Janssen Research & Development *

Clinical Protocol

An Open Label, Phase 2 Study to Assess the Clinical Efficacy and Safety of Daratumumab in Patients With Relapsed or Refractory Natural Killer/T-Cell Lymphoma (NKTCL), Nasal Type

Protocol 54767414NKT2001; Phase 2
AMENDMENT 4

JNJ-54767414 Daratumumab

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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	22 December 2016
Amendment 1	25 January 2017
Amendment 2	05 July 2017
Amendment 3	30 May 2018
Amendment 4	24 January 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (24 January 2019)

The overall reason for the amendment: The overall reason for the amendment is to update the hepatitis B virus (HBV) related sections to include a newly identified risk of hepatitis B reactivation associated with the use of daratumumab.

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).	
Time and Events Schedule	Added a footnote for HBV serology. Added a row for HBV DNA test and identified when the HBV DNA test would be conducted.
4.2 Exclusion Criteria (Criterion #8.1)	Clarified language to exclude subjects who are seropositive for hepatitis B.
Section 7.1.4 Management of Hepatitis B Virus Reactivation	Added a new section providing information for the management of HBV reactivation.
Section 8.1.1 Overview	Added footnote 'e' to 'Serology (hepatitis B and C)' in Table 4 mentioning that - For subjects with serologic evidence of resolved HBV infection (ie, positive antibodies to hepatitis B surface antigen [Anti-HBs] or positive antibodies to hepatitis B core antigen [Anti-HBc]) at Screening, more samples may need to be collected to perform HBV DNA testing during the treatment and during follow up.
Section 8.6 Safety evaluations	Mentioned that Hepatitis B Screening would include tests for HBsAg, Anti-HBc, and Anti-HBs and added information detailing the conduct of HBV serology and DNA tests.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (30 May 2018)

The overall reason for the amendment: To provide clarification that all the efficacy evaluations will be based on blinded independent central review (BICR), to update rules of patient treatment management as per the central review process, adjust various pharmacokinetics (PK) and biomarker sampling timepoints, and to adopt daratumumab standard protocol language.

Applicable Sections	Description of Changes

Rationale: To clarify that efficacy evaluations and rules of patient treatment management will be based on BICR process.	
Synopsis Objectives; Synopsis Endpoints; 2.1 Objectives and Endpoints; 3.1 Overview of Study Design; 10.3.1 Primary Efficacy Endpoint; 10.3.2 Secondary Efficacy Endpoint	Clarified that efficacy assessments will be evaluated based on BICR.
8.1.3 Treatment Phase End-of-Treatment; 8.1.4 Posttreatment Phase (Follow-up); 8.2 Efficacy Evaluations; 8.2.6 Blinded Independent Central Review; 9.2 Discontinuation of study treatment/withdrawal from the study	Added the text which specified that the all efficacy evaluations including confirmation of progressive disease (PD) was based on BICR. In addition, clarified that discontinuation of study treatment due to PD would be based on central review process. Added new section "8.2.6: Blinded Independent Central Review" and described the role of BICR in the study.
Rationale: To update the time frame of study end after the last subject receives the first dose of daratumumab.	
Synopsis Overview of Study Design; Synopsis Statistical Methods; 3.1 Overview of Study Design; 10.2 Sample Size Determination	The word "approximately" was added to the following 2 sentences "Following that, additional patients (ie, approximately 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab" "study will end approximately 9 months after the last subject receives the first dose of daratumumab".
Rationale: To clarify and adapt the detailed requirements on various study procedures in Time and Events Schedule.	
Time and Events Schedule: ECOG, Weight, Height, footnote "f"; 8.6 Safety Evaluations	Added Eastern Cooperative Oncology Group (ECOG) assessment at End-of-Treatment (EoT) visit and the footnote "f" was updated with the ECOG collection information. The ECOG assessment was no longer specified to be done prior to other assessments except prior to dosing of daratumumab on Day 1 of each cycle, and therefore, the text on the same was deleted from the footnote 'f'. The same changes were made in Section 8.6. Added assessment of weight and height during Screening Phase and deleted assessment of height during Treatment Phase.
Time and Events Schedule: Circulating plasma EBV-DNA quantification (central laboratory); 8.5 Biomarkers	Added assessment of circulating plasma Epstein-Barr Virus deoxyribonucleic acid (EBV-DNA) quantification (central laboratory) at EoT visit.
Time and Events Schedule: Bone marrow biopsy	Added optional assessment of bone marrow biopsy during Screening Phase. In addition, clarified that bone marrow assessment is required during Treatment Phase to confirm complete response (CR), regardless of whether biopsy was performed during Screening Phase.

Time and Events Schedule: Tumor biopsy (optional); 8.2.5 Tumor Biopsy Assessment	Added optional assessment of tumor biopsy if in case the lesion is reasonably accessible to confirm suspected PD during Screening and Treatment Phases. Added footnote "m" for indicating that biopsy was strongly recommended if the tumor lesion was accessible to confirm suspected PD. Added new section "8.2.5 Tumor Biopsy Assessment" which describes the tumor biopsy assessments.
Time and Events Schedule "Footnotes: g, k, l, n, and o"	Updated footnote "g" for the start timepoint collection of vital signs in case of infusion interruption due to infusion-related reactions (IRRs). Added a footnote "k" indicating the duration of follow-up in case of treatment discontinuation due to PD or any other reason. Added footnote "l" for clarification of the text indicating blood sample collection in case of IRRs which occurred on the same day. Added footnote "n" for clarity on baseline image data for Positron Emission Tomography (PET)/Computer Tomography (CT) or CT or magnetic resonance imaging (MRI) scan. Added footnote "o" for clarity of B-symptoms assessment in every disease evaluation assessment.
Time and Events Schedule: Whole Blood Collection	Deleted blood collection timepoints of C2D1, C6D1, and added blood collection timepoints C3D1, C7D1 to keep biomarker tests consistency with disease evaluation schedule.
Rationale: To clarify on disease evaluation method.	
8.2.3 Clinical Examination	Added text for collecting any clinical information which can support disease evaluation including palpable lesion.
Rationale: To clarify the schedule of PK/Immunogenicity.	
Time and Events Schedule: PK and Immunogenicity 'footnotes"	Deleted footnote "b" on time points of blood sampling. Added a footnote "d" stating that the EOT was within 30 days (+7) of the last dose and Follow-Up (FU) weeks 4 and 8 were 4 weeks (±7 days) and 8 weeks (±14 days) from the last dose. In addition, PK/Immunogenicity samples were to be collected at these timepoints regardless of subject discontinuation.
Time and Events Schedule: PK and Immunogenicity 'Pharmacokinetic Samples", Immunogenicity Samples	Defined time duration for collection of samples ("Before Infusion" means "within 2 hours before the start of infusion" and "End of Infusion" means "within 2 hours after end of infusion"). Deleted PK sample collection timepoints at +2, +5, and +24 hours. Deleted all PK/Immunogenicity sample collection timepoints of Cycle 1 Day 4.
8.3.3. Pharmacokinetics Parameters; 10.4. Pharmacokinetic Analyses	PK parameters: C_{trough}, Clearance (CL), half-life ($t_{1/2}$), Volume of distribution (V_d) were deleted as they are estimable based on PK sampling schedule. In addition, the definition of t_{max} was added to provide clarity.
Rationale: To clarify the time of primary analysis.	
3.1 Overview of Study Design	Added cross reference of Time and Events Schedule for Follow-up phase. Clarification to the time of primary analysis was made by adding the following sentence "the primary analysis will be performed at 6 months after the last subject receives the first dose of daratumumab".

Rationale: To clarify the requirement on subject overall status before including in the study.	
4.1 Inclusion Criteria	Added life expectancy of ≥ 3 months in inclusion criterion number 5.
Rationale: To clarify that the classification used for efficacy response assessment was "LUGANO" classification.	
Throughout the protocol:	The classification of Revised Criteria for Response Assessment was specified as "LUGANO Classification".
Rationale: To update the quantity of blood volumes for pharmacokinetic, biomarker research, and efficacy parameters as per the Time and Events Schedule.	
8.1.1 Overview; 15.1 Study Specific Design Considerations	Blood volumes were updated for pharmacokinetic/immunogenicity samples and circulating plasma EBV-DNA quantification for efficacy evaluation.
Rationale: To clarify the protocol text to avoid confusion and errors.	
3.1 Overview of Study Design	The phrase "as determined by investigator" was deleted from following sentence: "After study completion, the sponsor will ensure that subjects who are currently on treatment and receiving benefit, will continue to receive daratumumab until PD, unacceptable toxicity or other."
4.1 Inclusion Criteria	Text was added in "Note" of Section 4.1 to clarify that the subjects consented to provide the optional research samples had to follow the sample collection schedule listed in optional consent form.
5.3.2 Postinfusion Medication	Clarity to the days of steroid administration was added by adding following phrase "given on Day 2 for 2 days'.
8.1.3 Treatment Phase	Phrase "within-cycle" was added to word "visit" to clarify such visits (eg Cycle 1 Day15, Cycle 2 Day 22).
8.1.4 Posttreatment Phase (Follow-Up)	Updated text for study physician's confirmation of PD form during Follow-Up Phase of the study.
9.2 Discontinuation of StudyTreatment/Withdrawal from the Study	Added cross references of Sections 8.1.4 and 15.2.3 for clarity.
10.4 Pharmacokinetic Analysis	The definition of pharmacokinetic population was modified by adding a phrase "at least".
Rationale: To modify biomarker terms to define markers and analysis more precisely.	
3.2 Study Design Rationale; 8.5 Biomarkers; 15.1 Study-Specific Design Considerations	Replaced certain instances of CD59 with Complement Inhibitory Proteins (CIPs) to include assessments of other CIPs such as CD55 and CD46. Addition of immunofluorescent staining method.
8.5 Biomarkers	Added text regarding additional information needed for archived biopsy samples. In addition, text on methodology to be followed in case of re-biopsy of samples was added.
Rationale: To revise and place the text in appropriate section as per the global oncology therapeutic area and protocol review committee.	

11.3.1 All Adverse Events; 11.3.2 Serious Adverse Events	Moved paragraph explaining the text on “PD is not considered as adverse event (AE) or serious adverse event (SAE) during AE reporting period” from Section 11.3.2 to 11.3.1.
Rationale: To adopt the standard daratumumab protocol language	
1.3.1 Daratumumab	Updated background information on daratumumab IV infusion.
4.1 Inclusion Criteria	Updated the criteria on contraception of women and value of hemoglobin in mmoL/L.
5. Dosage and administration; 5.2 Daratumumab administration; 5.3.1 Preinfusion Medication; 5.3.3.1 Infusion-Related Events of Grade 1 or Grade 2 (mild to moderate); 5.3.3.2 Infusion-Related Reactions of Grade 3 (severe) or Higher; 5.3.2 Postinfusion Medication; 5.3.3 Management of Infusion-Related Reactions 5.3.3.3 Recurrent Infusion-Related Reactions	Adopted the standard daratumumab protocol language on guidelines for prevention of infusion reactions. Added new Section 5.3.3.3 Recurrent Infusion-Related Reactions as per standard daratumumab protocol language.
6.1.1 Daratumumab-Related Toxicity Management	Adopted the standard daratumumab protocol language.
7.1.2 Prophylaxis for Herpes Zoster Reactivation	Adopted the standard daratumumab protocol language on guidelines for prophylaxis for Herpes Zoster Reactivation.
9.2 Discontinuation of Study Treatment/Withdrawal from the Study	Updated one of the criteria for “Discontinuation of Study Treatment”. Deleted the following withdrawal reason from the study: “The study investigator, for any reason, stops the subject’s participation in the study”
Rationale: To align the protocol text per the current protocol template**.**	
Title page: Sponsorship Statement	Added “Janssen Pharmaceutical NV” (new operating company) added to the group of companies who act as legal entity for Janssen Research & Development in various countries.
8.6 Safety Evaluations	In the paragraph related to clinically significant abnormalities, changed "clinically stable endpoint" to "clinically stable condition".
Section 16.3 Subject Identification, Enrollment, and Screening Logs	To identify the subjects by their date of birth added a criterion “as allowed by local regulations” in parentheses next to date of birth.
16.11 Use of Information and Publications	Added the text “for the study” in the below sentence: "key assessment parameters of the study will be used to determine a coordinating investigator **for the study**."
Rationale: Minor errors were noted	

Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. List of Abbreviations and list of references was updated and abbreviations were added to the protocol text.

Amendment 2 (05 July 2017)

The overall reason for the amendment: The overall reason for the amendment is to clarify the mandatory and optional biomarker tests and update the blood volume to be collected for biomarker research.

