 further characterize the efficacy of JNJ-68284528	• Very good partial response (VGPR)/complete response (CR)/stringent complete response (sCR) rate, minimal residual disease (MRD) negative rate as defined by the IMWG response criteria, clinical benefit rate (CBR; CBR = ORR (sCR + CR + VGPR + PR) + MR (minimal response)]), duration of and time to response (DOR and TTR), progression-free survival (PFS), overall survival (OS).
• To compare the patient-reported outcomes (PRO) after treatment to subject's reported health state prior to treatment and to assess the sustained benefit of subject's perceived health-related quality of life (HRQoL) (Phase 2 only)	• Change in HRQoL (symptoms, functioning, and well-being) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and single items from EORTC QLQ-MY20.
Exploratory	
• To explore whether the infused CAR-positive T cell subsets impact pharmacodynamics, safety, and clinical activity of JNJ-68284528	• CAR+ central memory, effector memory T cells and expression of activation and exhaustion markers including, but not limited to CD25 and PD-1.
• To determine whether replication competent lentivirus is present in subjects that receive JNJ-68284528	• Presence of replication competent lentivirus.
• To explore whether there are predictive biomarkers of response or resistance to JNJ-68284528	• Tumor BCMA expression by flow cytometry, activation of T cells or T cell subsets, serum cytokine expression after and during T cell activation, or identify subject genetic risk.
• To determine if MRD negative rate correlates with duration of response, PFS, OS	• Correlation between MRD negative rate and duration of response, PFS, and OS.
• To assess the safety and efficacy of retreatment with JNJ-68284528	• Incidence and severity of adverse events • VGPR/CR/sCR rate, MRD negative rate, duration of and time to response after retreatment.

Objectives	Endpoints
• To describe pre-trial goals and expectations as well as post-treatment experience of JNJ-68284528 using semi-structured qualitative interviews (Phase 2 only)	• Description of the subject experience with JNJ-68284528 through a content analysis of the qualitative interview transcripts.
• To characterize the impact of JNJ-68284528 CAR-T process on medical resource utilization	• 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 • Tmax, Cmax, and phenotypic analysis of CAR-T cells • Neuroimaging (CT/MRI)

2.2. Hypotheses

Treatment with JNJ-68284528 will demonstrate acceptable safety and will have significant anti-myeloma activity (ie, the lower limit of two-sided 95% confidence interval [CI] for ORR, as assessed by the IRC, is greater than 30%) at the targeted recommended Phase 2 dose (RP2D) dose level in subjects with advanced relapsed or refractory multiple myeloma.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 1b-2, open-label, multicenter study of JNJ-68284528 administered to adult subjects with relapsed or refractory multiple myeloma. The aim of the study is to evaluate the safety and efficacy of JNJ-68284528. At least 24 and up to approximately 50 subjects will be enrolled in the Phase 1b portion of the study in which a RP2D of JNJ-68284528 will be established. Confirmation of the RP2D will be based on review of data from at least 24 subjects who were administered JNJ-68284528. Additional subjects (up to approximately 50) will be enrolled in the Phase 1b portion of the study to generate supplemental safety and efficacy data at the RP2D.

Safety evaluation team (SET) meetings will be convened as described in Section 3.5. All available data including safety, pharmacodynamic, pharmacokinetic, and efficacy data from subjects enrolled in Phase 1b study will be considered. The SET or sponsor may also determine that additional subjects are required to further evaluate safety and dose prior to proceeding to the Phase 2 portion of the study. Before administration of JNJ-68284528 in the Phase 2 portion of the study, clinical data will be shared with the relevant health authorities. The planned sample size for the Phase 2 portion will be approximately 60 subjects.

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 apheresis. Safety criteria that must be met prior to starting apheresis are presented in Section 6.1.1.

Eligible subjects will undergo apheresis for collection of peripheral blood mononuclear cells (PBMC). Study enrollment is defined at the day of apheresis. JNJ-68284528 will be generated

from T cells selected from the apheresis. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis.

Bridging therapy (anti-plasma cell directed treatment between apheresis and the first dose of the conditioning regimen) will be allowed when clinically indicated (ie, to maintain disease stability while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Additional cycles of bridging therapy may be considered based on subject's clinical status and timing of availability of CAR-T product. Investigator must contact the sponsor for approval. Bridging therapy must be a short-term treatment which previously generated at least a response of stable disease for the subject. The sponsor will not permit subjects who are found to be in CR after bridging therapy to receive JNJ-68284528.

After meeting safety criteria for treatment (Section 6.1.2), subjects will be administered a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. JNJ-68284528 will be administered at a total targeted dose of 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) 5 to 7 days after start of the conditioning regimen (Section 6.1). This is a dose range informed by the Legend-2 study as described in Section 3.2. In the event of excess toxicity, a dose de-escalation to dose level -1 (0.3 x 10^6 CAR-positive viable T cells/kg [range: 0.1-0.5 x 10^6 cells/kg]) for new subjects will occur (Section 3.3). Additionally, a dose escalation to dose level 2 (target dose not to exceed a 3-fold dose escalation [2.25 x 10^6 CAR-positive viable T cells/kg, range: ±30%, depending on target dose chosen for dose level 2]) will be considered if specified safety criteria are met (Section 3.4).

The first 6 subjects enrolled in the Phase 1b portion of the study will be hospitalized for at least 2 weeks after receiving an infusion of JNJ-68284528. Hospitalization and local stay requirements for subsequent subjects will be based on recommendations by the SET.

For the primary efficacy analysis, the disease status evaluation for each subject will be assessed by an Independent Review Committee (IRC). Disease status will be evaluated according to clinical judgement guided by the IMWG consensus recommendations for multiple myeloma treatment response criteria (Attachment 1). [11,12,32] The process and convention of the IRC will be detailed in a separate charter.

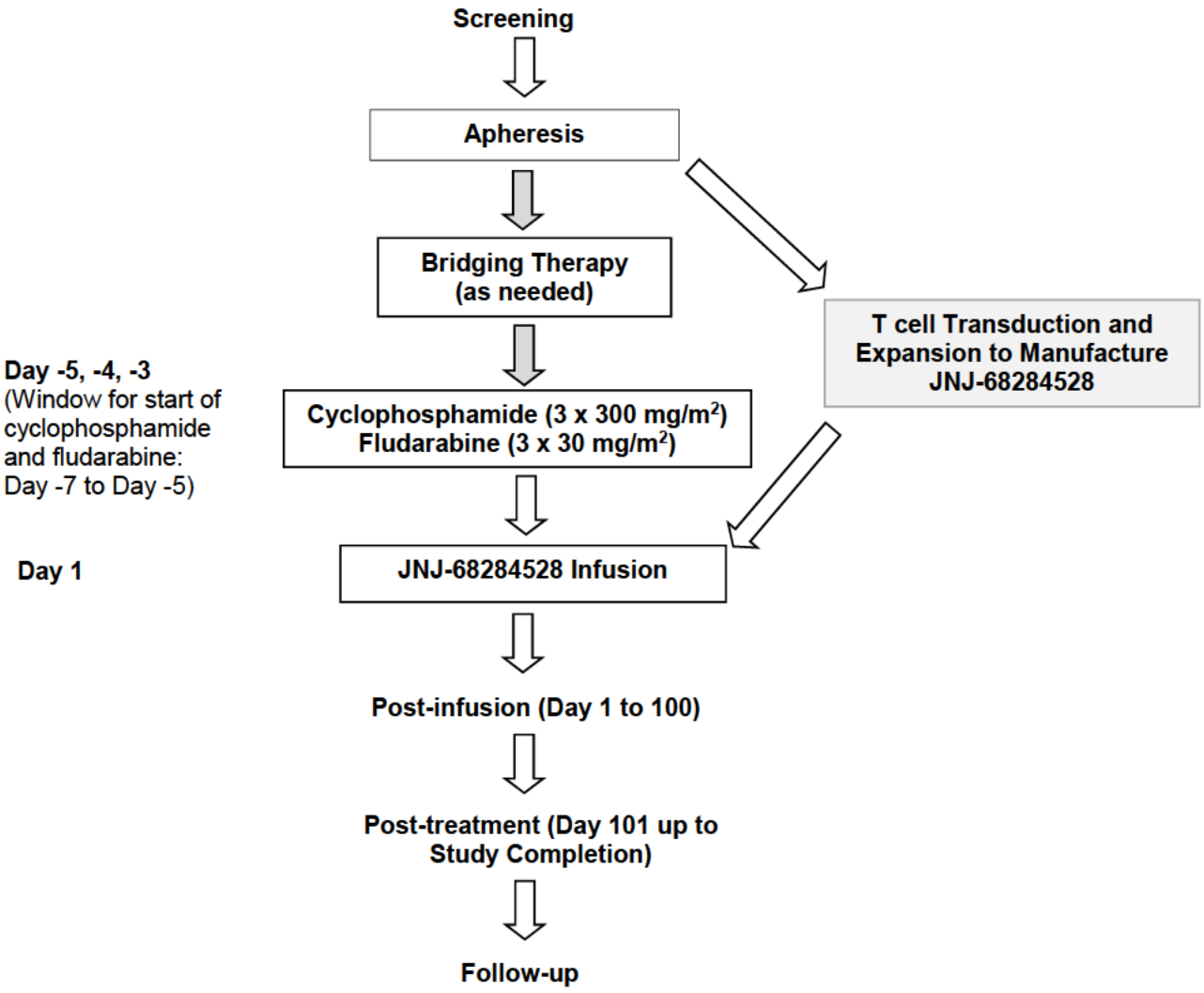
Safety evaluations will include a review of adverse events, laboratory test results, vital sign measurements, physical examination findings, handwriting assessments, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade. The safety profile will be evaluated at SET meetings during the Phase 1b portion of the study. Follow up of subjects for disease progression and survival will continue during the Posttreatment Phase. All study evaluations will be conducted according to the Time and Events Schedules (Table 1 and Table 2).

The sponsor will establish a data cutoff date for clinical study report (CSR) analyses. The first analysis will be conducted approximately 6 months after the last subject receives their initial dose of JNJ-68284528. An update of the analysis will be provided at approximately 9-12 months after

the last subject received their initial dose of JNJ-68284528 and at the end of the study, which is defined as 2 years after the last subject has received their initial dose of JNJ-68284528 (Section 17.9.1). Subjects will be followed for survival after the clinical cutoff for the primary CSR. The data cutoff will be communicated to the sites. The sponsor will monitor subjects treated with JNJ-68284528 for 15 years for complications of lentiviral integration, including second primary malignancies on a long-term follow-up study.

A diagram of the study is provided in Figure 2.

Figure 2: Schematic Overview of the Study Flow Chart



Criteria for JNJ-68284528 Retreatment:

Subjects may be considered for retreatment with JNJ-68284528 within the same dose range to which they were initially assigned, or the de-escalated dose if de-escalation is mandated. Subjects must satisfy the following criteria to be eligible for retreatment, with approval from the sponsor:

- Progressive disease (PD) after best response of minimal response (MR) or better.

- No ongoing Grade 3 or higher hematologic toxicity.
- No ongoing Grade 2 non-hematologic toxicity (with the exception of nausea, vomiting, hair loss, and constipation).
- At least 6 months between first JNJ-68284528 infusion and detection of PD.

Subjects must satisfy all inclusion and exclusion criteria (Section 4), except for exclusion criteria 1 and 2, to be eligible for retreatment. A maximum of 1 retreatment may occur per subject. Bridging therapy prior to retreatment may be considered based on subject's clinical status and timing of availability of CAR-T product. Investigator must contact the sponsor for approval.

A staggered strategy for retreatment will be applied. There must be an observation period of at least 2 weeks between retreatment with JNJ-68284528 to the first and second subject, the second and third, and third and fourth subjects, respectively.

Time and events schedules for retreatment are provided in Attachment 9 (Table 12 and Table 13). Subjects who received retreatment with JNJ-68284528 and are in follow-up at the end of the study (2 years after the last subject receives the initial dose of JNJ-68284528) will be monitored in the long-term follow-up study for 15 years from the time of last treatment (see Section 9.1.6.3).