Applicable Section(s)	Description of Change(s)
Rationale: To add a footnote for whole blood collection.	
Time and Events Schedule	Added a footnote "j" to specify that refer to the laboratory manual for the detailed instructions for the whole blood collection.
Rationale: To clarify that predose samples will be collected on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 6 Day 1 for biomarker research.	
Time and Events Schedule	In the row for whole blood collection, added "(predose)" in the column for "C1D1 and C2D1" and "C6D1".
Rationale: To update the blood volume to be collected for mandatory biomarker research and efficacy to be consistent with the laboratory manual and to update the blood volume and collection time point for exploratory genetic biomarker research per current genetic biomarker research plan.	
Table 4: Volume of Blood to be Collected From Each Subject (Based on assumption for a female subject completing a total of Cycle 7)	For "Circulating plasma EBV-DNA", volume per samples was revised from 2 mL to 4 mL, and approximate total volume of blood was revised from 14 mL to 28 mL. For "β2-microglobulin", volume per samples was revised from 5 mL to 2.5 mL, and approximate total volume of blood was revised from 5 mL to 2.5 mL. For "Pharmacodynamic/Biomarker samples", volume per sample was revised from 9.5 mL to 12 mL, and approximate total volume of blood was revised from 38 mL to 48 mL. The total volume per sample for all type of sample was revised from 34.5 mL to 36.5 mL, and the approximate total volume of blood for all samples was revised from 235 mL to 256.5 mL.
8.1.1. Overview	Revised the total blood volume to be collected from a subject who completed a total of Cycle 7 from 235 mL to 256.5 mL. Revised the total blood volume to be collected for efficacy from 19 mL to 30.5 mL. Revised the total blood volume to be collected for biomarker research from 38 mL to 48 mL. Revised the additional blood volume to be collected for exploratory genetic biomarker research from 11 mL to 2 mL. Specified that the exploratory genetic biomarker research will be collected prior to daratumumab infusion on Cycle 1 Day 1.
15.1. Study-Specific Design Considerations	Updated the total blood volume to be collected for each subject during screening, Cycle 1-6, Cycle 7 and thereafter, and at end-of-treatment visit.
Rationale: To add a footnote to clarify that safety evaluations will be conducted at local laboratory and the blood volume may vary among different local laboratories.	

Applicable Section(s)	Description of Change(s)
Table 4: Volume of Blood to be Collected From Each Subject (Based on assumption for a female subject completing a total of Cycle 7)	Added footnote "b" indicating that "safety evaluations will be conducted at local laboratory and the blood volume may vary among different local laboratories."
Rationale: To correct the errors in the text for blood volumes to be collected after Cycle 7.	
8.1.1. Overview	Original text: From Cycle 8 onwards until disease progression, 2 mL blood samples will be taken for Hematology, 5 mL for clinical chemistry and 10 mL for PK at Day 1 of each cycle. Only Cycle 12 Day 1 predose sample will be assessed for immunogenicity. Modified text: From Cycle 8 onwards until disease progression, 2 mL blood samples will be taken for Hematology, 3 mL for clinical chemistry, and 4 mL for Circulating plasma EBV‑DNA quantification on Day 1 of each cycle; 5 mL blood samples will be taken for PK on Day 1 every two cycles from Cycle 7, plus on Day 1 of Cycle 12.
Rationale: To modify text to indicate that immunophenotyping will be performed by both flow cytometry and mass cytometry/time-of-flight mass spectrometry (CyToF) considering that CyToF is a newly developed method that provides opportunity to analyze more cell populations and provide more information, which is complementary to flow cytometry.	
8.5. Biomarkers	Modified text to indicate that immunophenotyping will be performed by both flow cytometry and mass cytometry/time-of-flight mass spectrometry (CyToF).
Rationale: To clarify that DNA sequencing is also performed in optional exploratory biomarker research.	
8.5. Biomarkers	Modified text to clarify that DNA sequencing is also performed in optionale exploratory biomarker research.
Rationale: To add the scientific rationale of complement protein analysis, and remove other analysis that will not be conducted in the study.	
8.5. Biomarkers	Original text: Plasma samples may be analyzed for proteins associated with disease progression or daratumumab response, including complement proteins, soluble CD38 (sCD38), proteins indicative of infusion reaction (interleukin [IL]-1, IL-6, TNFα, IFNγ, tryptase), and exploratory proteomics. Analyses will determine whether specific proteins are associated with daratumumab response. Modified text: Since CDC is one of the key mechanisms of action for daratumumab, and normal function of complement system in the body is required for CDC activity, plasma samples will be analyzed for complement proteins, to study whether specific complement protein level is associated with daratumumab response.
Rationale: To clarify that fasting blood glucose will be tested.	
8.6. Safety Evaluations	In the serum chemistry panel, added "(fasting)" to clarify that fasting blood glucose will be tested.
Rationale: To clarify the scope of exploratory genetic analyses.	
10.6. Biomarker Analyses	Modified text to clarify that Exploratory genetic analyses will be summarized in separate technical reports.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the timing of interim analysis and to make it consistent with section 10.2 Sample Size Determination	
Synopsis Statistical Methods; 3.1. Overview of Study Design; 10.9. Interim Analysis	Modified text to clarify that an interim analysis will be conducted after approximately 15 subjects have received at least one dose of study drug and had at least one post-baseline disease evaluation.
Rationale: To correct a format error in the Time and Events Schedule.	
Time and Events Schedule	Moved the row for "β_2-microglobulin" from biomarkers section to clinical laboratory assessments section.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (25 January 2017)

The overall reason for the amendment: The overall reason for the amendment is to add radiographic (CT/MRI) assessments to collect additional radiological data on disease response and clarify the schedules of PK/immunogenicity samplings.

Applicable Section(s)	Description of Change(s)
Rationale: Radiographic assessments (CT/MRI) were added to collect additional radiological data on disease response.	
Time and Events Schedule	A row for CT or MRI imaging (neck, chest, abdomen, and pelvis) and a footnote were added.
4.1. Inclusion Criteria	Revised criterion 4 to specify that each subject must have at least 1 measurable site of disease.
8.2. Efficacy Evaluation	One section (Section 8.2.1) to specify the definition of measurable disease, assessable disease, target lesion, and non-target lesion and 1 section (Section 8.2.3) for radiographic (CT/MRI) assessments were added.
Rationale: Clinical examination for skin lesions was added.	
8.2.4. Clinical Examination	A section to specify the clinical examination for skin lesions was added.
Rationale: Clarified the schedules of PK/Immunogenicity.	
Time and Events Schedule: PK and Immunogenicity;	Added a "X" in the row for before-infusion pharmacokinetic samples on Cycle 12 Day 1 to clarified that there will be a predose PK/immunogenicity sampling on Cycle 12 Day 1; The visit window was revised as per defined in the main Time and Events Schedule; A footnote was added to clarify that for complete study drug administration schedule beyond Cycle 3, refer to the main Time and Events Schedule; Added a footnote "m" indicating that "If EOT sample is collected within 3-5 weeks after the last dose, ie, the window of FU-Wk4 visit, then FU-Wk4 sample does not need to be collected."

Applicable Section(s)	Description of Change(s)
8.3.4. Immunogenicity Assessments	Added a sentence to clarify that daratumumab serum concentration will also be determined from all immunogenicity samples.
Rationale: The inclusion criteria regarding contraception and pregnancy were modified to be consistent with the current global standard protocol language for Daratumumab.	
4.1. Inclusion Criteria	Inclusion criterion 7, 8, 9, 10 and 11 were removed. Two new inclusion criteria (7 and 8) regarding contraception and pregnancy were added.
Rationale: Clarified that the biomarker analysis is not restricted in CD38 expression.	
4.2. Exclusion Criteria	Deleted "CD38 expression determination" and added "retrospective biomarker determination" in the exclusion criterion 1.
Rationale: The exclusion criterion for screening 12-lead ECG was revised to be consistent with the current global standard protocol language for Daratumumab.	
4.2. Exclusion Criteria	Revised the wording of the criterion for screening 12-lead ECG as "Screening 12-lead ECG showing a baseline QT interval as corrected (QTc) >470 msec."
Rationale: Wordings regarding CD59 IHC were revised to clarify that it is not mandatory.	
3.2. Study Design Rationale; 8.5. Biomarker	Revised the wordings regarding CD59 IHC to clarify that it is not a mandatory test and will be performed whenever samples are available.
Rationale: Clarified that adverse events will be monitored until 30 days after the last dose of study drug.	
11.3.1. All Adverse Events	Revised the AE reporting period as "until 30 days after the last dose of study drug, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy".
Rationale: Updated the market authorization status of daratumumab in the US.	
1.3.3. Clinical Studies	Added a sentence to specify that FDA has approved daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for patients with multiple myeloma who has received at least one prior therapy.
Rationale: Clarified that signing the separate informed consent for optional samples will not impact subject enrollment.	
4.1. Inclusion Criteria	Listed inclusion criterion 15 as a note instead of a separate inclusion criterion.
Rationale: Immunohistochemistry will not be used for bone marrow evaluation.	
8.2.5. Bone Marrow Assessment	Deleted "IHC staining".
Rationale: Revised the wording regarding the administration of preinfusion medication to avoid misunderstanding.	
5.3.1. Preinfusion Medication	Deleted "Preinfusion medications for subjects receiving daratumumab will be administered as described in the T&E Schedule".
Rationale: Clarified the procedure of discontinuation of study treatment due to disease progression.	
8.1.3. Treating Phase; 9.2. Discontinuation of Study Treatment/Withdrawal from the Study	Wordings were revised to specify that disease progression will be documented by completing a disease progression form; study treatment discontinuation will be recorded in IWRS.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

An Open Label, Phase 2 Study to Assess the Clinical Efficacy and Safety of Daratumumab in Patients With Relapsed or Refractory Natural Killer/T-Cell Lymphoma (NKTCL), Nasal Type

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. Given the high frequency of CD38 expression in NKTCL and the significant daratumumab treatment-related reduction of NK cells in other settings, we are conducting a proof of concept Phase 2 study to assess the clinical efficacy and safety of daratumumab in relapsed or refractory NKTCL.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

The primary objective of the study is to evaluate the efficacy of daratumumab in subjects with NKTCL by objective response rate (ORR) including complete response (CR) and partial response (PR) based on a blinded independent central review (BICR) per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin Lymphoma: LUGANO classification.

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of daratumumab in NKTCL by CR rate, progression free survival (PFS), duration of response (DoR), time to response based on a BICR, and overall survival (OS).
- To evaluate safety and tolerability
- To evaluate pharmacokinetics (PK) and immunogenicity.

Primary Endpoint

ORR based on BICR

Secondary Endpoints

- CR rate based on BICR
- DoR based on BICR
- Time to response based on BICR
- PFS based on BICR
- OS
- Safety.

Hypothesis

It is hypothesized that treatment with daratumumab results in an ORR of >30% versus a null hypothesis of at most 15% in relapsed or refractory NKTCL, nasal type subjects who failed (relapsed or refractory after achieving complete or partial remission) at least one line of chemotherapy.

OVERVIEW OF STUDY DESIGN

Up to 32 subjects, age ≥18 years, who have histologically confirmed extranodal NK/T-cell lymphoma, nasal type that was refractory to or relapsed after at least 1 line of chemotherapy will be enrolled into the study. Following that, additional patients (ie, approximately 35 patients) may be enrolled in an expansion

phase to confirm the clinical response rate of daratumumab. All the subjects enrolled into the study will be required to provide archival or fresh tumor samples for assessment of CD38 expression. Daratumumab (16 mg/kg) will be administered by intravenous (IV) infusion to subjects once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end.

Interim analysis divides the study into 2 stages: Stage 1 and Stage 2. The study will end approximately 9 months after the last subject receives the first dose of daratumumab. After study completion, the sponsor will ensure that subjects, who are currently on treatment and receiving benefit will continue to receive daratumumab until PD or unacceptable toxicity or other. Additional samples for pharmacokinetic, immunogenicity and biomarker evaluations will be collected during the study. Safety will be measured by adverse events (AEs), laboratory test results, electrocardiograms (ECGs), vital signs measurements, physical examination findings, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status score. All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

STATISTICAL METHODS

The study is a Simon's 2-stage design with an interim analysis conducted after approximately 15 subjects have received at least one dose of study drug and had at least one post-baseline disease evaluation. Enrollment may be put on hold pending the decision of interim analysis unless the decision is clear based on available data before IA. If the study proceeds to the second stage, the total sample size will be 32 with 2 stages combined. Following that, additional patients (ie, approximately 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab, if supported by emerging data.

An estimate of ORR and CR rate will be presented along with a 2-sided 95% exact confidence interval (CI). The number and percentage of subjects falling into each response category will be descriptively tabulated.

For time to event endpoints (eg, PFS, OS, time to response, DoR), Kaplan-Meier estimates will be presented. Median along with corresponding 95% CIs will be obtained from the Kaplan-Meier estimates. Analysis of time to response and DoR will be for responders only.

TIME AND EVENTS SCHEDULE

Phase	**Screening**	**Treatment Day 1 of each cycle (4-week cycles)**							**EoT**	**FU[k]**
Period	Within 21 days of Cycle 1 Day 1	Cycle 1 and 2				Cycle 3 to 6		Cycle 7+	Within 30 days of last dose	Q8 weeks
Day	-21 to -1	D1	D8	D15	D22	D1	D15	D1		±2 weeks
Study Procedures										
Screening/Administrative										
Informed consent	Subjects must sign the ICF before any study-specific procedures are performed.									
Inclusion/exclusion criteria[a]	X									
Medical history and demographics	X									
FEV1 for subjects with COPD	X									
Tumor sample[c]	X									
ECOG[f]	X	X				X		X	X	8 wks post PD
Pregnancy test (serum/urine)[b]	X	As clinically indicated							X	
Study Drug Administration										
Daratumumab[h]		X	X	X	X	X	X	X		
Safety Assessments										
Physical examination (including neurological examination, lymphoma B-symptoms will be recorded separately)	X	Symptom and disease directed exam as clinically indicated								
Weight[e]	X	X				X		X		
Height	X									
Vital signs[g]	X	X	X	X	X	X	X	X		
12-lead ECG	X					C3D1, C6D1			X	
Lymphoma B-symptoms[o]	X	X				X		X	X	
Clinical Laboratory Assessments										
Hematology[d]	X	X	X	X	X	X	X	X	X	
Clinical chemistry[d]	X	X				X		X	X	
Hepatitis B[p] and C serology (local laboratory)	X									
HBV DNA testing[q]	X	Every 12 weeks upto 6 months after last dose of daratumumab								
ABO, Rh and IAT		X (predose)								
β_2-microglobulin (central laboratory)	X									
Pharmacokinetics/ Immunogenicity										

TIME AND EVENTS SCHEDULE

Phase	**Screening**	**Treatment Day 1 of each cycle (4-week cycles)**							**EoT**	**FU[k]**
Period	Within 21 days of Cycle 1 Day 1	Cycle 1 and 2				Cycle 3 to 6		Cycle 7+	Within 30 days of last dose	Q8 weeks
Day	-21 to -1	D1	D8	D15	D22	D1	D15	D1		±2 weeks
Study Procedures										
Daratumumab PK and Immunogenicity	Please see T&E Schedule: PK and Immunogenicity In addition, any time an IRR is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential immune response analysis[l]									
Disease Evaluations: Refer to Section 8.2 for details.										
PET-CT scan	X[n]	Every 8 weeks (±7 days) for the first 6 months; thereafter, every 16 weeks (±7 days)								
CT or MRI imaging (neck, chest, abdomen, and pelvis)[i]	X[n]	Every 8 weeks (±7 days) for the first 6 months; thereafter, every 16 weeks (±7 days)								
Circulating plasma EBV-DNA quantification (central laboratory)		X				X		X	X	
Bone marrow biopsy	X (optional)	Required to confirm CR, regardless of whether biopsy was performed at screening								
Tumor biopsy (optional)	X[m]	As clinically indicated[m]								
Subsequent therapy										X
Other new malignancy										X
Survival										X
Biomarkers										
Whole blood collection[j]		C1D1 (predose)				C3D1 (predose)		C7D1 (predose)	X	
Ongoing Subject Review										
Concomitant therapy	continuous from the time of signing of ICF until 30 days after last dose of study drug; See Section 7 for detailed instructions.									
Adverse events	continuous from the time of signing of ICF until 30 days after last dose of study drug; See Section 11 for detailed instructions.									

Abbreviations: Anti-HBc= antibodies to hepatitis B core antigen; Anti-HBs= antibodies to hepatitis B surface antigen; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; EBV=Epstein Barr virus; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=end-of-treatment; FEV1= forced expiratory volume (in 1 second); FFPE= formalin-fixed, paraffin-embedded; FU=follow-up; HBV=hepatitis B virus; HBsAg= hepatitis B surface antigen; IAT=indirect antiglobulin test; ICF=informed consent form; IRR=infusion related reaction; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetics; Q8 weeks=every 8 weeks; SIPPM=site investigational product procedures manual; Wk=week.

Footnotes:

a. Diagnosis of NKTCL is performed by the local hospital and the pathology report will be verified by the sponsor before enrolment.
b. Women of childbearing potential only, within 14 days of C1D1.
c. Fresh biopsy within 21 days prior to C1D1 or archived sample FFPE sample (block or slides) should be sent to sites prior to C1D1.
d. For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to 2 days before other infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional time points, as clinically indicated. To be done by local lab. Refer to Section 8.6 for parameters to be tested.
e. If a subject's weight changes by more than 10% from baseline, the dose of the study drug will be re-calculated.
f. ECOG assessment should be obtained prior to dosing of daratumumab on Day 1 of each cycle. ECOG is also required to be collected in every disease evaluation assessment date.
g. Vital signs (blood pressure, temperature, pulse) measured in sitting position. On Cycle 1 Day 1: before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5,1 hr after end of infusion. If an IRR occurred during the infusion due to which infusion is stopped and later the infusion is resumed, the site will follow initial infusion start time point for the vital sign collection. For all other infusions, vital signs will be measured immediately before infusion start and at end of daratumumab infusion.
h. Refer to SIPPM for recommendations on daratumumab infusion rate. Administer pre- and postinfusion medications as per Section 5.3.
i. May be performed with oral contrast only if the subject is intolerant of IV contrast agents. If other areas of disease are involved, they can be imaged by either CT or MRI. All scans will be collected and reviewed centrally. The similar methodology should be used throughout the study.
j. Refer to the laboratory manual for the detailed instructions for the whole blood collection.
k. Follow- up will begin once a subject discontinues study treatment; if subject discontinue due to PD, follow-up will occur at least every 8 weeks (±2 weeks). If subject discontinue due to other reasons (not PD), follow-up will occur at least every 8 weeks (±2 weeks), including regular scheduled scan until PD is confirmed, and follow-up visit will be continued after PD confirmation.
l. If more than one IRRs occurs during dose administration, blood sample should be collected only when the first IRR occurs.
m. Tumor biopsy may be conducted as clinically indicated and is strongly recommended if lesion is reasonably accessible to confirm suspected PD.
n. If PET/CT or CT or MRI is performed before ICF signed date due to site's routine practice and if it fulfills the study requirement in the image manual, those image data will be considered as baseline image data as long as the image scanned date is within 21 days prior to Cycle 1 Day 1.
o. B-Symptoms assessment is also required to be collected in every disease evaluation assessment date.
p. Local testing for HBsAg, Anti-HBs, and Anti-HBc. Refer to Section 8.6.
q. For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 8.6.

Note: The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. For Cycles 1-6, there may be ±1 day window for the scheduled infusion within the cycle. The EoT visit may occur +7 days of scheduled day. After PD is documented, subjects will continue to be followed for survival, second primary malignancies, and subsequent anticancer therapy.

TIME AND EVENTS SCHEDULE: PK AND IMMUNOGENICITY (ALL SAMPLES SHOULD BE SENT TO THE CENTRAL LABORATORY)

	Treatment Phase																	EoT[d]	Follow-up Phase	
	Weekly for 8 infusions								Biweekly for 8 infusions				Once every 4 weeks							
Cycle	Cycle 1				Cycle 2				Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 9	Cycle 11	Cycle 12	Cycles 13, 15, 17+			
Study Day (Day)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		**FU-Wk4[d]**	**FU-Wk8[d]**
Visit Window (day)	0	±1	±1	±1	±3	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	±7	±14
Study Drug Administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pharmacokinetic Samples																				
Before Infusion (within 2 hours before the start of infusion)	X	X		X	X			X	X	X	X	X	X	X	X	X	X[b]	X	X[c]	X
End of infusion (within 2 hours after end of infusion)	X							X	X											
Immunogenicity Samples (NO additional immunogenicity samples needed and will be taken from PK samples for the planned time points.)																				
Before Infusion (within 2 hours before the start of infusion)	X												X			X		X	X[c]	X

Footnote:

a. For complete study drug administration schedule beyond Cycle 3, refer to the main Time and Events Schedule.
b. Samples will be collected at every other dose from Cycle 13+, ie, at Cycle 13, 15, 17, etc.
c. If EoT sample is collected within 3-5 weeks after the last dose, ie, the window of FU-Wk4 visit, then FU-Wk4 sample does not need to be collected.
d. The EoT is within 30 days (+7) of the last dose. FU-Wk4 and FU-Wk8 is 4 weeks (±7 days) and 8 weeks (±14 days) from the last dose, respectively.

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event(s)
ANC	absolute neutrophil count
Anti-HBc	antibodies to hepatitis B core antigen
Anti-HBs	antibodies to hepatitis B surface antigen
BICR	blinded independent central review
CDC	complement dependent cytotoxicity
CI	confidence interval
CIP	Complement Inhibitory Protein
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete remission
CT	computed tomography
DNA	deoxyribonucleic acid
DoR	duration of response
DTT	dithiothreitol
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EoT	end-of-treatment
FDA	Food and Drug Association
FDG	^{18}F-fluorodeoxyglucose
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDi	longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
mAb	monoclonal antibody
MDR	multidrug resistant
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphomas
NKTCL	natural killer/T-cell lymphomas
ORR	objective response rate
OS	overall survival
PD	progressive disease
PCR	polymerase chain reaction
PET	positron emission tomography

PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	orally
PQC	product quality complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
RBC	red blood cell(s)
RhD	Rhesus factor–D antigen
RNA	ribonucleic acid
SAE	serious adverse event(s)
SD	standard deviation
SDI	short diameter
SIPPM	site investigational product procedures manual
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WHO	World Health Organization

DEFINITIONS OF TERMS

Clinical outcome assessment	Includes Clinician Reported Outcomes
C_{max}	Maximum observed concentration
t_{max}	The actual sampling time to reach maximum observed concentration
AUC	Area under the concentration – time curve
SMILE regimen	chemotherapeutic combination regimen of Steroid=dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, and Etoposide

1. INTRODUCTION

Natural killer/T-cell lymphomas (NKTCL) are a rare, Epstein–Barr virus (EBV)-associated and distinct subtype of peripheral T-cell lymphoma (PTCL), which are predominantly extranodal and mostly of the nasal type.[22] The disease is more common in Asia and Central/South America, and accounts for around 3-16% of all the non-Hodgkin's lymphomas (NHL) in China, Korea, Taiwan, and Japan (refer to Table 1 for detailed prevalence).[20,23] The outcome of patients with NKTCL is very poor. According to a report from the International T-cell Lymphoma Project, the 5-year overall survival (OS) rate for all patients with NKTCL was 32%, and the median OS was about 8 months.[1,9,23]

Table 1: Disease Distribution by Region

Country or area	NKTCL% of PTCL	NKTCL% of NHL
Europe	4.3	0.2-0.4
North America	5.1	0.3-0.5
China	48	16
Taiwan	23	3
Korea	28.7	6
Japan	10.4	3

PTCL: Peripheral T-cell Lymphoma.

Randomized studies comparing different regimens have not been conducted, to date, because NKTCL are rare malignancies. Therefore, standard therapy has not been established for patients with this disease. Localized NKTCL is radiosensitive; however, radiotherapy alone is inadequate because of a high systemic failure rate. It responds poorly to the anthracycline-based regimens used in other lymphomas because NKTCL cells are associated with a high expression of P-glycoprotein leading to multidrug resistance. Current data indicate that regimens employing non–multidrug resistant (MDR)-dependent drugs together with radiotherapy give good local disease control with around 70-90% of patients achieving complete remission (CR).[22]

For patients relapsing after radiotherapy or combined radiotherapy and anthracycline-containing chemotherapy, it is found that the use of an L-asparaginase–containing regimen may offer benefit. Asparaginase can hydrolyze and exhaust serum asparagines in NKTCL cells, and this drug is not influenced by P-glycoprotein. L-asparaginase–containing regimens that incorporate non–MDR dependent drugs demonstrated activity in the treatment of advanced-stage and relapsed/refractory NKTCL. Clinical trials on L-asparaginase in the treatment of NKTCL are limited to non-randomized studies. In a Phase 2 study of the SMILE regimen (combination chemotherapeutic regimen with L-asparaginase, methotrexate, ifosfamide, etoposide, and dexamethasone), 38 patients were treated. The objective response rate (ORR) and complete response rate after 2 cycles of SMILE chemotherapy were 79% and 45%, respectively. The 1-year overall survival rate was 55%.[26]

However, more than 20% of patients with NKTCL are primarily resistant to asparaginase-based treatment and around 50% of patients with advanced disease relapse after the treatment with asparaginase.[24,26] Viewing the high failure rate of the available treatments and the limited choices of the therapies, new treatments are needed to improve the outcomes of patients with advanced-stage NKTCL.

1.1. CD38 Expression in NKTCL

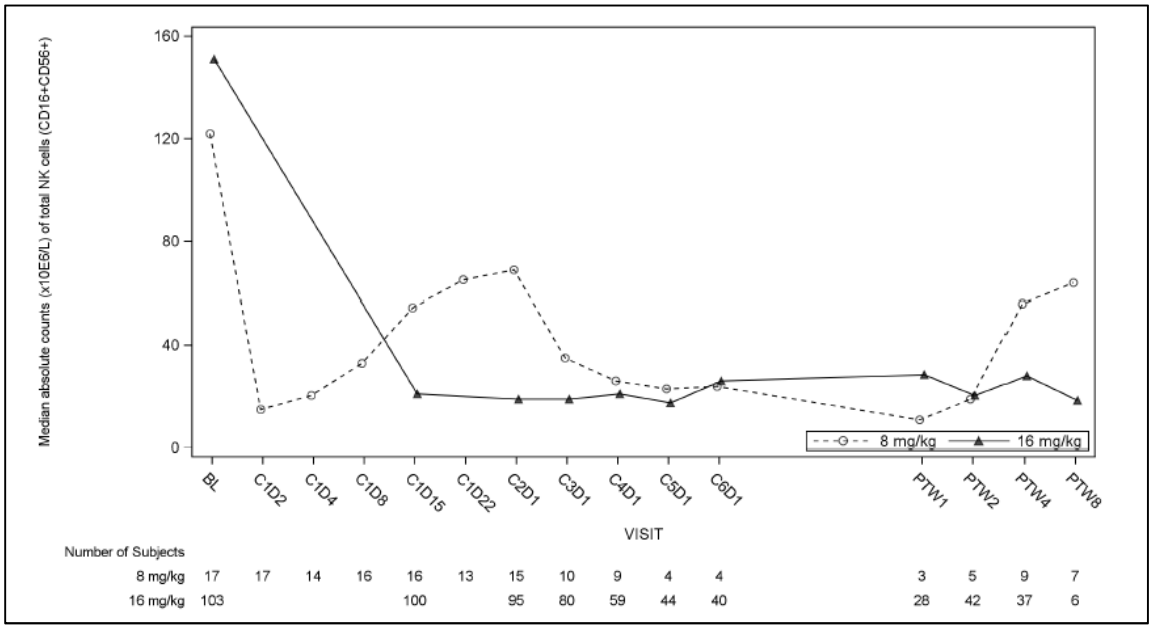
CD38 expression was analyzed by Janssen in 8 cases of relapsed/refractory NKTCL, as it is the targeted population in this proposed study. It was found that all relapsed/refractory cases were positive for CD38 expression. Five cases (62.5%) showing relatively high expression (defined as tumor with more than 50% cells CD38 positive).