3.2. Rationale of Dose and Administration Schedule Selection

The conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 doses will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 before JNJ-68284528 infusion (Day 1) is consistent with the lymphodepletion regimen used in the marketed CAR-T products Kymriah[19] and Yescarta[34].

JNJ-68284528 will be administered at a targeted infused dose of 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 with a maximum total dose of 1.0 x 10^8 CAR-positive viable T cells) for this Phase 1b-2 study. This dose is informed by the Legend-2 clinical study performed at 4 study sites across China. The number of viable CAR-positive T cells prepared for the 74 subjects from the Legend-2 study ranged from 0.07 to 2.10 x 10^6 CAR-positive viable T cells/kg (mean 0.642 x 10^6 cells/kg, median 0.513 x 10^6 cells/kg).

Across all 74 subjects, the safety profile supports doses up to 1.5 x 10^6 cells/kg with regards to occurrence of CRS (Table 4). Analysis of the safety of doses above 1.5 x 10^6 in the Legend-2 study is not possible due to the very small number of subjects who received a dose above this concentration. As discussed in Section 1.4, the JNJ-68284528 drug product expresses the same CAR protein and is produced using a modified manufacturing process relative to the drug product used in the Legend-2 study. Differences in clinical activity and safety profiles due to the updated manufacturing process are possible. Thus, the targeted infused dose (post-freeze) of 0.75 x 10^6 CAR-positive viable T cells/kg proposed for JNJ-68284528 was reduced to half of the prepared dose (pre-freeze) of 1.5 x 10^6 cells/kg supported by the safety analysis summarized in Table 4. Acknowledging that each CAR-T cell product may have unique factors that influence the safety

and efficacy of a given dose, for subjects weighing <200 kg, the selected target dose is also below the lower end of the dose range (150-800 x 10^6 CAR-T cells) currently being investigated for bb2121[4], a different BCMA-directed CAR-T cell study drug.

The sponsor will confirm the safety of this target dose in the current study.

Table 4: Summary of CRS Grade by Weight-adjusted Total CAR-positive T Cell Dose (Legend-2 Study)

	Weight-adjusted total CAR+ cells dose range (x10^6 cells/kg)			
	≤0.5	>0.5to ≤1	>1<to ≤1.5	>1.5
Cytokine release syndrome toxicity grade				
N	34	27	8	5
Grade 0 (No CRS)	4 (11.8%)	2 (7.4%)	0	0
Grade 1	20 (58.8%)	12 (44.4%)	3 (37.5%)	2 (40.0%)
Grade 2	8 (23.5%)	12 (44.4%)	4 (50.0%)	1 (20.0%)
Grade 3	1 (2.9%)	1 (3.7%)	1 (12.5%)	2 (40.0%)
Grade 5	1 (2.9%)	0	0	0

Key: CRS = Cytokine Release Syndrome

At 3 of the 4 sites (65 of 74 subjects) in the Legend-2 study, the dose was split into more than 1 infusion, the most common regimen was 3 infusions given over 7 days. At the 4th site, 9 subjects received LCAR-B38M CAR-T cells as a single administration on Day 1. Review of safety (occurrence of CRS) and efficacy data from the 9 subjects who received a single infusion of LCAR-B38M CAR-T cells did not discern a meaningful difference between split doses versus single dose administration. Single dose administration is consistent with the dosing regimens of the 2 currently approved CAR-T products (Kymriah, Yescarta), and bb2121.

Based on totality of the Legend-2 clinical data, the proposed target starting dose of 0.75 x 10^6 CAR-positive viable T cells/kg for JNJ-68284528 in single administration should be a reasonable dose for testing in the clinic. As an added safety precaution (for the study as a whole), a dose de-escalation will occur for future subjects in the event of excess toxicity being observed following dosing in the first 6 subjects (Section 3.3). Additionally, a dose escalation will be considered if specified safety criteria are met (Section 3.4).

3.3. Dose De-escalation

The dose de-escalation evaluation period is defined as 21 days after the infusion of JNJ-68284528. Toxicities that are considered at least possibly related to JNJ-68284528 and that occur during the dose de-escalation evaluation period will be considered for dose limiting toxicity (DLT) assessment. DLT criteria are listed in Table 5.

Table 5: Dose Limiting Toxicity Criteria

Toxicities for Dose De-escalation	
CRS	Grade 4 CRS not improved to Grade 2 or lower within 72 hours
Neurotoxicity	Grade 3 or 4 neurotoxicity not improved to Grade 2 or lower within 72 hours
Other non-hematologic toxicity	Grade 3 or 4 non-CRS toxicity of heart, liver, lungs, kidney that does not resolve to Grade 2 or lower within 7 days
Hematologic and non-hematologic toxicity	Any Grade 5 toxicity

If >1 out of the first 6 subjects at any dose level meets DLT criteria during the 21-day evaluation period, a dose de-escalation to a target dose (dose level -1) of 0.3 x 10^6 CAR-positive viable T cells/kg (range: 0.1-0.5 x 10^6 cells/kg) for future subjects will be mandated as determined by the SET (see Section 3.5). For the duration of the Phase 1b portion of the study, a dose de-escalation will be mandated if, at the time of the SET meeting, DLT criteria are met for ≥20% of subjects for any dose level reaching the evaluation milestone (eg, 6, 12, or 18 subjects).

Adverse events should be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0), with the exception of CRS and CAR-T cell-related neurotoxicity (eg, ICANS). CRS should be evaluated according to the ASBMT consensus grading (Lee 2019)[22] (Attachment 11). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASBMT consensus grading (Attachment 13). Assessments for ICE should be performed as specified in the Time and Events Schedule (Table 1 and Table 12) in both the Phase 1b and Phase 2 portions of the study.

3.4. Dose Escalation

At the time of the SET meeting, if fewer than 20% of subjects enrolled in the study at the target starting dose (dose level 1) meets DLT criteria during the 21-day dose de-escalation evaluation period described above, the SET may approve a dose escalation (dose level 2). The target dose level and range for dose level 2 will be decided by the SET after review of all available safety, pharmacokinetic, pharmacodynamic, and preliminary efficacy data, and will not exceed a 3-fold dose escalation of the initial target dose (2.25 x 10^6 CAR-positive viable T cells/kg [range: ±30%, depending on target dose chosen for dose level 2]) (see Table 6). Dose escalation beyond dose level 2 will not be permitted. After dose escalation, the same criteria for dose de-escalation described in Section 3.3 will be used for mandated de-escalation back to 0.75 x 10^6 cells/kg (dose level 1).

The RP2D will be confirmed by the SET after evaluation of safety, preliminary efficacy, pharmacokinetic, and pharmacodynamic data from at least 24 Phase 1b subjects. The RP2D will be a dose level examined in Phase 1b at which <20% of subjects experienced a DLT. If there is more than one dose level that meets this safety threshold, the preliminary overall response rate among subjects that have had at least two post-infusion efficacy assessments will be considered with additional consideration given to the rate and level of JNJ-68284528 CAR-T cell persistence.

3.5. Safety Evaluation Team

To ensure safety monitoring and sponsor oversight of the study, the sponsor will establish a SET. The SET will be chaired by the sponsor Study Responsible Physician. Membership will include the study principal investigators, a sponsor clinical scientist, safety physician, statistician, clinical pharmacologist, and additional sponsor staff, as appropriate. SET meetings will occur only during the Phase 1b portion of the study. Written documentation of meeting outcomes will be maintained by the sponsor. Decisions with the potential to impact subjects' safety (eg, unfavorable change in risk/benefit assessment) will be promptly communicated to regulatory authorities and study sites as appropriate.

SET meetings will occur approximately after 6 subjects at the same dose level have completed the 21-day dose evaluation period: 1) during the Phase 1b study to evaluate for escalation and de-escalation of dose level after completion of the DLT evaluation period of every 6 subjects through 24 subjects and every 12 subjects thereafter, and 2) after SET evaluation of at least 24 subjects evaluated, administration of JNJ-68284528 to subjects in the Phase 2 portion of the study may begin concurrently with ongoing administration of JNJ-68284528 to subjects in the Phase 1b portion of the study. Ad-hoc SET meetings may be convened at the discretion of the sponsor. Administration of the conditioning regimen and dosing with JNJ-68284528 will be paused between dosing of the sixth subject and the conclusion of the first SET meeting. These meetings will ensure the safety of subjects is maintained prior to continued dosing of subjects and will consider the need to reduce the dose and if it is safe to escalate the dose for upcoming subjects. This SET will consider all available treatment emergent data (eg, pharmacokinetic, pharmacodynamics, safety, efficacy) for these decisions. The SET may advise on modifications in study conduct, including whether hospitalization, local stay, or staggered dosing with JNJ-68284528 is required for subsequent subjects or stopping further enrollment if treatment-emergent toxicity is believed to result in an unfavorable risk-benefit profile. All SET decisions will be communicated to all study sites and archived in writing in the Trial Master File.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to apheresis. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria, the investigator must consult with the Study Responsible Physician, Study Responsible Scientist or delegate and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. ≥18 years of age.

2. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 3).

3. Criterion modified per Amendment 2

   3.1. Measurable disease at Screening as defined by any of the following:

   - Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements

4. Criterion modified per Amendment 1

   4.1. Criterion modified per Amendment 3

   4.2. Received at least 3 prior multiple myeloma treatment lines of therapy or are double refractory to an IMiD and PI (refractory multiple myeloma as defined by IMWG consensus criteria[30]). Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single line of therapy.

   - Undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy.

5. Criterion modified per Amendment 3

   5.1 Received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody (prior exposure can be from different monotherapy or combination lines of therapy).

6. Criterion modified per Amendment 2

   6.1. Criterion modified per Amendment 3

   6.2. Subject must have documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or within 12 months of their last line of therapy (Attachment 1). Confirmation may be from either central or local testing. Also, subjects with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are eligible.

7. ECOG Performance Status grade of 0 or 1 (Attachment 5).

8. Criterion modified per Amendment 1

8.1. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted).*
Platelets	≥50 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Lymphocyte count	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥0.75×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Creatinine clearance	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 6) or a 24-hour urine collection.
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)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dl (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

9. Women of childbearing potential must have a negative pregnancy test at screening and prior to the first dose of cyclophosphamide and fludarabine using a highly sensitive serum pregnancy test (β human chorionic gonadotropin [β-hCG]).

10. Criterion modified per Amendment 3

10.1 When a woman is of childbearing potential the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form (ICF) until 1 year after receiving a JNJ-68284528 infusion. 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;
  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)

In addition to the highly effective method of contraception a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion

- Who is sexually active with a woman who is pregnant must use a condom

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after the last dose of study treatment.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

11. Subject must sign an ICF indicating that he or she understands the purpose of procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

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

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

2. Any therapy that is targeted to BCMA.

3. Criterion modified per Amendment 2

   3.1. Diagnosed or treated for invasive malignancy other than multiple myeloma, except:

   - Malignancy treated with curative intent and with no known active disease present for ≥2 years before enrollment; or
   - Adequately treated non-melanoma skin cancer without evidence of disease.

4. Prior antitumor therapy as follows, prior to apheresis:

   - 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.
   - Monoclonal antibody treatment for multiple myeloma 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 portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

5. Toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

6. The following cardiac conditions:

   - New York Heart Association (NYHA) stage III or IV congestive heart failure
   - Myocardial infarction or coronary artery bypass graft (CABG) ≤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 of apheresis).

7. Criterion revised per Amendment 2

   7.1. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

8. Received either of the following:

   - An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD).
   - An autologous stem cell transplant ≤12 weeks before apheresis

9. Criterion modified per Amendment 2

   9.1. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

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

11. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

12. Seropositive for human immunodeficiency virus (HIV).

13. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

14. Criterion modified per Amendment 2

    14.1. Hepatitis B infection as defined according to Attachment 8). In the event the infection status is unclear, quantitative levels are necessary to determine the infection status.

15. Criterion modified per Amendment 1

    15.1. Criterion modified per Amendment 2

    15.2. 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 [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

16. Supplemental oxygen use to maintain adequate oxygenation.

17. Known life threatening allergies, hypersensitivity, or intolerance to JNJ-68284528 or its excipients, including DMSO (refer to Investigator's Brochure).

18. Serious underlying medical condition, such as:

    - Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection
    - Active autoimmune disease or a history of autoimmune disease within 3 years
    - Overt clinical evidence of dementia or altered mental status

19. 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.

20. Criterion modified per Amendment 3

    20.1 Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 year after receiving study treatment.

21. Criterion modified per Amendment 3

    21.1 Plans to father a child while enrolled in this study or within 1 year after receiving study treatment.

22. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

5. INTERVENTION ALLOCATION AND BLINDING

Randomization will not be used in this study. Subjects will receive study treatment if all inclusion/exclusion criteria are met. As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE, ADMINISTRATION, AND GUIDANCE

For this study, study treatment refers to both cyclophosphamide/fludarabine and JNJ-68284528. All dosing information must be recorded in the Dosage Administration page of the electronic case report form (eCRF).

6.1. Study Treatment Administration

Approximately 4 weeks after apheresis, and after the site is notified in writing by the Janssen team that manufacture and quality testing of JNJ-68284528 has been completed, each subject will receive a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 at 3 daily doses; sponsor approval must be obtained to change the conditioning regimen schedule. 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). 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 site investigational product procedures manual (SIPPM) and investigational product preparation instructions (IPPI).

A strategy of staggered dosing with JNJ-68284528 will be applied. There must be an observation period of at least 4 weeks between administration of JNJ-68284528 to the first and second subject, and an observation period of at least 2 weeks between administration of JNJ-68284528 to the second and third and third and fourth subjects, respectively. No observation periods are mandated after the fourth subject receives JNJ-68284528. Administration of the conditioning regimen and dosing with JNJ-68284528 will be paused between JNJ-68284528 dosing of the sixth subject and conclusion of the first SET meeting.

Exceptional Release Criteria

In the event a JNJ-68284528 product that did not meet pre-specified release criteria is produced during the manufacturing procedures, 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 the event the supply of the affected product is deemed appropriate, the investigator should inform the study subject that the product did not meet release specifications prior to administration.

6.1.1. Criteria for Apheresis

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

- Clinical laboratory values required for enrollment (inclusion criterion 8, Section 4.1) resulted within 24-hours prior to apheresis
- No plasma cell leukemia at the time of apheresis (>2.0 x 10^9/L plasma cells by standard differential) (exclusion criterion 11, Section 4.2).
- ECOG performance status grade of 0 or 1
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to apheresis
- No antitumor therapy within timeframe detailed in Section 4.2 and presented below:
  - 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.
  - Monoclonal antibody treatment for multiple myeloma 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 portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
- Cumulative dose of corticosteroids should not exceed equivalent to ≥70 mg prednisone within the 7 days prior to the first dose of conditioning regimen
- 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 ≤2 weeks prior to apheresis
- No live, attenuated vaccines ≤4 weeks prior to apheresis
- No supplemental oxygen use to maintain adequate oxygenation
- 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 screening assessments should be collected before the second apheresis: weight, hematology laboratory assessments, chemistry laboratory assessments, and echocardiogram or MUGA (if clinically indicated). If the second apheresis falls outside of the 28-day window, all screening assessments (except bone marrow collection) must be repeated).

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

The investigator should contact the sponsor if evidence of rapid disease progression is observed between apheresis and cyclophosphamide and fludarabine dosing. Subjects must meet the following criteria to proceed with cyclophosphamide and fludarabine dosing:

- Clinical laboratory values required for enrollment (Section 4.1), with the following exception: lymphocyte count of ≥0.3 x 10^9/L. Transfusion support is permitted to maintain a hemoglobin of ≥8.0 g/dl (≥5mmol/L) 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 up to 1 day prior to the start of the conditioning regimen. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited.
- Echocardiogram or MUGA scan for subjects who receive bridging therapy that includes agents with known cardiac toxicity, including but not limited to anthracyclines and carfilzomib (per prescribing information), verification of non-impaired cardiac function (LVEF ≥45%) should be performed after completion of bridging therapy and prior to the first dose of the conditioning regimen.
- ECOG performance status grade of 0 or 1
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to the first dose of the conditioning regimen
- No antitumor therapy within timeframe detailed in Section 4.2 and presented below:
  - 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.
  - Monoclonal antibody treatment for multiple myeloma 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 portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
- No active Grade 3 toxicity to any bridging therapy
- 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 >10 mg per day in the week prior to the start of the conditioning regimen.
- No signs of active infection. For subjects requiring systemic anti-microbial treatment or with temperature ≥38.0 Celsius within 7 days prior to the first dose of conditioning regimen, the investigator must receive approval to proceed from the sponsor.
- No major surgery ≤2 weeks prior to conditioning regimen dosing
- No live, attenuated vaccines within 4 weeks prior to conditioning regimen dosing

- No supplemental oxygen use to maintain adequate oxygenation
- No new arrhythmia or other cardiac adverse events unless controlled with medical management and approved by the medical monitor
- Washout from bridging therapy completed as specified in Section 4.2, criterion 4.

Subjects should be evaluated for the presence of an indwelling catheter prior to the first dose of the conditioning regimen.

6.1.3. 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 6.1.2), the investigator should contact the 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 Celsius 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).

6.1.4. JNJ-68284528 Administration

JNJ-68284528 will be administered as summarized in Table 6.

Table 6: 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 3.2. 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). If the dose level is de-escalated to dose level -1 or escalated to dose level 2, the maximum total dose of cells would be adjusted accordingly as the maximum weight adjusted dose (CAR-positive viable T cells/kg) calculated for a 100-kg subject at that dose level. The dose and administration schedule may be altered for safety purposes based on emerging data. 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.
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.
Dosing Instructions	The actual dose for study treatment administration will be based on the subject's weight (kg) at apheresis.
Schedule of Administration	One intravenous infusion
Hospitalization Requirements	The first 6 subjects enrolled will be hospitalized for at least 2 weeks after receiving an infusion of JNJ-68284528 and 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 discharge. Subjects who are not hospitalized 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 the 2 weeks following study treatment. Hospitalization and local stay requirements will be evaluated by the SET for subsequent subjects. 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 8. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS) temporally associated with CRS. 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 Time and Events Schedule (Table 1).

6.2. Pre-infusion Supportive Therapy

Prior to JNJ-68284528 infusion, subjects should receive premedication as noted below (Table 7). Corticosteroids should not be used during pre-infusion.

Table 7: Pre-infusion Medications

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

6.3. Management Guidelines for Potential Risks

6.3.1. 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 events were Grade 1 or Grade 2. All events of CRS started with fever after the infusion of CAR-T therapy (See Section 1.5). Of the subjects who developed CRS, approximately 84% experienced transiently increased aspartate aminotransferase (AST). AST increase was Grade 3 or Grade 4 in 31% and 6% of subjects with CRS, respectively. Subjects should be monitored for increased AST, and consumptive coagulopathy, indicated by an increase in D-dimers and a decrease in fibrinogen if CRS is suspected.

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.[21] 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 CRP) when fever or other signs of potential CRS are present (see Table 1). In addition, pulmonary, renal and hepatic function will be monitored closely (see Table 1). Cytokine release syndrome will be captured as an adverse event of special interest (see Section 12.3.3).

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, soluble CD25, and cytokines (such as IFNγ and IL-6), and low serum levels of fibrinogen (Neelapu 2018)[25]. 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 prior to administration of JNJ-68284528. Vital signs and laboratory parameters must be monitored at regular intervals until normal. Additional specimens for pharmacokinetic and pharmacodynamic testing should be collected as per the schedule outlined in Table 2.

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 8. At the first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation. 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 per investigator discretion when other sources of fever have been eliminated and 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 monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) may be used based on institutional practice, especially for cases of CRS which does not respond to tocilizumab. 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 8: Guidelines for the Management of Cytokine Release Syndrome

CRS Grade	Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥38°C[c]	May be considered	N/A
Grade 2	Temperature ≥38°C[c] with either: Hypotension responsive to fluids and not requiring vasopressors. Or, oxygen requirement of low-flow nasal canula[d] or blow-by	Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.
Grade 3	Temperature ≥38°C[c] with either: Hypotension requiring one vasopressor with or without vasopressin. Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥38°C[c] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above, or administer methylprednisolone 1000 mg intravenously per day for 3 days per investigator discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

a: Refer to tocilizumab prescribing information for details[1]
b: Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
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).
d: Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.
Note: At first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation.

Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen) should be administered according to the clinical manifestations of the subject's illness. Similarly, ancillary testing such as B-type natriuretic peptide (BNP) assessment, echocardiograms, arterial blood gas, assessments of coagulation laboratory tests, should be performed if clinically indicated.

6.3.2. Neurologic Toxicities

Based on the specific mode-of-action of JNJ-68284528, severe or serious neurological toxicities (including CAR-T cell-related neurotoxicity, eg, ICANS [Immune Effector Cell-Associated Neurotoxicity Syndrome]) may occur (Section 6.3.2.1). Subjects should be monitored for neurotoxicity for 1-year post JNJ-68284528 infusion (Section 6.3.2.2).

6.3.2.1. 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; Attachment 12) performed at baseline (within 24 hours prior to infusion of JNJ-68284528 infusion) and daily after the first symptoms of CAR-T cell-related neurotoxicity (eg, ICANS) are suspected and until resolution. Consider performing ICE-Tool more frequently until neurotoxicity symptoms resolve. Consider performing neuroimaging (eg, magnetic resonance imaging [MRI]) at screening and/or neurology consultation if pre-existing disease is suspected; see Section 9.2 Safety Evaluation.

Subjects should be monitored for neurological toxicities including, but not restricted to, speech disorders, aphasia, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. If these or other neurological 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 (eg, ICANS) temporally associated with CRS.

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered for all neurological toxicities. 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 for additional testing (eg, pharmacokinetic or biomarkers) as clinically indicated. For signs of seizures or raised intracranial pressure (ICP)/cerebral edema, consider neuroimaging (CT/MRI), transfer the subject to the intensive care unit (ICU) and treat according to institutional guidelines or practices.

General management for CAR-T cell-related neurotoxicity (eg, ICANS) with or without concurrent CRS is summarized in Table 9. All neurological adverse events, including CAR-T related neurotoxicity (eg, ICANS), will be captured as an adverse event of special interest (see Section 12.3.3).

Table 9: Guidelines for the Management of CAR-T Cell-related Neurotoxicity (eg, ICANS)

ICANS Grade	Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] or depressed level of consciousness[c]: awakens spontaneously.	Management of CRS as appropriate per Table 8. Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion. Consider dexamethasone.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score-3-6[b] or depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 8 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 3	ICE score-0-2[b] or depressed level of consciousness[c]: awakens only to tactile stimulus, or seizures[c], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging[c].	Administer tocilizumab per Table 8 for management of CRS. In addition, administer dexamethasone[d] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 4	ICE score-0[b] or depressed level of consciousness[c] either: • subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]:	Administer tocilizumab per Table 8 for management of CRS. As above, or consider administration of methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 or more days, per investigator discretion.	As above, or consider administration of methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of raised ICP/cerebral edema, refer to Table 10 for additional management guidelines.	

Table 9: Guidelines for the Management of CAR-T Cell-related Neurotoxicity (eg, ICANS)

ICANS Grade	Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
	• deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral edema[c], 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.		

a Management is determined by the most severe event, not attributable to any other cause
b If subject is arousable and able to perform Mental Status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (see Attachment 12; ICE-Tool).
c Attributable to no other cause.
d **All references to dexamethasone administration are dexamethasone or equivalent**

Table 10: Guidelines for the Management of Raised ICP / Cerebral Edema[a]

• Elevate head of patient's bed to an angle of 30 degrees. • If patient has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg. • Hyperventilation to achieve target partial pressure of arterial carbon dioxide (PaCO2) of 28–30 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): o Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 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, o Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50–75 ml/hr while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/l, o For patients 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 9: Guidelines for the Management of CAR-T Cell-Related Neurotoxicity (ie, ICANS)

6.3.2.2. Other Neurotoxicities

If any neurologic or psychiatric symptoms are noted (see below and Section 1.6), the medical monitor should be contacted, and the subject should be referred immediately to a neurologist for a full evaluation. Subjects should be monitored for neurotoxicity for 1-year post JNJ-68284528 infusion. Particular attention should be paid to the appearance of any of the following:

- personality changes
- lack of facial expression
- being less communicative

- difficulty with short term memory
- slowing of movements
- difficulty performing simple tasks
- difficulty swallowing
- joint or muscle stiffness or inflexibility
- shuffling gait
- restlessness
- micrographia

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)[24]

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 9.4 of the protocol, if cerebral spinal fluid (CSF) or other relevant biological sample analysis is clinically indicated, a sample of CSF may be requested for additional analysis by the sponsor, as allowed by local regulations.