In a separate study, clinical data of 94 patients with NKTCL had been reviewed in Sun Yat-sen University.[25] All the tumors expressed CD38, among which 47 samples (50%) are strong positive (defined by author's laboratory). This study also analyzed the prognostic value of CD38 expression for NKTCL. In the Cox regression model, CD38 turned out to be an independent prognostic factor for poor outcome, suggesting that CD38 may be a new prognostic biomarker and a novel therapy target for NKTCL. Combining Janssen's in-house data and published data at Sun Yat-sen University, CD38 expression was detected in all NKTCL patients in the target population for this study, which supports further investigation of daratumumab to treat NKTCL.

1.2. Preliminary Findings on NK Cell Reduction Following Daratumumab Treatment

Preliminary evidence of decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells was observed in blood and bone marrow collected from multiple myeloma (MM) patients in the single-agent daratumumab studies, GEN501 and MMY2002.[7,14] Figure 1 presents decrease in NK cells with daratumumab treatment.

Figure 1: NK Cells Decreased With Daratumumab Treatment



Similar to single agent studies, total NK cells were also reduced in the peripheral blood and bone marrow of all patient cohorts receiving combination treatment regimens in the GEN503 and MMY1001 studies.[3,17] These data indicate that NK cells may be sensitive to daratumumab-mediated lysis.

Daratumumab induces tumor cell lysis through immune effector functions such as complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) as well as apoptosis in cells that express CD38. Daratumumab induced >20% apoptosis in 11 out of 16 cell lines in the presence of a cross-linking agent. In tumor cell killing assays, daratumumab induced >25% ADCC in 7 out of 16 cell lines and >30% CDC in 6 out of 16 cell lines. While no linear correlation was observed between CD38 expression and the extent of ADCC and CDC, tumor cell lysis >10% was observed only in cell lines with >50,000 CD38 receptors/cell. Although some preclinical data suggest that a threshold of CD38 expression may be required for daratumumab-induced CDC and ADCC, selection of patients suitable for daratumumab therapy based on CD38 expression was not considered justified yet in the reported clinical studies. In MM trials, a large overlap in baseline CD38 expression was observed between responders and nonresponders. Some subjects continued to maintain a good clinical response to daratumumab with the reduction in CD38 expression levels in the MM cells. Correlation between CD38 expression level and the disease response to daratumumab needs to be further investigated. Therefore, the role of CD38 expression in predicting NKTCL tumor response to daratumumab treatment will be explored in this study.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB).[18] 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.

1.3. Background

1.3.1. Daratumumab

Daratumumab for Intravenous Infusion

In the US, intravenously administered daratumumab (Daratumumab IV) is indicated for use as follows: in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant; in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy; in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor; as monotherapy, for the treatment of patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent.[14]

In the EU, Daratumumab IV is indicated for use as monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated PD on the last therapy. And in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy.[15]

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the IB (IB Daratumumab).[18] 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.

1.3.2. Nonclinical Studies

Pharmacologic Profile

An extensive series of experiments were performed to assess the pharmacology and mechanism of action of daratumumab. The pharmacology studies focused on scientifically relevant primary and secondary pharmacodynamic aspects including binding properties, CDC, ADCC, ADCP, apoptosis, agonistic activity, inhibition of CD38 enzymatic activity, reactivity with normal human tissues and species cross-reactivity. For more details on the design and key findings of all pharmacology studies, please refer Appendix 1 in the IB.[18]

Based upon the pharmacology studies, daratumumab is believed to induce CDC, ADCC, ADCP, direct apoptosis after cross-linking, and to modulate CD38 enzymatic activity. In mouse xenograft models, daratumumab reduced tumor growth in both preventive and therapeutic settings. Daratumumab had no effect on proliferation of human peripheral blood mononuclear

cells (PBMCs), and cytokine release was similar to other marketed therapeutic antibodies. Hence, daratumumab can recruit multiple effector mechanisms to facilitate the lysis of malignant cells in vitro and in vivo. These observations suggest a strong potential for the treatment of CD38-expressing malignancies.

Positive Indirect Coombs Tests in Subjects Treated with Daratumumab

In Phase 1/2 clinical studies (Study GEN501 and MMY2002), in which the safety and efficacy of daratumumab were evaluated, it was observed that blood plasma of subjects who had received daratumumab tested positive on routine antibody screens in the blood bank (indirect Coombs testing).[7,16] This is likely due to low-level of expression of CD38 on the surface of erythrocytes.[5,27] The binding of daratumumab to CD38 on red blood cells triggers a positive readout on indirect Coombs testing, and as a result, interferes with the ability to detect red cell alloantibodies.

Flow cytometry analyses of erythrocytes indicated that erythrocytes express a low level of CD38 (301-634 CD38 molecules per cell). In preclinical studies, plasma spiked with daratumumab induced concentration-dependent agglutination of erythrocytes in an indirect Coombs test.[20] Additional studies to evaluate various mitigation strategies such as neutralization of daratumumab using soluble CD38, anti-idiotype antibody, or pretreatment of reagent or donor red blood cells (RBCs) with dithiothreitol (DTT) to circumvent the positive readout on indirect Coombs testing were conducted. These methods successfully mitigated the interference of daratumumab with indirect Coombs test and allowed for identification of alloantibodies in the serum containing daratumumab.[11, 22]

1.3.3. Clinical Studies

No clinical studies with daratumumab have been conducted in NKTCL. As of June 2015, 9 clinical studies in MM and 1 clinical study of daratumumab in NHL (diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma) are ongoing. More than 1,300 subjects with MM and 29 subjects with NHL have been enrolled in the clinical studies of daratumumab. Daratumumab was approved by the US Food and Drug Administration (FDA) in November 2015 for the treatment of patients with MM who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. In November 2016, US FDA approved daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for patients with multiple myeloma who has received at least one prior therapy. Additionally, in May 2016, the European Commission granted conditional approval to daratumumab administered as monotherapy in adult patients with relapsed and refractory MM, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent and who had demonstrated progressive disease (PD) while on the last therapy. A dose of 16 mg/kg is the recommended dose for global clinical trials in MM and NHL.

Human Pharmacokinetics

The PK of daratumumab following intravenous (IV) administration was evaluated in subjects with relapsed and refractory MM at dose levels from 0.1 mg/kg to 24 mg/kg, and included the recommended 16 mg/kg dose and regimen. The population PK analysis included 223 subjects with MM receiving daratumumab in 2 clinical trials, GEN501 and MMY2002 (150 subjects received 16 mg/kg) [7,16] Over the dose range from 1 to 24 mg/kg, increases in area under the concentration-time curve (AUC) were more than dose-proportional. Clearance decreased with increasing dose and repeated dosing, indicating target-mediated PK. Following the recommended schedule and dose of 16 mg/kg, the mean [standard deviation (SD)] serum C_{max} value was 915 (410) µg/mL at the end of weekly dosing, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL. Based on the population PK analysis, daratumumab steady state is achieved approximately 5 months into the every-4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance was approximately 18 (9) days. Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also showed that age (31 to 84 years) and gender do not have clinically important effects on the PK of daratumumab.

Based on data from Study GEN501 and MMY2002, no subjects were positive for antibodies to daratumumab [7,16] Anti-daratumumab antibody production after long-term treatment will be investigated.

Safety and tolerability

In general, daratumumab is tolerated well. Maximum tolerated dose has not been reached following IV infusion up to 24 mg/kg. No dose dependent toxicity was identified.

In the daratumumab monotherapy studies MMY2002, GEN501, and MMY1002, , Among the 156 subjects treated with 16 mg/kg daratumumab as monotherapy , the most frequently reported AEs were fatigue (39%); nausea and anemia (27% each); back pain (23%); neutropenia (22%); pyrexia and cough (21% each), and thrombocytopenia and upper respiratory tract infection (20% each).[2,7,16] The most frequently reported Grade 3 or 4 AEs in 16 mg/kg group were anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia (6%), leukopenia, pneumonia, and hypertension (5% each). Across all dose groups, the most frequently reported SAEs were pneumonia (5%), pyrexia and general physical health deterioration (3% each). The incidence and types of SAEs in the 16 mg/kg group were similar to the total population of subjects who received daratumumab monotherapy.

Infusion-related reactions (IRRs) were reported in approximately half (75/156 subjects; 48%) of all subjects treated with 16 mg/kg daratumumab monotherapy. Of the subjects who experienced an IRR, 95% experienced an IRR at the first infusion; 5% (8/156) had an IRR in more than

1 infusion. The most common IRRs in the 16 mg/kg group were nasal congestion (11%), cough (8%), chills (7%), allergic rhinitis, and throat irritation (6% each), dyspnea, nausea, and vomiting (5% each). Bronchospasm was reported in 4 subjects (2.6%), and laryngeal edema was reported in 1 subject (0.6%). Grade 3 IRRs were reported in 3% of subject; no Grade 4 or 5 IRRs were reported. No subject in the 16 mg/kg group discontinued treatment due to an IRR. The types and incidence of IRRs across all dose groups were similar to what was reported in the 16 mg/kg group. In the 16 mg/kg group, the median duration of the first infusion was 7 hours, which decreased to 4.6 hours at the second infusion, and to 3.4 hours in subsequent infusions.

Across all dose groups, 15 subjects (6%) died within 30 days of last dose of study drug (14 subjects in the 16 mg/kg group and 1 subject in the 8 mg/kg group). Twelve deaths were due to PD and 3 deaths were due to AEs considered not related to daratumumab. In the 16 mg/kg group, 11 subjects (7%) died due to PD, and 3 subjects (2%) died due to AEs, all of which were considered not related to daratumumab treatment. Adverse events (AEs) leading to death included cardiorespiratory arrest in the setting of H1N1 influenza, general physical health deterioration secondary to aspiration pneumonia, and pneumonia. None of the fatal AEs were considered related to daratumumab.

1.4. Overall Rationale for the Study

This Phase 2 study is set up due to the high frequency of CD38 expression in NKTCL and the significant daratumumab treatment-related reduction of NK cells. It will be conducted to assess the clinical efficacy and safety of daratumumab in relapsed or refractory NKTCL. The role of CD38 expression in predicting tumor response to treatment with daratumumab will be explored.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of the study is to evaluate the efficacy of daratumumab in subjects with NKTCL by ORR including complete response (CR) and partial response (PR) based on a blinded independent central review (BICR) per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin Lymphoma: LUGANO classifcation.[12]

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of daratumumab in NKTCL by CR rate, progression free survival (PFS), duration of response (DoR), time to response based on a BICR, and OS
- To evaluate safety and tolerability
- To evaluate PK and immunogenicity.

Exploratory Objectives

The exploratory objectives are:

- To explore the role of CD38 expression in predicting response to daratumumab treatment
- To explore the role of circulating plasma EBV-DNA in monitoring tumor response to daratumumab treatment
- To explore the role of biomarkers in predicting tumor response to daratumumab treatment, such as CD59, blood NK cell counts, etc.
- To explore the PK/pharmacodynamic relationship of daratumumab, such as exposure-response relationship for efficacy/safety endpoints and/or disease-related or mechanism-based biomarkers.

2.1.2. Endpoints

Primary Endpoint

Objective response rate (ORR) is defined as the proportion of subjects who achieve CR or PR per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin lymphoma: LUGANO classification based on BICR.[12]

Secondary Endpoints

- CR rate, PFS, DoR, Time to response based on BICR, OS
- Safety: AEs, vital sign measurements, ECG, physical examination findings, and clinical laboratory tests.

Exploratory Endpoints

- CD38 expression
- Plasma circulating EBV-DNA quantification.

Refer to Section 8, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

It is hypothesized that treatment with daratumumab results in an ORR of >30% versus a null hypothesis of at most 15% in relapsed or refractory NKTCL, nasal type subjects failed (relapsed or refractory after achieving complete or partial remission) at least one line of chemotherapy.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open label, single arm, multicenter, Phase 2 study to evaluate the efficacy and safety of daratumumab monotherapy in subjects with relapsed and refractory extranodal NKTCL, nasal type. The study is a Simon's 2-stage design with up to 32 subjects to be enrolled. Following that, additional patients (ie, approximately 35 patients) may be enrolled in an expansion phase.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days prior to Cycle 1, Day 1. Prior to enrollment, diagnosis of NKTCL must be verified by the sponsor from the local pathology report. Before enrollment to the study, sites will be required to provide archival or fresh tumor samples for assessment of CD38 expression. Fresh biopsy samples are preferred if available. Otherwise, archived formalin-fixed, paraffin-embedded (FFPE) blocks/slides are also acceptable.

The Treatment Phase will extend from Cycle 1, Day 1 until study drug discontinuation. After the first dose, disease evaluations will occur every 8 weeks for the first 6 months and thereafter, every 16 weeks. Subjects will be monitored for safety and assessed for PK and immunogenicity according to the scheduled assessments in the Time and Events (T&E) schedules (T&E Schedule and T&E Schedule: PK and Immunogenicity). Subjects will be treated until PD, unacceptable toxicity, or other reasons as listed in the protocol. End-of-Treatment (EoT) Visit is to occur within 30 days (+7-day window) after the last dose of all study treatments.

The Follow-up Phase will begin once a subject discontinues study treatment, and will continue until death, lost to follow up, consent withdrawal for study participation, or end of study, whichever occurs first. The follow-up schedule is presented in the T&E Schedule.

The study is a Simon's 2-stage design with an interim analysis conducted after approximately 15 subjects have received at least one dose of study drug and had at least one post-baseline disease evaluation. The purpose of the interim analysis is to evaluate efficacy and safety data in stage 1 and facilitate the early preparation for the next step of development. The totality of efficacy (ORR), safety, and biomarker data will be analyzed at the interim. Enrollment may be put on hold pending the decision of interim analysis unless the decision is clear based on available data before the interim analysis. The futility criteria are defined in Section 10.9. The study may be terminated if the futility criteria are met and supported by totality of data. In addition, at interim, the association between daratumumab activity and CD38 expression level will be explored. A population enrichment strategy may be applied after the interim analysis if such a strategy is supported by emerging data. The primary analysis will be performed at approximately 6 months after the last subject receives the first dose of daratumumab.