Per section 9.7of the protocol, qualitative changes in handwriting since baseline are being explored by the sponsor as a potential early clinical predictive marker for neurotoxicity.

6.3.3. Tumor Lysis Syndrome

Although TLS is uncommon in subjects with multiple myeloma, one subject in the Phase 1 Legend-2 Study experienced fatal TLS. Subjects must be monitored closely for symptoms of TLS. Management of TLS, including hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, is highly recommended. It is also required 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 and primary or secondary uricosuric agents, as indicated). TLS will be captured as an adverse event of special interest (see Section 12.3.3).

6.3.4. Cytopenia

Subjects may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and JNJ-68284528 infusion. In the Legend-2 study, Grade 3 and 4 cytopenias included leukopenia (25.7%), thrombocytopenia (18.9%), anemia (14.9%), and neutropenia (2.7%). Prolonged neutropenia may increase the risk of infection. Blood counts should be monitored after JNJ-68284528 infusion. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (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.

6.3.5. Hypogammaglobulinemia

Hypogammaglobulinemia may occur in subjects receiving JNJ-68284528. Monitor immunoglobulin levels after treatment as detailed in the Time and Events Schedule (Table 1) and more frequently if clinically indicated and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection.

Subjects with IgG < 400 mg/dL and recurrent infections may receive prophylactic IVIG as per institutional guidelines.

6.3.6. Infections

Administration of JNJ-68284528 may increase the risk of infection due to cytopenias or hypogammaglobulinemia. Subjects should be monitored frequently for infection and should have blood cultures obtained and empiric antibiotics administered per institutional standards. 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 Attachment 16). Perform screening for HBV, HCV, and HIV and monitor as clinically indicated (see HBV monitoring recommendations in Section 9.2 and Attachment 8, 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 who appear to have resolved hepatitis B infection.

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 Attachment 17.

6.3.7. 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 ampicillin or 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 6.2.

6.3.8. Second Primary Malignancy

Second primary malignancy is a theoretical possibility due to the risk of lentiviral insertion. Second primary malignancies 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 yearly until 15 years post 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.

7. INTERVENTION COMPLIANCE

Apheresis and infusion of JNJ-68284528 will be done 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 SIPPM for a description of the chain of identity and chain of custody procedures associated with the apheresis product and JNJ-68284528.

8. PRESTUDY AND CONCOMITANT THERAPY

Throughout the study, investigators may prescribe concomitant medications or treatments (except for those listed in Section 8.2) deemed necessary to provide adequate supportive care. All medications (including prescription and over-the-counter products, and transfusions of blood products) different from the study treatment must be recorded throughout the study beginning with the signing of the ICF until at least 100 days after infusion of JNJ-68284528, or until the start of subsequent systemic anticancer treatment, if earlier. After 100 days, only adverse events that are considered related to study drug need to be reported until the end of the study. This includes concomitant therapy and any medication used to treat or support adverse events or serious adverse events (within or beyond 100 days after infusion). 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 (Attachment 17). Recorded information will include a description of the type of the drug, dosing regimen, route of administration, duration of treatment, and its indication. All medications, including details of previous anticancer treatment, should be documented in the appropriate section of the eCRF.

Anti-myeloma therapy (medications which the subject has previously received) is permitted during bridging therapy (see Section 3.1) (Attachment 4).

8.1. Permitted Medications

The following are examples of supportive therapies that may be used during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H_2] antagonists or proton pump inhibitors, 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 initiated (if not already being administered) unless contraindicated within 1 week prior to the first dose of study treatment and continued until disease progression is established. In the case of severe adverse events such as hypercalcemia, bisphosphonates may be administrated as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- 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 (Section 6.1.2).
- 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 toxicities are permitted upon consultation with the sponsor (see Section 6.3).

8.2. Prohibited Therapies

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

- Corticosteroid use should be avoided, except for the treatment of CRS or CAR-T cell-related neurotoxicity (eg, ICANS), as described in Table 8 and Table 9. Alternative therapies, if feasible, should be given prior to corticosteroids.
- Any chemotherapy, anticancer immunotherapy (other than JNJ-68284528), or experimental therapy, except as described in Section 3.1 (bridging therapy), or protocol- specific therapies which may be used in conjunction with JNJ-68284528.
- While in follow-up, emergency orthopedic surgery or radiotherapy is generally prohibited, but may be allowed in the absence of disease progression. Cases must be discussed and approved by the sponsor. 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.
- 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.

- Other immunosuppressant agents unless used as protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS).
- Vaccination with live, attenuated vaccine after signing consent and in the ≤4 weeks prior to the infusion of JNJ-68284528, and for 100 days after infusion of JNJ-68284528.
- 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.
- Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited within the first 100 days after infusion of JNJ-68284528 (Section 6.1.2).

8.3. Subsequent Anticancer Therapy

Subsequent anticancer therapy administered after JNJ-68284528 should be only administered after confirmed PD per IMWG criteria and recorded in the eCRF. The start and end date and best response should be documented in the eCRF, if available.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarizes the frequency and timing of procedures and assessments applicable to this study (Table 1 and Table 2); for subjects who are eligible for retreatment with JNJ-68284528, follow the Time and Events Schedules in Attachment 9 (Table 12 and Table 13).

All planned assessments, including laboratory tests, on the day of JNJ-68284528 dosing must be completed and the results reviewed prior to the start of the infusion. Treatment decisions will be based on safety assessments performed at the local laboratory and disease assessments performed at the central laboratory.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: 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 study treatment infusion, 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.

The approximate volume of blood drawn from each subject in this study (up to 2 years' post-treatment) is 958 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Based on emerging data, adjustments to the planned schedule of assessments may be made by the sponsor to protect subject safety. These decisions will be documented in writing by the SET (see Section 3.5) and appropriately communicated to participating investigators prior to implementation.

9.1.2. 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 apheresis. 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. Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening phase (to reassess eligibility). The last result obtained prior to apheresis 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.

9.1.3. Apheresis

Prior to apheresis, review of safety assessments should be completed per Time and Events Schedules (Table 1 and Table 2). 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); two apheresis collections may be performed to attain this target. Instructions for processing and shipping apheresis product are provided in the SIPPM.

9.1.4. Cyclophosphamide and Fludarabine Conditioning Regimen

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 eligibility, safety assessments and disease characteristics should be completed per Section 6.1. The details regarding safety monitoring and study visits during this phase are included in the Time and Events Schedules (Table 1 and Table 2).

9.1.5. JNJ-68284528 Administration

Administration of JNJ-68284528 is fully described in Table 6.

9.1.6. Post-treatment Phase

The post-treatment phase starts after the completion of JNJ-68284528 infusion and includes the post-infusion period and the post-treatment period.

9.1.6.1. Post-infusion Period

The post-infusion period starts after the completion of JNJ-68284528 infusion on Day 1 and lasts until Day 100. Any subject who receives an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments as per the Time and Events Schedules (Table 1 and Table 2). 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) and will be instructed to report any fever (≥100.4ºF or ≥38ºC) to the study doctor immediately to initiate monitoring for development of CRS.

Hospitalization requirements are described in Table 6. Subjects will be provided a "wallet (study) card" with pertinent information about the study and be asked to carry this card with them for the duration of the post-infusion and post-treatment period.

9.1.6.2. Post-treatment Period

The post-treatment period starts on Day 101 and lasts until study completion, defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528. Assessments are to be performed per the Time and Events Schedules (Table 1 and Table 2), and include safety and disease assessments every 28 days. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of the study, whichever occurs first. Once disease progression is confirmed, subsequent disease assessment is not required unless the subject receives retreatment with JNJ-68284528 (see Attachment 9).

After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until the end of study, unless the subject has died, is lost to follow-up, or has withdrawn consent. If the information 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, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

9.1.6.3. Long-term Follow-up

Second primary malignancies will be reported for the duration of the study, defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528. Following completion of this study, assessment for replication competent lentivirus (RCL) and second primary malignancies will continue for up to 15 years after dosing with JNJ-68284528 on a follow-up study. In addition, subjects who received retreatment with JNJ-68284528 and are in follow-up at the end of the study (2 years after the last subject receives his or her initial dose of JNJ-68284528) will be monitored in this long-term follow-up study. A tumor sample should be collected and DNA, RNA or protein analysis may be performed to investigate the presence of lentiviral elements.

9.2. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurological examination), assessment of ICE-Tool scores, handwriting assessments, and assessment of ECOG performance status grade. Clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF. 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 endpoint is reached. Safety monitoring assessments may be performed more frequently, if clinically indicated.

The study will include the following evaluations of safety according to the time points provided in the Time and Events Schedules (Table 1 and Table 2).

Adverse Events

Adverse events (except for neurological adverse events, second primary malignancy, HBV reactivation, and COVID-19 infection) will be reported (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until 100 days after last administration of any study treatment or until the start of subsequent anticancer therapy, if earlier. Second primary malignancies will be reported for the duration of the study and, subsequently, will be collected on a long-term follow-up study yearly until 15 years' post dosing of JNJ-68284528. Events of HBV reactivations and COVID-19 infections, and new neurological adverse events or exacerbation of existing neurological adverse events will be reported during the first year post-dosing of JNJ-68284528. See Attachment 18 for additional adverse event reporting guidance for this study.

Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0), with the exception of CRS and CAR-T cell-related neurotoxicity (eg, ICANS). CRS should be evaluated according to the ASBMT consensus grading (Lee 2019)[22] (Attachment 11). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASBMT consensus grading (Attachment 13). Subjects with Grade 3 or higher toxicity or unresolved adverse events that lead to treatment discontinuation 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 comes first.

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 for 1-year post infusion of JNJ-68284528.

Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Attachment 15 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.

Clinical Laboratory Tests

Clinical laboratory assessments will be collected as shown in the Time and Events Schedule Table 1. Disease-related laboratory evaluations are detailed in Section 9.6.

For all laboratory evaluations, the investigator must review the laboratory results, document this review, and record clinically relevant changes occurring during the study in the adverse event section of the eCRF. 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.

The following tests will be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory:

Hematology	
Hemoglobin	Absolute lymphocyte count
White blood cell count	Platelet count
Absolute neutrophil count	
Coagulation	
Prothrombin time / International normalized ratio	Activated partial thromboplastin time
Fibrinogen	D-dimer
Chemistry	
Sodium	Total bilirubin[a]
Potassium	Alkaline phosphatase
Chloride	Lactic acid dehydrogenase
Bicarbonate	Uric acid
Blood urea nitrogen/ urea	Calcium and albumin-adjusted calcium[b]
Creatinine	Phosphate
Glucose	Albumin
Aspartate aminotransferase (AST)	Total protein
Alanine aminotransferase (ALT)	Magnesium
Gamma-glutamyl transpeptidase	Creatine phosphokinase (CPK)
Ferritin	C-reactive protein
Urinalysis	
Standard urine dipstick[c]	**If dipstick abnormal then microscopy should be performed**
Glucose	Sediment
Protein	Red blood cell count
Blood	White blood cell count
Ketones	Epithelial cells
Bilirubin	Crystals
Urobilinogen	Casts
Nitrite	Bacteria
Leukocyte esterase	
Pregnancy Test	

Pregnancy Test: serum (<5 IU/mL) β-hCG
Tests at Screening only
Serology: - **Hepatitis B[d]:** 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-HBs positive and anti-HBc positive) (Attachment 8) - **Hepatitis C:** HCV antibody, HCV RNA (for subjects who are anti HCV positive) - **HIV**
Tests at Apheresis only (as applicable per local regulations)
HIV, Hepatitis B, Hepatitis C, HTLV and other infectious diseases as applicable per local regulations
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; 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-cell lymphotropic virus.

a. Direct bilirubin if Gilbert's disease.
b. Performed by central laboratory.
c. Suggested urine dipstick evaluation; however, perform according to locally available test equipment.
d. See Attachment 8 to determine eligibility for enrollment in the study and additional safety monitoring recommendations.

Electrocardiogram

Twelve-lead ECGs will be performed at the timepoints specified in the Time and Events Schedule Table 1. ECGs should be obtained prior to any other study procedures planned for the same day.

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.

Echocardiogram or MUGA scan

Assessment of cardiac function is required at screening using either echocardiogram or multiple-gated acquisition (MUGA) scan (results obtained ≤8 weeks of apheresis are acceptable for determining eligibility). At a minimum, this will include assessment of left ventricular ejection fraction (LVEF) reported as a percentage. This value should be recorded in the eCRF.

Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure and oxygen saturation monitoring will be performed as specified in the Time and Events Schedule. 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). Blood pressure and pulse/heart rate measurements will be with a completely automated device, when available.

Physical Examination

The screening physical examination will include, at a minimum, subject's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, and lymphatic system. Thereafter, a symptom-directed physical examination will be conducted as clinically indicated at subsequent timepoints. Abnormalities will be recorded in the appropriate section of the eCRF. Body weight will be measured prior to infusion of JNJ-68284528 (see the Time and Events Schedule Table 1). Clinically significant post-baseline abnormalities should be recorded as adverse events.

ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's daily living activities (Attachment 5) and will be assessed as noted in the Time and Events Schedule Table 1.

Neurologic Examination (Phase 1b and Phase 2)

Magnetic resonance imaging (MRI) at screening or neurology consultation should be considered if pre-existing disease is suspected. For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of brain and an EEG. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using ASBMT consensus grading. Other neurological adverse events not associated with ICANs should be graded based on CTCAE version 5.0 throughout both phases of the study. Findings from neurological testing that support CAR-T cell-related neurotoxicity (eg, ICANS) should be reported in the CRF.

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

The ICE test was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR-T products (Lee 2019)[22] (Attachment 12). The ICE tool will be collected as noted in the Time and Events Schedule (Table 1 and Table 12) to guide management throughout both phases of the study. It will also be used to grade the severity of ICANS (Attachment 13). 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 (Attachment 15).

Handwriting assessments will be collected on a writing log according to the Time and Events Schedule (Table 1) 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.

9.3. Pharmacokinetics and Immunogenicity

The goal of the pharmacokinetic assessment of JNJ-68284528 in this study is to evaluate pharmacokinetic parameters, and immunogenicity effects on the pharmacokinetic profiles and parameter values. Pharmacokinetic/pharmacodynamics, dose-response (safety and efficacy) relationships will be explored. The recommended dose regimen for dose expansion will be determined based on information including the pharmacokinetic and pharmacodynamic information obtained in Phase 1b. Immunogenicity assessments will also be utilized in these evaluations. See Section 9.1.1 for sample collection instructions.

9.3.1. Evaluations

Blood and serum samples will be collected for JNJ-68284528 pharmacokinetics, and immunogenicity (antibodies to JNJ-68284528) assessment as specified in the Time and Events Schedule (Table 2). Also, pharmacokinetic and immunogenicity samples will be collected at the time onset of suspected CRS or CAR-T cell-related neurotoxicity (eg, ICANS) regardless of causality (as specified in Table 2 and Table 13). In addition, pharmacokinetic and immunogenicity samples will be collected following the end of study treatment as shown in Table 2. 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.

Venous blood samples will be collected for measurement of CAR-T positive cellular concentration and transgene levels of JNJ-68284528.

Bone marrow samples will be collected for measurement of transgene levels and cellular concentrations of JNJ-68284528 (see Time and Events schedules, Table 2 and Table 13).

Blood samples will be collected for exploratory evaluations of soluble circulating BCMA (sBCMA). This data may be used for mechanistic pharmacokinetic/pharmacodynamic modeling.

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

9.3.2. Analytical Procedures

Pharmacokinetics

Post-dose blood and bone marrow samples will be analyzed to determine CAR-T positive cellular concentration and transgene levels of JNJ-68284528 using specific and sensitive assay methods that are validated by or under the supervision of the sponsor.

Immunogenicity

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.

9.3.3. Pharmacokinetic Parameters

Blood and bone marrow samples will be collected for the measurement of JNJ-68284528 cellular concentrations and transgene levels for pharmacokinetic analyses (Time and Events Schedule Table 2). Pharmacokinetic parameters will be estimated for individuals, and descriptive statistics will be calculated. Correlation of C_{max} and AUC with dose may also be explored. Pharmacokinetic parameters include, but are not limited to, AUC_{inf}, $AUC_{(0-t)}$, AUC_{tau}, C_{max}, half-life, and T_{max} parameters will be calculated if sufficient data are available for estimation.

9.3.4. Immunogenicity Assessment/Antibodies to JNJ-68284528

Antibodies to JNJ-68284528 will be evaluated in serum samples collected during the Treatment Phase (Table 2). Additionally, serum samples should also be collected at the final visit from subjects who discontinued treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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 or further characterize the immunogenicity of JNJ-68284528.

9.4. Biomarker Evaluations

Biomarker assessments will focus on several objectives: 1) evaluate infused CAR-T cell subsets and activation markers including, but not limited to, $CD4^+$, $CD8^+$, CD25+, central memory, effector memory cells; 2) determine the ability of JNJ-68284528 to induce MRD negativity in subjects with relapse/refractory multiple myeloma who have achieved CR; 3) serum or plasma proteomic profiling of cytokines (such as IL-6, IL-15, and IL-10) and other immune related proteins (such as perforin and granzymes); 4) immunophenotyping of biomarkers of response/resistance on myeloma cells (such as BCMA and PD-L1); 5) determine the clinical benefit (ORR, DOR, TTR, PFS, and OS) of JNJ-68284528 in subjects with cytogenetic modifications (del17p, t(4;14), t(14;16), or other high-risk molecular subtypes); and 6) 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 peripheral blood mononuclear cells (PBMCs) from whole blood. Additional sample(s) for cytokines will be collected as clinically indicated (Table 2).

The potential presence of RCL will be evaluated from whole blood samples of subjects treated with JNJ-68284528. RCL will be evaluated using a qPCR assay against the lentiviral vesicular

stomatitis virus-G gene yearly for up to 15 years in the present study or a separate long-term follow-up study.. 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. 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 (TCR) analysis (both clonality and/or diversity of TCR), 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 from previously collected bone marrow samples during or after study completion for a retrospective analysis. For subjects diagnosed with a SPM, a tumor sample should be collected. 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 this case, 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, as allowed by local regulations.

9.4.1. Pharmacodynamic/Predictive Markers

The baseline of the JNJ-68284528 subsets and dynamic changes/persistence and activation of 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, or CyTOF, or next generation sequencing (whole exome and RNA sequencing) or both. T cell receptor (TCR) sequencing may be performed to study T cell clonality that may affect drug 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, IL-15, IL-10, and IFN-γ) and other circulating proteins (such as granzymes and perforin) will be analyzed to identify potential pharmacodynamic and predictive biomarkers of response or resistance.

9.4.2. Minimal Residual Disease

Minimal residual disease (MRD) negativity is being evaluated as a potential surrogate for PFS and OS in multiple myeloma treatment. MRD will be monitored in subjects using next generation sequencing (NGS) on bone marrow aspirate DNA. Baseline bone marrow aspirates will be used to define the myeloma clones, and post-treatment samples will be used to evaluate MRD negativity. A fresh bone marrow aspirate will be collected prior to the first dose of conditioning regimen (≤7 days). If the NGS MRD method is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. Additional timepoints for MRD assessment are reflected in the Time and Events schedule (Table 2).

In the event fresh bone marrow aspirate will not be collected at Baseline, 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 MRD endpoints by NGS.

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

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

9.6. Efficacy Evaluations

Disease evaluations must be performed as specified in the Time and Events Schedule Table 1. Disease evaluations will be performed by a central laboratory (additional samples may be collected for analysis by the local laboratory) until disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of the study, whichever occurs first. However, if a subject receives retreatment with JNJ-68284528 after a confirmed disease progression (see Section 3.1), then disease evaluations will continue according to the Time and Events schedule provided in Attachment 9. This study will use the IMWG-based response criteria.[30] If it is determined that the study treatment interferes with the immunofixation assay, CR will be defined as the disappearance of the original M-protein associated with multiple myeloma on immunofixation, and the determination of CR will not be affected by unrelated M-proteins secondary to the study treatment.[11]

For quantitative immunoglobulin (QIg) at baseline, M-protein, immunofixation, and free-light chain (FLC) measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Disease progression must be consistently documented across clinical study sites using the criteria in Attachment 1.

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, however this does not include screening assessments. 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.

9.6.1. 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. Only one serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests. Assessments will be performed as specified in the Time and Events Schedule (Table 1 and Table 12).

- Serum quantitative Ig
- 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
- Serum β2-microglobulin

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule Table 1 and Table 12 until the development of confirmed disease progression. 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 and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or non-quantifiable). For subjects with light chain multiple myeloma, serum and urine immunofixation tests will be performed routinely as per the Time and Events Schedule (Table 1 and Table 12).

9.6.2. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL [>2.9 mmol/L]) may indicate disease progression or relapse if it is not attributable to any other cause. Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Attachment 7.

9.6.3. Bone Marrow Examination

Bone marrow aspirate or biopsy (acceptable if aspirate is not possible) will be performed for clinical assessments. Bone marrow aspirate will be performed for biomarker evaluations. Clinical staging (morphology, cytogenetics, and immunohistochemistry or immunofluorescence or flow

cytometry) should be done by a local laboratory. A portion of the bone marrow aspirate will be sent to the central laboratory for immunophenotyping and to monitor BCMA, checkpoint ligand expression in CD138-positive multiple myeloma cells, and checkpoint expression on T cells. If feasible, bone marrow aspirate also will be performed to confirm CR and sCR and at disease progression. In addition, MRD will be evaluated as specified in the Time and Events schedules.

9.6.4. Skeletal Survey

A skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed during the screening phase and evaluated by the local laboratory by either roentgenography ("X-rays") or low-dose computed tomography (CT) scans without the use of IV contrast. If a CT scan is used it must be of diagnostic quality. Following JNJ-68284528 infusion, 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. Magnetic resonance imaging (MRI) is an acceptable method for evaluation of bone disease, and may be included at the discretion of the investigator; however, it does not replace the skeletal survey (see the disease response criteria in Attachment 1). If a radionuclide bone scan is used at screening, in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. Note: a radionuclide bone scan does not replace a complete skeletal survey.

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.

9.6.5. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented ≤14 days prior to the first dose of the conditioning regimen. Clinical examination or MRI may be used to document extramedullary sites of disease. 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 extramedullary plasmacytomas. However, PET/CT fusion scans can be used to document extramedullary plasmacytomas if the CT component of the PET/CT fusion scan is of sufficient diagnostic quality.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at ≤14 days prior to the first dose of the conditioning regimen, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed, measured, and evaluated locally every 4 weeks (for physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may 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 (MR), the sum of products of the perpendicular diameters of the existing extramedullary 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 Attachment 1). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary 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 extramedullary 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.

9.7. Sample Collection and Handling

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 are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual. Refer to the Time and Events Schedule (Table 1 and Table 2) for the timing and frequency of all sample collections.

9.8. Patient-reported Outcome Assessments (Phase 2 Only)

The subjects' HRQoL (disease-related symptoms, functioning, and general well-being) will be captured using patient-reported outcome (PRO) measures. The PRO measures will be administered for the Phase 2 part of the study, during site visits, to understand how the PRO endpoints change over time. These measures will be administered according to the Time and Events Schedule (Table 1); 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. At completion, the study coordinator should verify that the questionnaires are completed in full or document the reason for missing information. Full training documentation will be provided to site coordinators before the start of data collection. PRO assessments will be conducted beyond disease progression or subsequent anticancer therapy. If no site visits are scheduled for additional disease evaluations, subjects will have the option of completing the PRO assessments after disease progression or subsequent anticancer therapy via telephone.