The end of study is defined as approximately 9 months after the last subject receives the first dose of daratumumab. After study completion, the sponsor will ensure that subjects who are currently on treatment and receiving benefit, will continue to receive daratumumab until PD, unacceptable toxicity or other.

Assessment of tumor response and PD will be based on BICR in accordance with the Revised Criteria for Response Assessment - LUGANO Classification.[12]

Subjects will be monitored for safety during the Screening and Treatment Phases and up to 30 days after the last dose of study drug. Adverse events (AE), including laboratory AEs, will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Measures to prevent infusion-related reactions will include preinfusion medication with methylprednisolone, acetaminophen (or paracetamol), and

an antihistamine before each daratumumab infusion. Blood samples will be drawn for assessment of PK, immunogenicity, and biomarkers.

Additional patients (ie, approximately 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab if supported by emerging data.

3.2. Study Design Rationale

Daratumumab Dose Rationale

An established dose regimen of 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter), administered via IV until PD or unacceptable toxicity, was selected based on an acceptable safety profile, clinical activity, and pharmacokinetics consistent with saturation of the target (CD38).

Rationale for Pharmacokinetics and Immunogenicity

Data obtained from the current study will provide information about the pharmacokinetic profile of daratumumab in subjects with NKTCL.

Immunogenicity to daratumumab is possible. Therefore, samples to determine the presence of antibodies to daratumumab (immunogenicity) will be collected from all subjects. The pharmacokinetic assessments collected at all immunogenicity time points will be used to interpret the immunogenicity data. The information from these samples and data from other studies will be used to determine the immunogenicity of daratumumab.

Biomarker Collection

Biomarkers collected in this study will evaluate tumor CD38 levels as a predictive marker of response. Exploratory analysis of Complement Inhibitory Proteins (CIPs, such as CD59, CD55 and CD46) expression from previous studies has indicated that high expression of CIPs might be predictive of lower or lack of response to daratumumab. Therefore, samples collected in this study might evaluate both CD38 and CIPs expression levels by immunohistochemistry (IHC) or immunofluorescent staining. CD38 IHC is a mandatory test, and CIPs staining will be performed whenever samples are available. Specific immune cell subtypes (NK cells, T cells, and B cells) and their subtypes will be analyzed to evaluate the effects of daratumumab on immune cells. This will provide information on potential prognostic markers in NKTCL to better understand this disease, as well as potential markers that predict response to daratumumab.

4. SUBJECT POPULATION

Adult subjects age 18 and older with extranodal NK/T-cell lymphoma, nasal type, are eligible for the study.

Screening for eligible subjects will be performed within 21 days before Cycle 1, Day 1, before administration of the study drug.

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 below, the

investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 10.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. At least 18 years of age
2. Documented as histologically confirmed extranodal NK/T-cell lymphoma, nasal type according to the World Health Organization (WHO) classification,[10,13,20] and the pathology report will be verified by the Sponsor.
3. Criterion modified per Amendment 1:

3.1 Failed (relapsed or refractory after achieving complete or partial remission) at least 1 line of chemotherapy, and who, according to treating physician or investigator, is not candidate to receive other treatment modalities.

4. Criterion modified per Amendment 1:

4.1 At least 1 measurable site of disease (see Section 8.2.1), which should be positive ^{18}F-fluorodeoxyglucose (FDG) uptake in nodal or extranodal sites on positron emission tomography (PET) scan.

5. ECOG performance status score of 0, 1 or 2. (refer Attachment 1) and life expectancy ≥ 3 months.
6. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:
    a. hemoglobin ≥7.5 g/dL (≥4.65 mmol/L) without transfusion support within 7 days;
    b. absolute neutrophil count (ANC) ≥0.75x10^9/L (ie, ≥750/µL) without growth factor support within 7 days;
    c. platelet count ≥50x10^9/L without transfusion support within 7 days;
    d. aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN);
    e. alanine aminotransferase (ALT) ≤2.5 x ULN;
    f. total bilirubin ≤1.5 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 x ULN required);
    g. calculated creatinine clearance of ≥30 mL/min (refer Attachment 5: Calculation of Creatinine Clearance using Cockcroft-Gault formula);
7. Criterion modified per Amendment 1:

7.1 Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal

ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

8. Criterion modified per Amendment 1:

8.1 A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the final dose of study drug.

9. Criterion removed per Amendment 1

10. Criterion removed per Amendment 1

11. Criterion removed per Amendment 1

12. A woman of childbearing potential must have a negative serum/urine pregnancy test (highly sensitive serum [β-human chorionic gonadotropin]) within 14 days prior to the first study agent administration.

13. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF

14. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

Note: Each subject must sign a separate informed consent form if he or she agrees to provide optional samples for research. If subject agreed to provide optional samples for research study, subject should follow the sample collection schedule that is listed in the optional consent form. Refusal to give consent for the optional research samples does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 1:

1.1 No fresh or archived FFPE tumor samples for retrospective biomarker determination

2. Received daratumumab or other anti-CD38 therapies previously

3. Chemotherapy or radiotherapy within 3 weeks before the first study agent administration, or corticosteroids as part of disease treatment within 2 weeks before the first study agent administration, with the exception of an emergency use of corticosteroids such as in the management of severe lymphoma symptoms or life-threatening allergic reaction.

4. Previous allogenic stem cell transplant; or autologous stem cell transplant within

12 weeks before the first administration of the study drug

5. History of active malignancy (other than NKTCL) within 2 years before the first study drug administration (exceptions are adequately treated squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's study responsible physician, is considered cured with minimal risk of recurrence within 2 years)

6. Clinical symptoms of central nervous system (CNS) involvement

7. Subject has either of the following:

   a. Known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted

   b. Known moderate or severe persistent asthma within the past 2 years (refer Attachment 4: National Heart, Lung, and Blood Institute (NHLBI) table of asthma severity), or uncontrolled asthma of any classification. (**Note**: subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study)

8 Criterion modified per Amendment 4:

8.1 Seropositive for hepatitis B or hepatitis C.

Note: Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

If Hepatitis C antibody is positive, RNA PCR needs to be performed and confirmed negative prior to the first study agent administration.

9. Seropositive for human immunodeficiency virus (HIV)

10. Unresolved or unstable, serious toxicity from prior administration of another investigational drug and/or of prior cancer treatment.

11. Subject has any concurrent medical condition or psychiatric condition or disease (eg, active infection, diabetes mellitus, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.

12. Criterion modified per Amendment 1:

12.1 Subject has clinically significant cardiac disease, including:

   a. Myocardial infarction within 6 months before the first study agent administration, or unstable or uncontrolled disease/condition related to or

affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)

b. Uncontrolled cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] [most recent version] Grade 3 or higher) or clinically significant ECG abnormalities

c. Screening 12-lead ECG showing a baseline QT interval as corrected (QTc) >470 msec.

13. Known allergies, hypersensitivity, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or IB), or known sensitivity to mammalian-derived products[18]

14. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments

15. Invasive investigational medical device within 4 weeks before the screening period or is currently enrolled in an interventional investigational study

16. Vaccination with live attenuated vaccines within 4 weeks of first study agent administration.

17. Pregnant or lactating

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 8.1.2, Screening Phase, describes options for retesting. Section 16.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

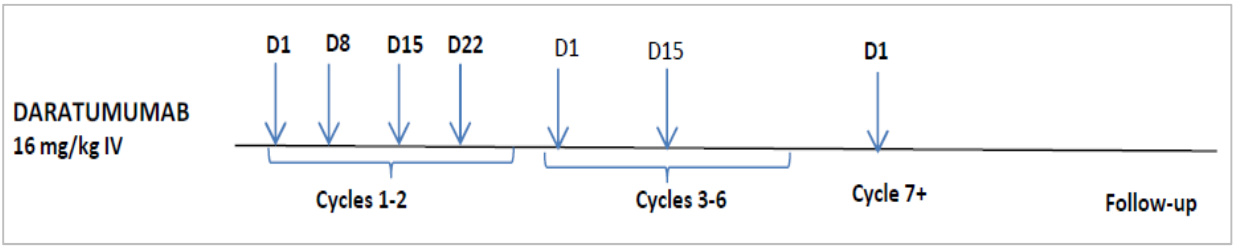
- Subjects agree to follow the contraceptive requirements as noted in the inclusion criteria.

5. DOSAGE AND ADMINISTRATION

Daratumumab is to be administered as described in Figure 2. Each cycle is of 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if within-cycle visits have shifted within the allowed window. In Cycles 1 through 6, daratumumab infusions may be given within ± 1 day of the scheduled day in order to accommodate the schedule of the site or subject.

A schematic of study treatment administration is provided in Figure 2.

Figure 2: Schematic Overview Study Treatment Administration



5.1. Daratumumab preparation

The infusion solution will be prepared on the day of the planned infusion. Detailed instructions for preparation and administration of daratumumab will be supplied in the Site Investigational Product Procedures Manual (SIPPM) or equivalent document.

5.2. Daratumumab Administration

Daratumumab will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 5.3.

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 2. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual).

Table 2: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate	Maximum Infusion Rate
First infusion	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Modified rates should only be used if the first infusion of daratumumab was well-tolerated as defined by an absence of > Grade 1 infusion-related reactions during the first 3 hours.
[b] Modified rates should only be used if the first 2 infusions of daratumumab were well-tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr.

As noted in the T&E Schedule, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. In instances of daratumumab-related toxicity management, schedule adjustments for daratumumab administration are outlined in Table 3.

5.3. Guidelines for Prevention of Infusion Reactions

5.3.1. Preinfusion Medication

In an effort to prevent infusion related reactions, all subject will receive the following medications 1 to 3 hours prior to each study drug administration (1 hour prior to study drug administration is preferred):

- An antipyretic: Paracetamol (acetaminophen) 650-1,000 mg IV or per oral (PO)
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine (see Attachment 3 for Family of antihistamine medications that may be used)
- A corticosteroid: Methylprednisolone 100 mg IV for the first 2 infusions, 60 mg IV for all subsequent infusions, administered approximately 1 hour prior to daratumumab infusion. If methylprednisolone is not available, an equivalent intermediate-acting or a long-acting corticosteroid may substitute (refer Attachment 2 for Conversion Table).
- Leukotriene inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent and can be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 1-3 hours before the infusion. If the preinfusion medication is provided via IV, it should be administrated within 1-3 hours prior to daratumumab infusion.

5.3.2. Postinfusion Medication

For the prevention of delayed IRRs, all subjects will receive long- or intermediate-acting corticosteroid PO (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following the first 3 daratumumab infusions (beginning the day after the infusion date). In the absence of infusion-related AEs after the first 3 infusions, postinfusion corticosteroids should be administered per investigator discretion.

For subjects with higher risk of respiratory complications (ie, subjects who have COPD with an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history or subjects with mild asthma), the following postinfusion medications are recommended:

- Antihistamine (diphenhydramine or equivalent) on the 2 days following all daratumumab infusions (beginning the day after the infusion)
- Leukotriene inhibitor (montelukast or equivalent)

- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD).

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after a daratumumab administration. If subjects are hospitalized, then their FEV1 should be documented before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject is taking postinfusion medications and experiences no major IRRs, then these medications may be stopped after 4 full doses, at the investigator's discretion.

Any postinfusion medication will be administered after the infusion has completed.

5.3.3. Management of Infusion-Related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any IRRs occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the investigational product preparation instructions (IPPI) for further details. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

5.3.3.1. Infusion-Related Events of Grade 1 or Grade 2 (mild to moderate)

If the investigator assesses a Grade 1-2 IRR adverse event to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion.

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

5.3.3.2. Infusion-Related Reactions of Grade 3 (severe) or Higher

For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment.

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

5.3.3.3. Recurrent Infusion-Related Reactions

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

6. TREATMENT COMPLIANCE

6.1. Dose Delays and Dose Modification

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

6.1.1. Daratumumab-Related Toxicity Management

Refer to Section 5.3 for details on management of IRRs. The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab. The criteria for a dose delay are:

1. Grade 4 hematologic toxicity, except for grade 4 lymphopenia
2. Grade 3 thrombocytopenia with bleeding
3. Febrile neutropenia
4. Neutropenia with infection, of any grade
5. Grade 3 or higher non-hematologic toxicities with the following exceptions:
    a. Grade 3 nausea that responds to antiemetic treatment within 7 days
    b. Grade 3 vomiting that responds to antiemetic treatment within 7 days
    c. Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    d. Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
    e. Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab.

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or better or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If a daratumumab administration does not commence within the prespecified window (Table 3) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 3: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Restart*
1 and 2	Weekly (Q1W)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (Q2W)	>7 days	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>14 days	next planned every 4 weeks dosing date

*Dosing on Day 1 of a cycle must not be skipped.

Cycles may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). If a dose is delayed on Day 1 of a cycle, then the dates of all the subsequent doses should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent doses should **not** be adjusted.

Any AE deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab. If a dose delay occurs, then PK and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.1.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

7. CONCOMITANT THERAPY

All prior oncologic therapies, including those since diagnosis, must be recorded at screening. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Routine systemic use of concomitant medications will be collected in the electronic case report form (eCRF) and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier. Concomitant medications to manage AEs and SAEs will be recorded as per Section 7.1.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

7.1. Recommended Therapies

In addition to the mandatory preinfusion medications outlined in Section 5.3.1, the following therapies are recommended.