Samples of the PRO measures are provided in Attachment 10:

- EORTC QLQ-C30
- EORTC QLQ-MY20: 4 single items
- EQ-5D-5L
- PGIS

- PGIC

The 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 multiple myeloma. Reliability, validity, and clinically meaningful change have been demonstrated.[32,33] The EORTC QLQ-MY20 was designed to use alongside the EORTC QLQ-C30 to address issues of more relevance to myeloma patients.[8] Four single items from the EORTC QLQ-MY20 will be administered to assess emotional health status (feel restless or agitated, thinking about your illness, worried about dying, worried about health in the future). Recall, response options, and interpretation are similar to the EORTC QLQ-C30.

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 Patient Global Impression of Severity (PGIS) is a single item to assess severity of pain. Subjects are asked to rate the severity of their current pain on a 5-point verbal rating scale. The Patient Global Impression of Change (PGIC) is a single item to assess the subject's perception in change of their overall health status using a 7-point verbal rating scale. The PGIC is only administered post-infusion.

9.9. Qualitative Interviews (Phase 2 Only)

Subjects enrolled in Phase 2 portion of the study will have the option of participating in pre-treatment (at screening) and post-treatment (Day 100 and approximately 6 months post infusion with JNJ-68284528) semi-structured interviews.

Pre- and post-treatment interviews have been used in early phase clinical trials to inform exploratory insight into subject experiences. The data from these interviews will not be reconciled with the safety database of the study. These interviews are semi-structured and are designed to allow subjects to provide their own impressions of JNJ-68284528 and not be restricted to items included in standard questionnaires. Interviewers will be trained on the interview guide and provided with note-taking pages to capture subject responses. Interviews will take place in the

local language and will be audiotaped with approval of the subject for transcription and content analysis. The content analysis will present the qualitative themes that emerge from the narrative data.

9.10. Medical Resource Utilization

Health economics data such as medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all Phase 2 subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. As per Table 1, all medical care encounters since the previous collection will be collected for all Phase 2 subjects. Medical resource evaluation data will be collected until Day 180 (± 7 days). 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, radiographic diagnostics, laboratory tests, 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)

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she dies before the end of the study, has not been lost to follow-up or has not withdrawn consent for study participation before the end of the study, defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528.

10.2. Discontinuation of Study Treatment

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
- Grade ≥3 nonhematologic toxicity related to cyclophosphamide and fludarabine occurs, and precludes retreatment with cyclophosphamide and fludarabine prior to JNJ-68284528 infusion per Section 6.1
- The subject received concurrent (non-protocol) anticancer treatment (with exception of sponsor-approved bridging therapy)

- Confirmed disease progression per IMWG criteria (Attachment 1) between the time of conditioning therapy and infusion of JNJ-68284528.
- Subject refuses further study treatment
- Noncompliance with study treatment or procedure requirements

The primary reason for treatment discontinuation will be documented in the eCRF and source documents, and the subject should be followed per standard of care until recovery from bridging therapy or cyclophosphamide and fludarabine conditioning regimen. If a subject's study treatment is discontinued for any reason, this will not result in automatic withdrawal of the subject from the study.

10.3. 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
- Failure to manufacture JNJ-68284528 after 2 apheresis attempts
- The sponsor discontinues the study

The reason(s) for subject withdrawal will be recorded on the eCRF and 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 withdraws consent following dosing with JNJ-68284528, study assessments for the last visit in the post-infusion period (Table 1: Day 100; Table 2: Day 100) should be completed prior to withdrawal of consent, if feasible.

10.4. Withdrawal from the Use of Research Samples

Withdrawal from the use of samples is future research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). If this occurs, then samples will be destroyed after they are no longer needed for the clinical study. Details of sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

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.

Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

The efficacy and safety data will be summarized separately for Phase 1b and Phase 2 part. Pooling of the two parts maybe considered when appropriate. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

The analysis populations for this study are defined as follows:

- **Modified Intent-To-Treat (mITT) Analysis Set:** This set consists of subjects who received a JNJ-68284528 infusion at the targeted RP2D dose and will be considered as the primary analysis set for all efficacy summaries.
- **All Treated Analysis Set:** This set consists of subjects who received JNJ-68284528 infusion and will be considered as the primary analysis set for safety summaries.
- **Pharmacokinetic Analysis Set:** This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose pharmacokinetic sample.
- **Immunogenicity Analysis Set:** This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose immunogenicity sample.

11.2. Sample Size Determination

At least 24 and up to approximately 50 subjects will be treated in Phase 1b part to establish the RP2D and assess safety. With 24 treated subjects, if the true incidence rate of certain adverse events (refer to Table 3) is 10%, the probability of observing at least one subject experiencing event is more than 90%. The probability of detecting at least one subject experiencing a certain adverse event under the assumed true incidence rate based on plausible sample sizes is provided in Table 11.

Table 11: Sample Size Scenarios in Phase 1b

Sample Size in Phase 1b	True incidence rate of the adverse event	Probability of observing at least one subject experiencing the adverse event
24	10%	92%
40	6%	91.6%
50	5%	92.3%

For therapies available to treat subjects with relapsed or refractory multiple myeloma at the time that this protocol was written (including daratumumab), the reported ORR is 30% or less.

The sample size for the Phase 2 portion of the study assumes that the overall response rate will be at least 50%. With 60 subjects treated with JNJ-68284528 in the Phase 2 portion of the study, there will be approximately 90% power to declare the ORR is higher than 30% at the 1-sided significance level of 0.025.

11.3. Efficacy Analyses

Endpoint Definitions:

Overall response rate (ORR) is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria.[10,11,30]

VGPR or better response rate (sCR+CR+VGPR) is defined as the proportion of subjects who achieve a VGPR or better response according to the IMWG criteria.[10,11,30]

Duration of response (DOR) will be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered as disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Time to response (TTR) is defined as the time between date of the initial infusion of JNJ-68284528 and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease, or in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

Progression-free survival (PFS) defined as the time from the date of the initial infusion of JNJ-68284528 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.

Overall survival (OS) is measured from the date of the initial infusion of JNJ-68284528 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.

For efficacy, assessment by the IRC will be used as primary.

The first analysis for the primary endpoint, ORR (PR or better), will be conducted approximately at 6 months after the last subject has received his or her initial dose of JNJ-68284528, and will be based on the mITT analysis set. The response rate and its 95% exact confidence interval (CI) will be calculated based on binomial distribution, and the null hypothesis will be rejected if the lower bound of the confidence interval exceeds 30%. Analysis of VGPR or better response rate, DOR, PFS, and OS will be conducted at the same cutoff as the ORR, and an update of these endpoints will be provided at approximately 9-12 months after the last subject has received his or her initial dose of JNJ-68284528 and at the end of the study, which is defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528. Additional safety data will be collected in a long-term follow-up study.

A sensitivity analysis of ORR will be performed based on the subjects in the mITT analysis set who received the JNJ-68284528 product that met all of the pre-specified release criteria.

The agreement on ORR between the determination by the IRC and the assessment by a validated computerized algorithm developed by the sponsor will be evaluated using the kappa statistic and 95% CI will also be provided.

The distribution (median and Kaplan-Meier curves) of DOR will be provided using Kaplan-Meier estimates for subjects who achieved response during the study. Similar analysis will be performed for OS, PFS, and TTR for the mITT analysis set.

11.4. Safety Analyses

All safety analyses are to be performed on data from the all treated analysis set. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of JNJ-68284528 infusion. The safety parameters to be evaluated are the incidence, severity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated. Adverse events will be summarized by system organ class, preferred term, worst grade experienced by the subject, and by dose level.

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 (MedDRA). Treatment-emergent adverse events are adverse events with onset after JNJ-68284528 infusion or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent adverse events 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 dose group.

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

Adverse events that occur after administration of the conditioning regimen and before JNJ-68284528 infusion will be summarized and listed separately.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan or Data Presentation Plan) will be used in the summary of laboratory data. 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 shift tables. A listing of subjects with any laboratory results outside the reference ranges will be provided.

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

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.5. 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.

- Description on the planned analyses for Cmax, AUC, Tmax,
- Responder vs. non-responder analyses

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.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then other PK/pharmacodynamic modeling may be performed, including exploring the relationship between JNJ-68284528 cellular concentrations, transgene levels, pharmacodynamic markers (eg, sBCMA, M-protein) and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

11.7. 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). The results will be summarized by dose level for subjects with appropriate samples for the detection of antibodies to 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.

11.8. Patient-reported Outcome Assessments (Phase 2 Only)

The EORTC QLQ-C30, EORTC QLQ-MY20 (4 items), EQ-5D-5L utility and visual analog scores, PGIC, 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.[12] Within-group change of the PRO endpoints will be assessed by change from baseline (screening phase) using mixed models for repeated measures.

11.9. Medical Resource Utilization

Medical resource utilization data will be summarized in descriptive statistics of medical encounters (eg, length of stay, inpatient, outpatient, test, and reason).

12. ADVERSE EVENT REPORTING

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.

12.1. Definitions

12.1.1. 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 treatment. 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 Conference 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 Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European 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 treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-68284528, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

12.1.3. 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). CRS should be evaluated according to the ASBMT consensus grading (Lee 2019)[22] (Attachment 11). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASBMT consensus grading (Attachment 13). Any adverse event or serious adverse event not listed in the NCI CTCAE Version 5.0 will be graded according to investigator clinical judgment 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.

12.2. Special Reporting Situations

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

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Medication error involving a sponsor product (with or without subject/subject exposure to the sponsor study treatment, eg, name confusion)
- Exposure to a sponsor study treatment from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events (with the exception of neurological adverse events, second primary malignancies, see Section 12.3.3, HBV reactivation, and COVID-19 infection) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 100 days after last administration of any study treatment or until the start of subsequent systemic anticancer therapy, if earlier, and may include contact for follow-up of safety. After 100 days, only adverse events that are considered related to study drug need to be reported until the end of the study. Events of HBV reactivations and COVID-19 infection, and new neurological adverse events or exacerbation of existing neurologic adverse events will be reported during the first year post-dosing of JNJ-68284528. Adverse events of special interest are defined in Section 12.3.3. Anticipated adverse events are defined in Attachment 14.

Serious adverse events, including those spontaneously reported to the investigator must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. See Attachment 18 for additional adverse event reporting guidance for this study.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the 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.

Exceptions:

- Expected progression of disease 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 (see Section 12.1).

All deaths not related to disease progression, regardless of attribution, should be reported to the sponsor following expedited reporting procedures.

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.

The investigator (or sponsor where required) must report suspected unexpected serious adverse reactions to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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 (at minimum):

- 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 staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

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.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed 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 made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, 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 treatment 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 administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.

12.3.3. Adverse Events of Special Interest

Cytokine release syndrome, neurotoxicity (including CAR-T cell-related neurotoxicity [eg, ICANS] and other neurotoxicities), TLS, and second primary malignancy of any grade will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality. These events should be reported to the sponsor in a timely manner, irrespective of seriousness (eg, serious and nonserious adverse events). Events of CRS, TLS, and neurotoxicity (any grade) must be reported until 100 days after last administration of any study treatment or until the start of subsequent anticancer therapy, if earlier, and followed until recovery or until there is no further improvement.

Second primary malignancies must be reported for the duration of the study, irrespective of treatment emergent status, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528.

The following events must be reported to the sponsor using the Serious Adverse Event Form within 24 hours of awareness of the event, irrespective of seriousness or causality (eg, serious and nonserious adverse events):

- ≥Grade 3 CRS,
- ≥Grade 3 neurotoxicity,
- ≥Grade 3 tumor lysis syndrome,
- Any grade movement and neurocognitive toxicity (ie, parkinsonism),
- Any grade second primary malignancies.

Adverse events of special interest that are considered to be non-serious by the investigator are to be included on the serious adverse event form and in the eCRF. All adverse events of special interest of any grade should be followed until recovery or until there is no further improvement.

12.3.4. 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 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.

12.4. 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.

13. 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.

13.1. 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 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. 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.

14. STUDY TREATMENT INFORMATION

14.1. Physical Description of Study Treatment

JNJ-68284528 therapy is a BCMA-directed genetically modified autologous T cell immunotherapy that involves reprogramming a subject's T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate BCMA-expressing malignant and normal cells. Upon binding to BCMA-expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination, and persistence of the JNJ-68284528.

14.2. Packaging

JNJ-68284528 will be provided in an infusion bag with specific subject identifiers.