7.1.1. Prophylaxis for *Pneumocystis Carinii*

Pneumocystis carinii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

7.1.2. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase as per institutional guidelines and continue for 3 months following treatment. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

7.1.3. Prevention of Steroid-Induced Gastritis

Steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).

7.1.4. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see Section 8.6).

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

7.2. Permitted Therapies

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

- Antivirals
- Colony stimulating factors and erythropoietin except during Cycle 1, and transfusion of platelets and red blood cells.
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Prophylactic antiemetics, with the exception of corticosteroids.

7.3. Prohibited Therapies

Use of the treatments listed below is prohibited during the study:

- Prophylactic use of hematopoietic growth factors during Cycle 1
- Other agents that target CD38
- Concurrent radiation therapy is prohibited while on study.
- Administration of commercially available agents with activity against or under investigation for NKTCL, including systemic corticosteroids (≥20 mg/day of prednisone or its equivalent per day for more than 7 days during study, unless reviewed/approved by the study responsible physician) (other than those given for IRRs as described in Section 5.3.2) is prohibited.

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

8. STUDY EVALUATIONS

8.1. Study Procedures

8.1.1. Overview

The T&E Schedule summarizes the frequency and timing of assessments of safety and efficacy, PK, immunogenicity, and biomarker, measurements applicable to this study.

Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The number of blood samples and volume of blood that will be required from each subject for the various study procedures is outlined in the Laboratory Manual. The number of samples and the blood volume will vary depending on the number of cycles of the study drug that the subject

receives as well as which part the subject is enrolled. This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. Unscheduled blood samples may be required for safety issues of individual subjects.

The total blood volume to be collected from a subject who completed a total of Cycle 7 is approximately 240.5 mL (78 mL for safety, 34.5 mL for efficacy, 80 mL for PK/immunogenicity, and 48 mL for biomarker research). If a subject agrees to participate in the exploratory genetic biomarker research, about 2 mL of additional blood samples will be collected prior to daratumumab infusion at Cycle 1 Day 1.

Table 4: Volume of Blood to be Collected From Each Subject (Based on assumption for a female subject completing a total of Cycle 7)

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a]
Safety[b] (including screening and posttreatment assessments			
- Hematology	2	19	38
- Serum chemistry[c]	3	9	27
Serology (hepatitis B and C)[e]	3	1	3
Serum β-hCG pregnancy tests	5	2	10
Efficacy			
Circulating plasma EBV‑DNA quantification	4	8	32
β2-microglobulin	2.5	1	2.5
Pharmacokinetic/Immunogenicity samples	5	16	80
Pharmacodynamic/Biomarker samples	12	4	48
Approximate Total[d]	36.5	60	240.5

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Safety evaluations will be conducted at local laboratory and the blood volume may vary among different local laboratories.
c. Serum chemistry includes serology (hepatitis B and C) and serum β-hCG pregnancy tests.
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
e. For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, more samples may need to be collected to perform HBV DNA testing during the treatment and during follow up. Refer to Section 8.6.

Note: An indwelling intravenous cannula may be used for blood sample collection. [If a mandarin (obturator) is used, blood loss due to discard is not expected.]

From Cycle 8 onwards until PD, 2 mL blood samples will be taken for Hematology, 3 mL for clinical chemistry, and 4 mL for Circulating plasma EBV‑DNA quantification on Day 1 of each cycle; 5 mL blood samples will be taken for PK on Day 1 every two cycles from Cycle 7, plus 5 mL PK and immunogenicity sample on Day 1 of Cycle 12.

8.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures in the screening phase. The Screening Phase begins when the first screening assessment is conducted (that was not performed as part of the subject's standard of care, typically signing of the ICF). During this phase, eligibility criteria will be reviewed as specified in the T&E Schedule. Screening procedures will be performed within 21 days before first dose.

Pathological confirmation of Diagnosis

Diagnosis of NKTCL is performed by the local hospital and the pathology report will be verified by the sponsor. This diagnosis report must include immunophenotype of NK/T–cells. Subject must be documented as histologically confirmed extranodal NKTCL, nasal type according to the WHO classification.[10,12,20] The report containing this information must be sent to sponsor for confirmation of the diagnosis prior to enrollment.

Determination of CD38 expression

Before enrollment to the study, subjects will be required to provide tumor samples (fresh biopsy is preferred. When not available, archived FFPE samples are acceptable) for assessment of CD38 expression. An investigational IHC assay will be used by the central laboratory to determine CD38 expression levels. The role of CD38 expression in predicting tumor response to the treatment of daratumumab will be analyzed retrospectively in the study. Only subjects who agree to provide the required tumor samples and that the sample are available are considered for participation in the study.

8.1.3. Treatment Phase

The Treatment Phase will begin at first intake of study drug and will continue until study drug discontinuation due to PD, consent withdrawal or unacceptable toxicity. Details of the procedures performed during the Treatment Phase are outlined in the T&E Schedule. A window of ±3 days is allowed for visits to the clinic. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if within-cycle visits (eg Cycle 1 Day 15; Cycle 2 Day 22) have shifted within the allowed window.

Subjects will be closely monitored for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If PD is diagnosed, then the subject will discontinue study treatment, complete the EoT Visit, and enter the Follow-up Phase.

End-of-Treatment

Unless a subject withdraws consent for study participation or is lost to follow up, an EoT Visit is to occur within 30 days (+7 days' window) after the last dose of all study treatments. Every effort should be made to conduct the EoT Visit before the subject starts subsequent treatment eg, anticancer therapy. If a subject is unable to return to the site for the EoT Visit, then the subject should be contacted to collect information on AEs and concomitant medications that occur up to 30 days after the last dose of study treatment.

Subjects will be discontinued from study treatment if they have objective radiological PD based on real time BICR according to LUGANO Classification.[12] Following centrally confirmed radiological PD, site will document the PD by completing and faxing a PD form to the sponsor and the study responsible physician will provide written confirmation based on the central confirmed radiological PD that study treatment may be discontinued and recorded in interactive web response system (IWRS) before the subject can enter the Follow-up Phase.

For subjects who have PD as evidenced by unambiguous clinical information (eg. pathologically demonstrated as PD) without confirmation by BICR, they may be discontinued from study treatment at the investigator's discretion. Before such subjects discontinue study treatment, sites will document PD by completing and faxing a PD form to the sponsor as soon as possible and within 48 hours of PD assessment. The study responsible physician will provide written confirmation that treatment should be discontinued. After written confirmation from the sponsor, study treatment may be discontinued and recorded in IWRS before the subject can enter the Follow-up Phase.

Subjects should be discontinued from study treatment if they have objective radiological PD by BICR, however, subjects may be allowed to continue study treatment if PD was documented only by local evaluation and the investigator believes, and sponsor study physician concurs, that the subject could continue to receive benefit and will not experience serious toxicity, and there is no available better alternative treatment that could benefit the subject. These subjects will continue study procedure as per T&E Schedule. If subsequent PD is confirmed either by centrally diagnosis or clinical judgement per investigator discretion, the subject must be discontinued from the study treatment, a subsequent PD form is required for study physician to provide the written confirmation for subject discontinued the study treatment.

8.1.4. Posttreatment Phase (Follow-Up)

The Follow-up Phase will begin once a subject discontinues study treatment, the date of discontinuation of study treatment is based on the study physician's written confirmation date in the PD form. Subjects who discontinue before PD (for other reasons such as an AE) must continue to have their regularly scheduled scans according to the T&E Schedule until centrally confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow-up, or the end of the study. After PD is centrally evidenced with study physician's confirmation of PD form, follow-up will occur at least every 8 weeks (±2 weeks). Subsequent anticancer therapy, second primary malignancies, and survival status will be recorded.

If the follow-up 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 in the eCRF.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the informed consent form (refer to Section 15.2.3, Informed Consent).

8.2. Efficacy Evaluations

Disease evaluations will be performed at Screening, every 8 weeks (±7 days) for the first 6 months and thereafter, every 16 weeks (±7 days) until PD, withdrawal of consent from study participation, or the end of study.

Radiological and PET-CT scans should be performed and collected according to instructions from the independent imaging laboratory. A BICR will be performed to review all the imaging data and clinical information per pre-defined independent central review charter.

The central reviewers will assess disease status based on the Revised Criteria for Response Assessment: LUGANO classification, provided in Attachment 6.[12] Similar methodology should be used for disease assessment at screening and throughout the course of the study. The treatment discontinuation due to PD should be based upon the real time reading results conducted by the central readers. On the basis of clinical information, if PD is confirmed, then for all such subjects, as soon as PD is confirmed by local assessment, the sponsor should be informed immediately.

In order to maximally reduce potential bias between different readers, rigorous methodology will be employed and thus, ensure robustness of the primary endpoint assessment of ORR which is based on BICR. All radiological scans and collected clinical information will be sent to a sponsor appointed Clinical Research Organization (CRO) for a real time BICR. All treatment decisions will be based on such timely central review result. Subjects who are determined to have progressed according to LUGANO classification by the investigator will have scans centrally reviewed for confirmation of objective disease progression. If PD is not confirmed after central review, daratumumab treatment should be continued until centrally documented PD. This procedure may not be followed if the clinical information of subject (eg, Pathologically demonstrated PD) is sufficient enough to demonstrate PD, for such cases, PD confirmation from sponsor study physician is also required.

Definition of Measurable Disease, Assessable Disease, Target Lesion, and Non-Target Lesion

Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should be greater than 1.0 cm in any axis. The measurable site of disease should be clearly measurable in 2 perpendicular dimensions (LDi and short diameter [SDI]). Measurement must be determined by local imaging evaluation. All other sites of disease are considered assessable, but not measurable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the gastrointestinal tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. Note: Lesions to be used as measurable disease for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.

Up to 6 measurable sites of disease with FDG uptake positive (5-point scale 4 or 5) might be identified as target lesions and will be followed during the course of study treatment. Eligible subjects must have at least 1 measurable target lesion. Target lesions should be chosen such that they are representative of the subject's disease (this includes splenic and extranodal disease). If

there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in 2 perpendicular dimensions, at least 1 lymph node mass from each region should always be included. In addition, selection of target lesions should be from as disparate regions of the body as possible. Skin lesions will be considered as target lesion only if there are no other measurable lesions available elsewhere. All the other measurable/assessible diseases are considered as non-target lesions.

8.2.1. PET-CT Scan

During the study, disease response will be assessed using whole-body ^{18}F-FDG PET-computed tomography (CT) scans (skull base to the upper 1 third of the thighs). PET-CT scans are reported using a fixed display and color table scaled to the standardized uptake value (SUV) to assist with consistency of reporting. Contrast enhancement is preferred for the CT portion in order to obtain diagnostic CT imaging. When follow-up PET-CT is performed, it is recommended to use the same scanner with the same reconstruction algorithm as in the initial scan.

Positive uptake is defined as any focal or diffuse area of increased activity, in a location incompatible with normal anatomy or normal variant. For response assessment, the lesions should be scored according to the Deauville Score (DS) using a 5-point scale with the following criteria:[10]

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesion

X. (New) areas of uptake unlikely to be related to lymphoma.

Additional scan or biopsy may be considered for suspicious PD at the investigator's discretion (eg, in case that EBV-DNA persistently detectable or rising from a previous unquantifiable level after apparent remission, uncertain etiology of new lesions, etc).

8.2.2. Radiographic (CT or MRI) Assessments

During the study, disease response will be assessed using CT scans with IV contrast of the neck, chest, abdomen, and pelvis and any other location where disease was present at Screening. Subjects who are intolerant of IV CT contrast agents will have CT scans performed with oral contrast.

Hybrid PET-CT scanners may be used to acquire the required CT images only if CT produced by the scanner is of diagnostic quality, adheres to specified scan parameters, and includes contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only CT scan for the timepoint. Diagnostic CT images with contrast and adequate slice thickness with a standalone CT scanner is required if PET-CT is unable to acquire diagnostic CT images.

Evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as necessary (to be performed throughout the study using the same method of assessment used to assess disease at baseline), and review of hematology and clinical chemistry results may also occur at the site level.

Magnetic resonance imaging (MRI) may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required only if clinically indicated.

8.2.3. Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (eg, skin lesions). In the case of skin lesions, documentation by color photography, including ruler/calipers to measure the size of the lesion in millimeters (mm), is required. Any clinical information which can support disease evaluation should be collected (eg, palpable lesion).

8.2.4. Bone Marrow Assessment

A bone marrow biopsy is required for documentation of a CR; a confirmatory bone marrow biopsy should be done preferably within 30 days of the initial documentation of CR. Bone marrow evaluation must include morphological examination and ISH for Epstein–Barr virus-encoded ribonucleic acid (EBV-encoded RNA; EBER), if warranted, to confirm the presence or absence (CR) of lymphoma.

8.2.5. Tumor Biopsy Assessment

Lymphoma lesion biopsy may be conducted in a clinically indicated way. It is strongly recommended if lesion is reasonably accessible to confirm suspected PD. Tumor biopsy evaluation must include morphological examination and ISH for EBV-encoded RNA; EBER. Such pathological data from site will also be used for central oncology review.

8.2.6. Blinded Independent Central Review

An independent review of all scans and clinical information used in the assessment of tumors will be conducted according to the Revised Criteria for Response Assessment: LUGANO classification.[12] All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to a sponsor appointed CRO for central analysis. The central review process will be clearly defined in a BICR charter in advance of the start of the study.

The treatment discontinuation due to PD will be based upon the results of the real time central review. This procedure may not be followed if the clinical information of subject (eg, Pathologically demonstrated PD) is sufficient enough to demonstrate PD, for such cases, PD confirmation from sponsor study physician is also required.

The efficacy analysis for this study will be based on the BICR data.