JNJ-68284528 will be provided in an infusion bag with specific subject identifiers, this will include subject number and subject apheresis identification number or donor identification number (DIN), subject name and subject date of birth, as allowed by local regulations.

14.3. Labeling

Study treatment labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

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 IPPI for additional guidance on study treatment preparation, handling, and storage.

14.5. Drug 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 treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

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 under appropriate environmental conditions. Unused study treatment 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.

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Investigator's Brochure
- ECG machine and manual
- IPPI/SIPPM (includes apheresis and cell processing instructions)
- Laboratory Manual
- Interactive web response system manual
- Electronic data capture (eDC) manual
- Sample ICF
- Subject diaries and instructions/educational materials

- PRO instruments and completion guidelines (Phase 2)
- Thermal printer and barcode scanner (for sites utilizing Vineti chain of custody/chain of identity software in Phase 2)

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before exposure to the public. As discussed in Section 1.5, 74 subjects with relapsed or refractory multiple myeloma have received treatment with LCAR-B38M CAR-T cells in a clinical study setting. An analysis of safety data for these subjects demonstrated a manageable safety profile consistent with its known mechanism of action. In view of the Legend 2 study results and the prognosis for the subject population being considered for this study, a positive risk-benefit profile is anticipated. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit.

Apheresis risks may include hypotension, faintness, blurry vision, dizziness, coldness, sweating, infection, abnormal blood clotting, allergic reaction, bleeding, seizures, abdominal cramps, and tingling in the limbs. Subjects will be closely monitored during the procedure and will be evaluated for hospitalization in the case of CRS.

The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacokinetic/pharmacodynamic characteristics of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each subject during the study. The volume of blood to be drawn is considered to be customary and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the timeframe of the study, based upon the standard of the American Red Cross.

Potential subjects will be fully informed of the risks and requirements of the study prior to enrollment and, during the study, subjects will be given any additional 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.

16.2. Regulatory Ethics Compliance

16.2.1. 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.

16.2.2. 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)
- Investigator's Brochure (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 Investigator's Brochure 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 treatment
- 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).

16.2.3. Informed Consent

Each subject 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 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 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 physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject 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 the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject 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 is obtained.

16.2.4. 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. For tracking and traceability of the apheresis material and investigational product, subject name and date of birth, as allowed by local regulations, will be collected to ensure chain of identity of the investigational product for the subject. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject 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 biomarker, pharmacokinetic, 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.

16.2.5. 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, understand multiple myeloma, understand differential drug responders, and 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 10.4, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the study, when 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, 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

17.3. 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 enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

For tracking and traceability of the apheresis material and investigational product, subject name and date of birth, as allowed by local regulations, will be collected to ensure chain of identity of the investigational product for the subject.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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; drug receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment 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 4.1, Inclusion Criteria and Section 4.2, 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 electronic source 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 the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. 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, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the 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.

If necessary, queries will be generated in the eCRF 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 eCRF tool at their own initiative or as a response to an auto query (generated by the eCRF tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. 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, periodic monitoring visits by the sponsor, and where applicable 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.

17.7. 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.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study will be defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. 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 treatment development

17.10. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance

with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. 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.

17.11. Use of Information and Publication

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 CSR 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 CSR has been issued will be reported in a separate report and will not require a revision of the CSR. 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 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 substudy 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 of the availability of the final data (tables, listings, graphs), 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.

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Attachment 1: 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 2- to 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	• ≥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[c]	Any one or more of the following criteria: • Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥0.5 g/dL), *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 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 patients 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 patient has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy chain isotype (IgG, IgM, etc.).

[c] Clarifications to the criteria for coding 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) and Rajkumar (2011)[11,30], Kumar (2016)[18]

Attachment 2: Deleted

Attachment content removed in Amendment 2

Attachment 3: International Myeloma Working Group Diagnostic Criteria

Diagnostic criteria for myeloma must be met when the patient 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 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 (2011)[30]

Attachment 4: Prior Cancer Therapy for Multiple Myeloma and Refractory Myeloma Definition

Prior Therapy

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.

Refractory Myeloma

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy. There are 2 categories of refractory myeloma: "relapsed-and-refractory myeloma" and "primary refractory myeloma."

Relapsed and refractory myeloma

Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.

Source: Rajkumar (2011)[30]

Attachment 5: Eastern Cooperative Oncology Group Performance Status Grade

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

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken 1982).[26]

Attachment 6: Formulas for Estimating Glomerular Filtration Rate

Modified Diet in Renal Disease (MDRD) Formula

For serum creatinine in **mg/dL**, the estimated glomerular filtration rate (eGFR) for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

For serum creatinine in **µmol/L**, the eGFR for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (µmol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

Sources:
Levey (2006)[23]

Attachment 7: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
Serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L) =
Serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

Source: Burtis (1999)[6]

Attachment 8: 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 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 3 months for the first 12 months after dosing.

Subjects with positive anti-HBc and positive 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 3 months for the first 12 months after dosing.

Attachment 9: Time and Events Schedules for Retreatment with JNJ-68284528

Table 12: Time and Events Schedule for Study Procedures/ Assessments at Retreatment with JNJ-68284528

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Re-treatment	Post Infusion (Day 1X to Day 100X) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]										Post-treatment (Day 101X and up to Study Completion [a]
	≤28 days prior to apheresis	If Performed	Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7X to Day -5X	Day 1X (Infusion)	Day 3X	Day 7X (± 1 day)	Day 10X (± 1 day)	Day 14X (± 1 day)	Day 21X (± 2 days)	Day 28X (± 2 days)	Day 42X (± 2 days)	Day 56X (± 2 days)	Day 78X (± 2 days)	Day 100X (± 2 days)	(every 28 days after day 100X)[b] (± 7 days)
Screening Assessments															
Eligibility criteria	X														
Demography, Updated Medical History	X														
Disease Characteristics[c]			X (prior to start of conditioning regimen)												
ECOG	X		Prior to 1st dose only	X								X		X	
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated												
12-lead ECG	X											X			
Echocardiogram or MUGA scan	X (≤8 weeks of apheresis)		For subjects who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), assessment of cardiac function should be repeated after completion of bridging therapy and prior to the start of the conditioning regimen, then again as clinically indicated if the subject develops signs/symptoms of heart failure.												
ICE neurological test				X (≤24 hours prior to infusion)[q]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform daily until ICANS is resolved										

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Re-treatment**	**Post Infusion (Day 1X to Day 100X) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**										**Post-treatment (Day 101X and up to Study Completion[a]**
	≤28 days prior to apheresis	**If Performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7X to Day -5X**	**Day 1X (Infusion)**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**(every 28 days after day 100X)[b] (± 7 days)**
Handwriting sample				X (≤24 hours prior to infusion)[n]	X	X	X	X	X	X (also on Day 35)	X	X	X	X	up to Day 184
Safety Criteria (prior to apheresis and conditioning regimens)															
Safety criteria (See Section 6.1)		X (See Section 6.1.1)	≤72 hours of the 1st dose only (See Section 6.1.2)	X (See Section 6.1.3)											
Laboratory Assessments (See Section 9.2)															
Hematology[d]	X	X (within 24 hours prior to apheresis)	Prior to 1st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	
Chemistry[d]	X	X (≤72 hour window)	Prior to 1st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	
Serology[e]	X														
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X			As clinically indicated for subjects who have fever or other signs of potential CRS											
Urinalysis	X	As clinically indicated													
Serum Pregnancy test (in subjects with childbearing potential)	X	X (≤72 hour window)	Prior to 1st dose only	As clinically indicated											
Infectious Disease Testing[m]	X (within 60 days of apheresis; as applicable per local regulations)														

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Re-treatment**	**Post Infusion (Day 1X to Day 100X) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**										**Post-treatment (Day 101X and up to Study Completion [a]**
	≤28 days prior to apheresis	**If Performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7X to Day -5X**	**Day 1X (Infusion)**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**(every 28 days after day 100X)[b] (± 7 days)**
Study Intervention Administration															
Weight	X	X (for JNJ-68284528 dose calculation)	Prior to 1st dose only	X											
Vital signs, including oxygen saturation	X	X	X	X[f]	X	X	X	X	X	X		X			
Temperature				Measure at least twice a day[g]											
Apheresis		X													
Cyclophosphamide and fludarabine			X												
Pre-infusion medication (see Section 6.2 for requirements prior to dosing with JNJ-68284528)				X											
JNJ-68284528 (See SIPPM and IPPI for administration of JNJ-68284528)				X											

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Re-treatment**	**Post Infusion (Day 1X to Day 100X) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**										**Post-treatment (Day 101X and up to Study Completion [a]**
	≤28 days prior to apheresis	**If Performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7X to Day -5X**	**Day 1X (Infusion)**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**(every 28 days after day 100X)[b] (± 7 days)**
Serum and Urine Disease Evaluations (See Section 9.6 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory[p]. Following re-treatment with JNJ-68284528, disease evaluation should continue to be performed until confirmed second disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.) SPEP/UPEP collected before the retreatment dose will be used as the new baseline															
Serum β2-microglobulin	X[i]		X (prior to first dose of conditioning regimen [≤7 days])												
Quantitative Immunoglobulins			X (prior to first dose of conditioning regimen [≤7 days]) [h]							X		X	X	X	X
Serum M-protein quantitation by electrophoresis	X		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
24-hour urine protein electrophoresis sample	X[j]		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum calcium corrected for albumin	X		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum FLC and serum/urine immunofixation	X		Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (≤7 days) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed												

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Re-treatment**	**Post Infusion (Day 1X to Day 100X) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[a]**										**Post-treatment (Day 101X and up to Study Completion [a]**
	≤28 days prior to apheresis	**If Performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7X to Day -5X**	**Day 1X (Infusion)**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**(every 28 days after day 100X)[b] (± 7 days)**
Other Disease Evaluations															
Bone marrow aspirate and core biopsy [j]			X (prior to first dose of conditioning regimen [≤7 days])	To confirm CR, sCR, and at disease progression (immunohistochemistry or flow cytometry). See Table 13 for additional bone marrow collection for research.											
Skeletal Survey [k]	X		As clinically indicated to assess for disease progression												
Assess extramedullary Plasmacytomas [l]			X (≤14 days prior to first dose of conditioning regimen)	Measurable sites Day 28X, Day 56X, Day 78X, Day 100X then every 4 weeks for physical examination (if applicable) and Day 78X and Day 156X then every 12 weeks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others).											
MRD and biomarker evaluations			See Biomarker Time & Events Schedule (Table 13)												
Medical Resource Utilization															
MRU				X				X		X		X		X	X°
Ongoing Subject Review After an additional event of disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until study completion															
Adverse Events	Continuous from the time of signing of ICF until 100 days after retreatment. Second primary malignancies should be followed from the time of signing of ICF signing to study completion CRS should be evaluated according to the ASBMT consensus grading (Lee 2019)[22] (Attachment 11). Report new neurologic adverse events or exacerbation of existing neurologic adverse events up to 12 months after JNJ-68284528 infusion. CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according the ASBMT consensus grading (Attachment 13). Events of HBV reactivations and COVID-19 infection should be reported during the first year post-dosing of JNJ-68284528.														
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after retreatment. Concomitant usage for the treatment of adverse events after 100 days should be reported. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 17).														

Abbreviations: aPTT=activated partial thromboplastin time; CR=complete response; sCR=stringent complete response; CRS= cytokine release syndrome; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; FISH=fluorescence in situ hybridization; FLC=free light chain; HBV=hepatitis B virus; ICANS=immune-

effector cell-associated neurotoxicity syndrome; ICE=immune effector Cell-associated Encephalopathy; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; PRO=patient reported outcome; PT=prothrombin time; SIPPM=site investigational product procedures manual; SOC=standard of care; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

[a] For subjects who discontinue the study before Day 100X, the Day 100X assessments should be performed prior to withdrawal of consent if feasible. Subjects who discontinue after Day 100X but before study completion should have urine and serum disease assessments performed prior to withdrawal of consent if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. For subjects who receive retreatment with JNJ-68284528 and are in follow-up at the end of the study (2 years after the last subject receives the initial dose of JNJ-68284528), monitoring will continue in the long-term follow-up study (Section 9.1.6.3).

[b] Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion.

[c] Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable]), both of which may originate from prior to or during the screening period within 42 days before apheresis, or between apheresis and the conditioning regimen, as applicable.

[d] For subjects who are hospitalized for potential CRS, hematology and chemistry laboratory evaluations should be performed at least daily or more as clinically indicated

[e] Serology results performed as standard of care within 28 days prior to apheresis 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-HBs positive and anti-HBc positive); Monitor HBV-DNA, AST/ALT every 3 months for one year post-dose of JNJ-68284528. Hepatitis C**:** HCV antibody, HCV-RNA (for subjects who are anti HCV positive); HIV serology

[f] Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion. Monitor until normalized after a CRS event

[g] Temperature will be checked at least twice a day up to Day 28X. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with subject source documents.

[h] All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.

[i] UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.

[j] Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (see Table 13).

[k] Results from skeletal survey performed as routine follow-up within 42 days before start of apheresis may be used without these tests being repeated. The skeletal survey is to be performed by either roentgenography or low-dose computed tomography (CT) scans without the use of IV contrast. If a CT is used it must be of diagnostic quality. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression).

[l] Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated prior to the first dose of the conditioning regimen, by clinical examination or radiologic imaging.

[m] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations.

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

[o] Medical resource evaluation data will be collected until Day 180X (± 7 days)

[p] Local laboratory assessments may be used under specified circumstances (see Section 9.6)

Table 13: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling for Retreatment

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101X up to study completion)											At PD	At End of Study for subjects without PD
	≤28 days prior to apheresis	If performed	Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) [b]	Day 1X (Infusion)	Day 2X	Day 3X	Day 7X (± 1 day)	Day 10X (± 1 day)	Day 14X (± 1 day)	Day 21X (± 2 days)	Day 28X (± 2 days)	Day 42X (± 2 days)	Day 56X (± 2 days)	Day 78X (± 2 days)	Day 100X (± 2 days)	Day 184X (±7 days)		
Pharmacokinetics																		
PK CAR positive T cell cellular blood sample[c]			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as JNJ-68284528 infusion), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
PK CAR transgene levels blood sample[c]			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as JNJ-68284528 infusion), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
Soluble serum BCMA sample			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as JNJ-68284528 infusion), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X
PK CAR transgene levels bone marrow sample			X (prior to first dose of conditioning regimen [≤7 days])								X		X			X		

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments)[a] and Post-treatment (Day 101X up to study completion)**											**At PD**	**At End of Study for subjects without PD**
	≤28 days prior to apheresis	**If performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose)[b]**	**Day 1X (Infusion)**	**Day 2X**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**Day 184X (±7 days)**	
PK CAR positive T cell bone marrow sample			X Prior to 1st dose only (window 7 days to prior to 1st dose)								X		X			X	
ADA sample (serum)[c,d]				Pre-dose					X		X		X	X	X	X	X	X
Biomarker Sampling																	
Immuno-phenotyping (whole blood)		X	X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year		X	X[e]
Flow cytometry, (aspirate) (bone marrow)[e]			X (prior to first dose of conditioning regimen [≤7 days])								X		X			X	X	X
CyTOF (aspirate) (bone marrow)[e,f]			X (prior to first dose of conditioning regimen [≤7 days])													X	X	X

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101X up to study completion)**											**At PD**	**At End of Study for subjects without PD**
	≤28 days prior to apheresis	**If performed**	**Day -5X,* -4X, -3X (assessments may be conducted ≤72 hours predose) [b]**	**Day 1X (Infusion)**	**Day 2X**	**Day 3X**	**Day 7X (± 1 day)**	**Day 10X (± 1 day)**	**Day 14X (± 1 day)**	**Day 21X (± 2 days)**	**Day 28X (± 2 days)**	**Day 42X (± 2 days)**	**Day 56X (± 2 days)**	**Day 78X (± 2 days)**	**Day 100X (± 2 days)**	**Day 184X (±7 days)**		
CyTOF/ PBMC/ Plasma (whole blood)		X					X	X	X	X	X		X		X	X	X	X[e,f]
MRD (aspirate) (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])			Sample should be collected: • For all dosed subjects at Day 28X, and at approximately 6X, 12X, 18X, 24X months regardless of the status of disease measured in blood and urine • For subjects with suspected CR at the time of CR and then yearly for subjects that remain on study up to disease progression.												
Cytogenetics (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])														X	
Replication Competent Lentivirus (RCL) (whole blood)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose		At approximately 3X (Day 84), 6X (Day 168), and 12X (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 assessments within the first year are negative. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.											
Cytokine profiling[g] (serum)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose, 2hrs Post (±10 minutes)	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: ADA=anti-drug antibody; BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; PD= progressive disease; EOI=end of infusion; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; sCR=stringent complete response

[a] For subjects who discontinue the study before Day 100X, the Day 100X assessments should be performed if feasible.

[b] Window for start of conditioning regimen: Day -7 to Day -5

[c] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) Grade ≥2 (at onset of the event, and 24 and 72 hours after) or as clinically indicated; and 2) as indicated based on emerging data.

[d] ADA sample should be collected if a subject withdraws from the study after JNJ-68284528 administration but prior to disease progression or study completion.

[e] Sample should also be collected at suspected CR

[f] Sample should be collected at 12 months, relative to Day 1X, for subjects that achieve CR/sCR and remain on study.

[g] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) (at onset of the event, and then every 24 hours until CRS or ICANS event has stabilized or is resolving at which time additional collections should occur at 24, 48, and 72 hours) or as clinically indicated; and 2) as indicated based on emerging data.

Attachment 10: Patient Reported Outcomes (PRO) Measures

EORTC QLQ-C30

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

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

Single Items from the EORTC QLQ MY20

During the past week:

Item #		Not at all	A Little	Quite a Bit	Very Much
#44	Did you feel restless or agitated?	1	2	3	4
#48	Have you been thinking about your illness?	1	2	3	4
#49	Have you been worried about dying?	1	2	3	4
#50	Have you worried about your health in the future?	1	2	3	4

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

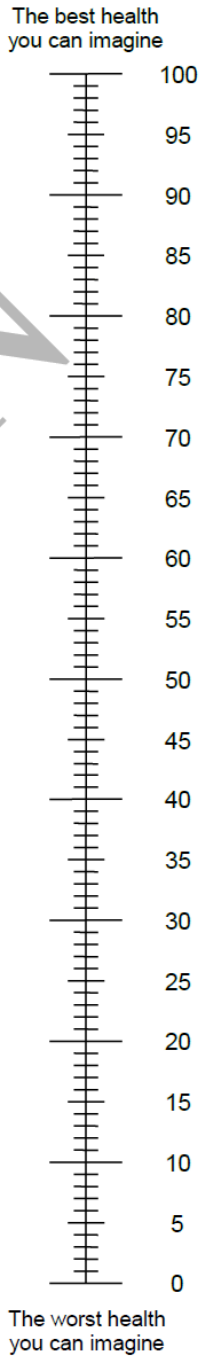
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



3

Patient Global Impression of Severity (PGIS)

Patient's Global Impression of Severity (PGIS)
Pain

Overall, how would you rate the severity of your pain currently? (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

Patient Global Impression of Change (PGIC)

Patient's Global Impression of Change (PGIC)
of Overall Health

Compared to before you received the CAR-T infusion in this study, how has your overall health changed? (Please select one response)

- ☐ 1. A lot better now
- ☐ 2. Moderately better now
- ☐ 3. A little better now
- ☐ 4. Neither better, nor worse (no change)
- ☐ 5. A little worse now
- ☐ 6. Moderately worse now
- ☐ 7. A lot worse now

Attachment 11: Cytokine Release Syndrome ASBMT Consensus Grading System

Grade	Toxicity
Grade 1	Fever[a] (Temperature ≥38°)
Grade 2	Fever[a] (Temperature ≥38°) 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°) 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°) 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

[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)[22]

Attachment 12: 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

Attachment 13: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) ASBMT 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.

a: Toxicity grading according to Lee et al 2019
b: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.
Note: all other neurological adverse events (not associated with ICANS) should continue to be graded with CTCAE Version 5.0 during both phases of the study

Attachment 14: Anticipated Adverse Events

Anticipated Event

An anticipated event is an adverse event that commonly occurs independent of exposure to the drug under investigation.

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

- Anaemia
- Bleeding
- Bone diseases
- Hypercalcaemia
- Hyperuricemia
- Infection
- Neutropenia
- Renal failure and insufficiency
- Thrombocytopenia

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 general disease population 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 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.

Attachment 15: Handwriting Adverse Event Toxicity Grading Criteria

Adverse Event Term	Grade 1	Grade 2
Micrographia: abnormally small or cramped handwriting	Mildly smaller letters or reduced spacing (eg, <50% decrease from baseline)	Moderate to severely smaller letters or reduced spacing (eg, >=50% decrease from baseline)
Dysgraphia: illegible writing or writing that takes an unusually long time or great effort	Mildly slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are legible	Moderate to severely slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are illegible
Agraphia: pathologic loss of the ability to write	Able to write part of a sentence (3 or more words); noted change from baseline	Able to write just 1 to 2 words, or unable to write any words; noted change from baseline

Attachment 16: 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)	At Neutropenia resolution (for example, ANC ≥ 500/µL)
Anti-Fungal	Fluconazole - 400 mg daily (or equivalent) *Alternatives*: Caspofungin or Micafungin Prolonged neutropenia > 3 weeks – Consider switching to Posaconazole, *or* as per institutional guidelines	At neutropenia onset (ANC < 500/µL)	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	Day 1 of infusion	Suggested for at least 12 months post infusion
***Pneumocystis* Pneumonia (PCP)**	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 PO daily	Day 1 of infusion	Suggested duration: 6 months OR until CD4 count ≥ 200 cells/µL, (whichever is longer)

Consider CMV serology at baseline, monitor with PCR testing as clinically indicated per institutional guidance

Attachment 17: COVID-19 Guidance on Study Conduct and Vaccine Timing

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.

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. If a participant has tested positive for COVID 19, the investigator should contact the sponsor’s responsible medical officer to discuss plans for study intervention and follow-up. 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 participant 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). Home health nursing can either be centrally sourced via sponsor agreement with a vendor, or done via site contract with a visiting nurse service independent of the sponsor.
- 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.
- For subjects eligible to receive retreatment, original protocol conduct must be followed until Day 100.
- 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 100 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 from another cilta-cel study 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 6.3.6).

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.

Attachment 18: Adverse Event Reporting Guidance for Study 68284528MMY2001

Reporting Guidelines for Adverse Events in eCRF:

Duration of Study					LTFU Study[a]
Signing of ICF	Day 1 Cilta-Cel	Day 100 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)[b, c]				
	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 Rheumatologic or Other 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] Refer to the CARTinue 68284528MMY4002 study for specific details.
[b] 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).
[c] In the event of malignancy, a tumor sample should be collected and vector integration site analysis may be performed for possible insertional mutagenesis.

Expedited Reporting Guidelines to Sponsor GMS:

Duration of Study		
Signing of ICF	Day 1 Cilta-Cel	End of Study
Expedited Reporting[a] of all SAEs (regardless of causality) for duration of study.	Expedited Reporting[a] of all SAEs, and following AESIs (regardless of causality or seriousness): • ≥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.

INVESTIGATOR AGREEMENT

JNJ-68284528
Relapsed or Refractory Multiple Myeloma Clinical Protocol 68284528MMY2001 – Amendment 5

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 drug, 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: PPD
(Day Month Year)

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

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Status: Approved, Date: 15 June 2022

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma

Protocol 68284528MMY2001; Phase 1b-2

JNJ-68284528

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Status: Approved
Date: 30 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-48939, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

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.

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. If a participant has tested positive for COVID 19, the investigator should contact the sponsor’s responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

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). Home health nursing can either be centrally sourced via sponsor agreement with a vendor, or done via site contract with a visiting nurse service independent of the sponsor.
- 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.
- For subjects eligible to receive retreatment, original protocol conduct must be followed until Day 100.
- 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.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-68284528 Clinical Protocol 68284528MMY2001

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

PPD

Signature: _____ Date: PPD
(Day Month Year)

Note: If the address or [redacted] during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 30 April 2020