8.3. Pharmacokinetics and Immunogenicity

For all subjects, serum samples will be evaluated for the PK of daratumumab, as well as the generation of anti-daratumumab antibodies, according to T&E Schedule: PK and Immunogenicity. Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

8.3.1. Evaluations

At specified time points, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and each serum sample will be divided into 3 aliquots (1 aliquot for PK analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

The exact dates and times of blood sampling must be recorded. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

8.3.2. Analytical Procedures

Pharmacokinetics and Immunogenicity

Serum samples will be analyzed to determine concentrations of daratumumab or for the detection and characterization of antibodies to daratumumab using validated, immunoassay methods by or under the supervision of the sponsor.

8.3.3. Pharmacokinetic Parameters

The PK parameters are defined as:

- C_{max} Maximum observed concentration
- t_{max} The actual sampling time to reach maximum observed concentration
- AUC Area under the concentration – time curve

All parameters will be estimated using the actual sampling times by non-compartmental analysis methods.

8.3.4. Immunogenicity Assessments

Anti-daratumumab antibodies will be evaluated in serum samples collected from all subjects according to the T&E Schedule. Daratumumab serum concentration will also be determined from all immunogenicity samples to ensure proper interpretation of the immunogenicity results.

Serum samples will be screened for antibodies binding to daratumumab and the titer of confirmed positive samples will be reported. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

When both serum concentration and immunogenicity analyses are specified, they are performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

A blood sample should be drawn, if possible, for determination of antibodies to daratumumab any time an infusion reaction is observed or reported during the study. Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the infusion reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of daratumumab immunogenicity/serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

8.4. Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, then other PK/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. Disease-related or mechanism-based biomarkers will be also explored, such as plasma EBV-DNA, blood NK cell counts, and tissue CD38 expression. If these analyses are performed, then the details and results will be presented in a separate report.

8.5. Biomarkers

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 justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in the T&E Schedule.

Circulating plasma EBV-DNA quantification

Circulating plasma EBV-DNA quantification will be monitored monthly as a biomarker of tumor load at the central laboratory. Circulating plasma EBV-DNA quantification will also be monitored at EoT visit.

Determination of CD38 and CIPs Expression

Before enrollment to the study, subjects will be required to provide tumor samples for assessment of CD38 expression based on central testing using investigational IHC methodology

under development (Section 8.1.2). Fresh biopsy samples are preferred, and if not available, archived FFPE blocks/slides are acceptable. Fresh tumor samples should be from core needle biopsy but not fine needle aspirates and should be done within 21 days of Cycle 1 Day 1; archived sample (slides or tumor block) can be acquired more than 21 days prior to Cycle 1 Day 1. If archived samples are provided instead of fresh biopsy, additional information should be provided, including but not limited to date of biopsy/resection, site/organ of biopsy, collection method, pathology report and diagnostic, treatment received after biopsy. If possible, it is also recommended to provide the following information: type of fixative used, time of execution to fix, fixation time. If FFPE sections are provided instead of block, date of section should be provided.

In addition to evaluating CD38 expression, fresh or archived biopsy samples may be evaluated in all subjects to identify markers predictive of response to daratumumab or prognostic markers for disease progression. Paraffin-embedded, formalin-fixed tumor tissue may also be subjected to DNA (eg, somatic mutations) and RNA analysis (eg, GEP, qRT-PCR, or RNA-seq) to determine if specific mutations or transcriptomic profiles (translocations, deletions, inversions, genes involved CD38 signaling pathways, or others) are associated with daratumumab response. Comparison of CD38 IHC results may be made to transcriptomic data. In addition to CD38, CIPs expression might be measured by IHC or immunofluorescent staining in a designated laboratory as an exploratory biomarker whenever samples are available. CD59, CD55 and CD46 are complement inhibitory proteins and can contribute to resistance to CDC, which may be important for daratumumab response.

If re-biopsy is needed for any clinical reasons, such as to confirm diagnosis or study pathology of new lesion, it is encouraged that FFPE slides/block to be submitted to determine CD38 and CIP expression. Correlation of biomarker expression and treatment response in the site will be studied, and the change of biomarker expression at new sites compared to the original site will also be analyzed. The information will be used to advance the understanding of daratumumab response and resistance mechanism in NKTCL patients.

Immunophenotyping.

Previous daratumumab clinical studies in MM have demonstrated that baseline immune profiles of subjects may be predictive of response to daratumumab, and that specific immune subpopulations increase (CD8+ T cells) or decrease (NK cells) with daratumumab treatment. Therefore, whole blood samples will be utilized for immunophenotyping, (performed by flow cytometry and mass cytometry/time-of-flight mass spectrometry [CyTOF]) which includes analysis of NK, T cells, and B cells as well as other potential immune cell subpopulations. NK cells are known to express CD38, and early clinical data indicates rapid decreases in absolute counts of circulating NK cells upon daratumumab dosing. It is not known how critical NK cells are for the clinical efficacy of daratumumab but based on the rapid and sustained decreased absolute counts observed across all subjects, NK cells (CD45+CD3-CD16+CD56+) can be used as a pharmacodynamic biomarker for daratumumab. In addition, preliminary data from clinical studies in MM indicate that the immune fitness of subjects at baseline may preclude response to daratumumab.

To investigate whether an immune fitness signature can be developed utilizing either flow cytometry or genomic profiling, whole blood samples may also be subject to DNA sequencing, RNA profiling or methylation assessment to identify potential predictive marker for daratumumab response and genomic alterations related to NKTCL disease mechanism, to evaluate novel technologies for immune profiling in whole blood, and to compare these methodologies to standard flow cytometry.

Since CDC is one of the key mechanisms of action for daratumumab, and normal function of complement system in the body is required for CDC activity, plasma samples will be analyzed for complement proteins, to study whether specific complement protein level is associated with daratumumab response.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded (FFPE) tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

8.6. Safety Evaluations

Safety will be measured by AEs, laboratory test results, ECGs, vital signs measurements, physical examination findings, and assessment of ECOG performance status score. All toxicities will be graded according to the NCI-CTCAE version 4.03. Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

Based on the previous human experience with daratumumab, in vitro studies, and animal toxicological findings, IRRs/allergic reactions, infection, hemolysis, and thrombocytopenia will be closely monitored. As a biologic agent, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and AEs should be evaluated by the investigator according to the standard practice, if clinically indicated.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, ECOG performance status, and other safety evaluations at specified time points as described in the T&E Schedule.

Adverse Events

Adverse events (AEs; with the exception of progression of NKTCL) will be reported by the subject (or, when appropriate, by a caregiver or surrogate) for the duration of the study. Adverse events (AEs) will be followed by the investigator as specified in Section 11, AE Reporting.

Clinical Laboratory Tests

Blood samples for serum hematology and chemistry will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory unless otherwise noted:

- Hematology Panel

  -hemoglobin
  -white blood cell (WBC) count
  -platelet count
  -Absolute neutrophil count (ANC) and Lymphocytes

- Serum Chemistry Panel

  -sodium
  -potassium
  -calcium
  -creatinine
  -blood glucose (fasting)
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -lactic acid dehydrogenase (LDH)
  -total bilirubin
  -direct bilirubin (for subjects with congenital bilirubinemia, such as Gilbert syndrome)
  -alkaline phosphatase

- Serum or Urine Pregnancy Testing (for women of childbearing potential only and as clinically indicated)
- Hepatitis B Screening (local laboratory)

  -HBsAg
  -Anti-HBc
  -Anti-HBs

HBV Serology

All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 4 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. Hepatitis B Virus serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for HBV DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule. Where required by local law, the results of HBV testing may be reported to the local health authorities.

- Hepatitis C Screening (local laboratory)
  - Hepatitis C antibody

    If Hepatitis C antibody is positive, RNA PCR needs to be performed and confirmed negative prior to first study agent administration.

Daratumumab Interference Indirect Antiglobulin Testing (IAT) results

Blood group, Rh type, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the indirect antiglobulin test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/ Rhesus factor–D antigen (RhD) grouping/typing.

CD38 is expressed at very low levels on erythrocytes. Preliminary data indicate that daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (also known as indirect Coombs test) and will make complete blood typing difficult while subjects are receiving treatment. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis was observed. Eleven of 78 subjects in Study GEN501 had blood transfusions during treatment with daratumumab.[16] The preliminary data indicate that transfusion of these subjects treated with daratumumab was not adversely affected. In alternate situations, blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol.[11]

Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends.

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

1. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
2. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs.

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice. For additional details, refer to the daratumumab IB.

β2-microglobulin

Baseline β2-microglobulin will be measured in serum to assess lymphoma tumor burden as well as disease prognosis.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 5.3 (Guidelines for Prevention of Infusion Reactions) for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG)

Electrocardiogram (ECGs) will be performed as specified in the T&E Schedule. 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. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Vital signs (pulse, temperature, and blood pressure) will be performed as specified in T&E Schedule. It is recommended that blood pressure (sitting) and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). All measurements will be recorded in the source documents. Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom and disease directed physical examination is required. Height will be measured at screening only; weight will be measured regularly as specified in the T&E Schedule. Abnormalities will be recorded in the appropriate sections of the eCRF. Eastern Cooperative Oncology Group (ECOG) Performance Status (refer Attachment 1) will be used to evaluate the impact of the disease status on the activities of daily

living. When scheduled, ECOG assessments should be obtained prior to dosing of daratumumab on Day 1 of each cycle.

8.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent)/sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the T&E Schedule for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

9. SUBJECT COMPLETION/WITHDRAWAL FROM THE STUDY

9.1. Completion

A subject will be considered to have completed the study if he or she has completed all protocol-specified procedures before the end of the study, has died before the end of the study, has not been lost to follow up, has not withdrawn consent for study participation before the end of the study, or has transitioned to commercial drug product.

9.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment

If a subject's study treatment must be discontinued, it will not result in automatic withdrawal of the subject from the study. The EoT Visits and Follow-up visit assessments should continue as specified in the T&E Schedule.

A subject's study treatment (daratumumab) should be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject withdraws consent for administration of study drug
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for NKTCL
- The subject experiences unacceptable toxicity, including IRRs described in Section 5.3

- The subject's dose of daratumumab is held for more than 4 weeks in Cycles 1-6 or for more than 6 weeks in Cycle 7 and beyond (unless sponsor approves continuation)
- The subject experiences PD (see below and Attachment 6). Relapse from CR is not considered as disease progression.
- Daratumumab becomes commercially available (or when daratumumab can be accessed from another source) for this disease. At this time, the subject will be transitioned from study drug to commercial product and will be withdrawn from the study. In these circumstances, the sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted.
- A subject who experiences a second primary malignancy that cannot be treated by surgery or radiotherapy alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically or with definitive radiotherapy may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of NKTCL.

Subjects should be discontinued from study treatment if they have objective radiological PD based on real time BICR according to LUGANO Classification. Following centrally confirmed radiological PD subjects will be discontinued from study treatment and enter the Follow-up phase.

For subjects who have PD as evidenced by unambiguous clinical information (eg. pathologically demonstrated as PD), before such subjects discontinue study treatment due to PD, sites will document PD by completing and faxing a PD form to the sponsor as soon as possible and within 48 hours of PD assessment; EoT steps will be performed. The study responsible physician will confirm that treatment should be discontinued. After confirmation from the sponsor, study treatment may be discontinued and the subject can enter into Follow-up phase. If a subject discontinues study treatment for any reason other than PD, then disease assessments should be obtained as specified in the T&E Schedule.

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
- Death
- Sponsor terminates the study.

If a subject is considered 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.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document (refer Section 8.1.4 and Section 15.2.3 for details on collection of long-term survival status). Study drug assigned to the withdrawn subject

may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the EoT, assessments should be obtained.

9.3. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 15.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

10. 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. Specific details will be provided in the Statistical Analysis Plan.

10.1. Subject Information

The primary analysis population is the safety population, which will include all treated subjects. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, SD, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

10.2. Sample Size Determination

The study is designed to evaluate the effect of daratumumab on ORR utilizing Simon's 2-stage design. The null hypothesis is that ORR is at most 15%, and the alternative hypothesis is that ORR is at least 30%. With a 1-sided α of 10%, and a power of 78%, a total of 32 subjects are to be enrolled into the study. The stage 1 analysis is to be performed when approximately 15 subjects are enrolled in the study and have sufficient data for response evaluation. The futility criterion of ORR is defined as when at most 1 out of 15 subjects have achieved CR/PR after stage 1 according to Simon's 2-stage design. Future enrollment into stage 2 may be terminated if it is determined during the first stage that the treatment group is considered as ineffective or not well-tolerated. If study proceeds to second stage with a total of 32 subjects with 2 stages combined, the null hypothesis is to be rejected if 8 or more responses are observed.

To achieve 1-sided α of 2.5% and a power of 80%, additional patients (ie, approximately 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab if supported by emerging data.

10.3. Efficacy Analyses

10.3.1. Primary Efficacy Endpoint

Objective response rate (ORR) is defined as the proportion of subjects who achieve CR or PR per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin lymphoma: LUGANO classification[12] based on BICR. An estimate of the primary efficacy endpoint ORR

will be presented along with a 2-sided 95% exact CI. The number and percentage of subjects falling into each response category will be descriptively tabulated**.**

10.3.2. Secondary Efficacy Endpoint

Complete response (CR) rate is defined as the proportion of subjects who achieve CR based on BICR and will be analyzed similarly as the primary efficacy endpoint.

Progression-free survival (PFS) is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse based on BICR or death, whichever comes first. For those subjects who are still alive without progression/relapse, PFS will be censored at the last adequate tumor assessment.

Duration of response (DoR) will be duration from the date of the initial documentation of a response to the date of first documented evidence of PD based on BICR (PD; or relapse for subjects who experience CR) or death. For those subjects who are still without progression/relapse, DoR will be censored at the last adequate tumor assessment.

Time to response is defined as the duration from the date of the first dose of daratumumab to the earliest date that a response (CR/PR based on BICR) is first documented. For nonresponders, it will be censored at the date of PD/relapse or the date of the last adequate disease assessment, whichever comes first.

Overall survival (OS) is defined as the duration from the date of the first daratumumab dose to the date of death. For those subjects who are still alive without progression/relapse, OS will be censored at the last date known to be alive.

For time to event endpoints (eg, PFS, OS, time to response, DoR), Kaplan-Meier estimates will be presented. Median along with corresponding 95% CIs will be obtained from the Kaplan-Meier estimates. Analysis for time to response and DoR will be for responders only.

10.4. Pharmacokinetic Analyses

Pharmacokinetic (PK): PK analyses will be performed on the PK-evaluable population, defined as subjects who have received at least 1 dose of daratumumab and at least 1 postinfusion sample.

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the clinical study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and PK parameters of daratumumab (C_{max}, $t_{max,}$ AUC) following the 1st infusion. Mean serum daratumumab concentration time profiles will be plotted after the first dose of study drug, and composite serum concentration time profiles may also be plotted.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab may be performed using nonlinear mixed-effects modeling and may include data from other studies. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

The relationship between derived PK parameters and covariates, such as actual dose, body weight, and selected laboratory parameters, may be evaluated graphically. Further exploratory analyses of PK data may be performed and reported separately.

10.5. Immunogenicity Analyses

The incidence of antibodies to daratumumab (immunogenicity) will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab. A listing of subjects whose sample(s) are positive will also be presented. Daratumumab concentrations will be summarized at all immunogenicity time points. The maximum titers of antibodies to daratumumab will be summarized for subjects who are positive for antibodies to daratumumab.

The impact of antibodies to daratumumab on drug exposure and efficacy/safety will be analyzed if there are positive samples.

10.6. Biomarker Analyses

All biomarker measurements will be listed, tabulated, and where appropriate, plotted. Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

Associations between baseline levels and changes from baseline in select markers and clinical response (CD38 expression, EBV-DNA quantification and other biomarkers PK/pharmacodynamic modeling) will be explored. Exploratory genetic analyses will be summarized in separate technical reports.

Results will be presented in a separate report.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. Disease-related or mechanism-based biomarkers will be also explored, such as plasma EBV-DNA, blood NK cell counts, and tissue CD38 expression. If performed, details and results of the analysis will be presented in a separate report.

10.8. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the Treatment Phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

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) 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. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE version 4.03 toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI-CTCAE (version 4.03). Clinical relevant changes (ie, causing a treatment intervention or need for concomitant therapy) will be also recorded on the AE eCRF. All other lab abnormalities need not be recorded as AEs.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs

Descriptive statistics of temperature 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.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

10.9. Interim Analysis

The study is designed with an interim analysis performed at the end of stage 1 when approximately 15 subjects have received at least one dose of study drug and had at least one post-baseline disease evaluation. Enrollment may be put on hold pending the decision of interim analysis unless the decision is clear based on available data before the interim analysis. The purpose of the interim analysis is to evaluate efficacy and safety data in stage 1 and facilitate the early preparation for the next step of development. The totality of efficacy (ORR), safety, and biomarker data will be analyzed at interim. The futility criterion of ORR is defined as at most 1 out of 15 subjects have achieved CR/PR after stage 1. This futility boundary is considered non-binding. Study may be terminated if the futility criteria are met or supported by the totality of data including biomarker and safety data.

In addition, at interim, the association between daratumumab activity and CD38 expression level will be explored. If a strong association between daratumumab activity and CD38 expression level is confirmed by emerging data or a low response rate is observed from stage 1 data due to low CD38 expression levels, then an enrichment strategy may be applied for stage 2 to mitigate the risk of low responses possibly attributed to low CD38 expression. The final analysis may be adjusted accordingly (eg, primary analysis would be based on enriched population) if an enrichment strategy is applied in stage 2.

11. 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.

11.1. Definitions

11.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), 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 AEs starting with the signing of the ICF (refer to Section 11.3.1, All AEs, for time of last AE recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The 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 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug 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, PD).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an AE will be determined by whether or not it is listed in the IB.[18]

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 11.1.2, Attribution Definitions.

11.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

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

Very Likely

An AE 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 (eg, it is confirmed by dechallenge and rechallenge).

11.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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

11.2. Special Reporting Situations

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

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

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

11.3. Procedures

11.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received additional treatment with therapeutic intent for NKTCL during the AE reporting period, only AEs that are considered to be possibly, probably, or definitely related to study drug must be reported (unless the subject has been withdrawn from the study). Serious adverse events (SAEs), including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs).

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

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

Progression of the disease under study is not considered an AE (or SAE), even if it results in death during the AE reporting period. If a clinical sign or symptom or a laboratory test abnormality is observed in a subject with PD, but is not related to PD under study, then the usual AE reporting requirements apply.

11.3.2. Serious Adverse Events

All SAEs 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 SAEs will be transmitted to the sponsor using the SAE 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 an SAE should be made by facsimile (fax).

All SAEs 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 drug 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 an SAE. 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 an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

11.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment.

Because the effect of the study drug 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.

11.4. 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.

12. 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.

12.1. 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 SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 11.3.2, SAEs). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

12.2. 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.

13. STUDY DRUG INFORMATION

13.1. Physical Description of Study Drug(s)

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

13.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL.

13.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

13.4. Preparation, Handling, and Storage

Daratumumab product must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C. Study drug must not be utilized after the expiry date printed on the label. The daratumumab product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

13.5. Drug Accountability

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

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's

study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

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

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

14. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- IB[18], Study protocol
- Daratumumab manual/study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE version 4.03
- eDC Manual
- IWRS Manual (if any)
- Sample ICF
- Investigator File
- Subject identification wallet card.

15. ETHICAL ASPECTS

15.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with IRRs; see Section 5.3 for prevention details. Based on the mode of action of daratumumab, a potential risk could be infection; therefore the protocol requires the review of hematological laboratory results prior to daratumumab infusion. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

The archived biopsy samples were originally taken prior to the clinical study as part of the subject's NKTCL disease clinical work-up or management. The archived biopsy tissue is then sent to the central laboratory biomarker status determination such as CD38 and CIPs. Therefore, there is no risk related to tissue biopsy for this study for subjects with archived tissue. For subjects undergoing re-biopsy for this study, the risks are included in the Janssen ICF, under the "Fresh Tissue Biopsy Risk" section.

Further, in the Simon's 2-stage design of the clinical study protocol, a futility analysis will be performed to evaluate efficacy and safety data at interim. If the futility criteria are met, the study may be terminated and further subject exposure will be limited.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is estimated about 15.5 mL for screening tests, 158 mL from Cycle 1-6, 26 mL at Cycle 7 and thereafter, 31 mL at the end-of treatment visit and 10 mL for follow-up visit. The total blood volume to be collected is considered to be within the normal range allowed for this subject population in a cancer clinical study and reasonable over the time frame of the study.

15.2. Regulatory Ethics Compliance

15.2.1. 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.

15.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- sponsor-approved ICF (and any other written materials to be provided to the subjects)

- IB (or equivalent information) and amendments/addenda[18]
- sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda[18]
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- 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).

15.2.3. 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 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.

Subjects will be asked for consent to provide optional samples for research. After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component.

Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will 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.

When prior consent of the subject is not possible, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject must be informed about the study as soon as possible and give consent to continue.

15.2.4. 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. 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, PK/pharmacodynamic, 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.

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to

understand NKTCL, to understand differential drug responders, and to develop tests/assays related to daratumumab and NKTCL. 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 9.3, Withdrawal From the Use of Samples in Future Research.

16. ADMINISTRATIVE REQUIREMENTS

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

16.2. Regulatory Documentation

16.2.1. 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.

16.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug 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.

16.3. 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.

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.

16.4. 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 AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug 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 following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking, all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments.

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:

- Subject must be documented as histologically confirmed extranodal NK/T-cell lymphoma, nasal type according to the World Health Organization (WHO) classification.[10,13,21]
- 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.

16.5. 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 electronic 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.

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

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

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

16.6. 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, and periodic monitoring visits by the sponsor, and direct

transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

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

16.7. 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.

16.8. 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).

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

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

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

16.9. Study Completion/Termination

16.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the T&E Schedule for the last subject participating in the study. 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.

16.9.2. 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 drug development.

16.10. 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.

16.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab 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 pharmacogenomic, or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic, or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study 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 8 weeks 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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.

REFERENCES

1. A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma. https://clinicaltrials.gov/ct2/show/NCT02076009. Accessed 29 April 2016.
2. A Study of Daratumumab in Japanese Participants With Relapsed or Refractory Multiple Myeloma. https://clinicaltrials.gov/ct2/show/study/NCT02116569. Accessed 29 April 2016.
3. A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (DVMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma. https://clinicaltrials.gov/ct2/show/NCT02195479. Accessed 29 April 2016.
4. A Study of JNJ-54767414 (HuMax CD38) (Anti-CD38 Monoclonal Antibody) in Combination With Backbone Treatments for the Treatment of Patients With Multiple Myeloma.

   https://clinicaltrials.gov/ct2/show/NCT01998971. Accessed 23 February 2016.
5. Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma. https://clinicaltrials.gov/ct2/show/NCT02136134. Accessed 29 April 2016.
6. Albeniz I, Demir Ö, Türker-Şener L, Yalçıntepe L, Nurten R, Bermek E. Erythrocyte CD38 as a prognostic marker in cancer. Hematology. 2007;12:409–414.
7. An Efficacy and Safety Study of Daratumumab in Patients With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor [PI] and Immunomodulatory Drug [IMiD]) or Are Double Refractory to a PI and an IMiD. https://clinicaltrials.gov/ct2/show/NCT01985126. Accessed 16 February 2016.
8. Artz AS1, Somerfield MR, Feld JJ, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. J Clin Oncol. 2010;28(19):3199-3202.
9. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood. 2009;113(17):3931-3937.
10. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27):3048-3058.
11. Chapuy, C, Nicholson R, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015; 55:1545-1554.
12. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3067.
13. Chinese Society of Hematology, Chinese Medical Association; Committee of Malignant Lymphoma, Chinese Anti-cancer Association; Chinese Society of Hepatology, Chinese Medical Association. Consensus on the management of lymphoma in patients with hepatitis B virus infection. Zhonghua Gan Zang Bing Za Zhi. 2013;21(11):815-820.
14. DARZALEX (daratumumab) injection [package insert]. Horsham, PA Janssen Biotech, Inc. May 2018.
15. DARZALEX (daratumumab) DARZALEX 20 mg/mL concentrate for solution for infusion [Summary Product Characteristics]. Beerse, Belgium, Janssen Cilag International NV, Aug 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/004077/WC500207296.pdf
16. Daratumumab (HuMax®-CD38) Safety Study in Multiple Myeloma.

   https://clinicaltrials.gov/ct2/show/NCT00574288. Accessed 16 February 2016.

17. Daratumumab in Combination With Lenalidomide and Dexamethasone in Relapsed and Relapsed-refractory Multiple Myeloma. https://clinicaltrials.gov/ct2/show/NCT01615029. Accessed 16 February 2016.

18. Investigator's Brochure: JNJ-54767414 (daratumumab), edition 14. Janssen Research & Development, LLC (05 October 2017).

19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–655.

20. Oostendorp M, van Bueren J, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion. 2015;55:1555-1562.Park S, Ko YH. Peripheral T cell lymphoma in Asia. Int J Hematol. 2014;99:227–239.

21. Pearlman BL and N Traub. Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More. Clin Infect Dis. 2011:52 (7): 889-900.

22. Tse E, Kwong YL.How I treat NK/T-cell lymphomas. Blood. 2013;121(25):4997-5005.

23. Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130.

24. Wang L, Wang ZH, Chen XQ, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119(2):348-355.

25. Wang L. CD38 expression predicts poor prognosis and might be a potential therapy target in extranodal NK/T cell lymphoma, nasal type. Ann Hematol. 2015;94(8):1381-1388.

26. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: The NK-Cell Tumor Study Group study. J Clin Oncol. 2011;29:4410–4416.

27. Zocchi E, Franco L, Guida L, et al. A Single Protein Immunologically Identified as CD38 Displays NAD+ Glycohydrolase, ADP-Ribosyl Cyclase and Cyclic ADP-Ribose Hydrolase Activities at the Outer Surface of Human ErythrocytesOriginal Research Article. Biochem Biophys Res Commun. 1993;196(3):1459–1465.

ATTACHMENT

Attachment 1: ECOG Performance Status Scale[19]

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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

Attachment 2: Conversion Table for Glucocorticosteroid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	0.6

Attachment 3: Family of Antihistamine Medications

The following antihistamines may be used for daratumumab preinfusion medication (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

*The IV formulation of promethazine should be avoided.

Attachment 4: Asthma Guidelines (NHLBI)

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV1 FEV1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

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Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			> 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
Recommended Action for Treatment		• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months			Step up 1 step	Step up at least 1 step	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps		• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options
					• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.			• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		

Attachment 5: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

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

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

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

- Serum creatinine (mmol/L) divided by 88.4 = serum creatinine (mg/dL)

Formula to measure creatinine clearance:

$$CrCl = \frac{U_{Cr} \times U_{vol}}{P_{Cr} \times T_{min}}$$

$$\text{Corrected CrCl} = CrCl \times \frac{1.73}{BSA}$$

Notes: U_{Cr}, Urine creatinine concentration; U_{vol}, Urine volume from 24 hrs collection; P_{Cr}, plasma creatinine concentration; T_{min}, collection time in minutes (24 hrs x 60 min); BSA, body surface area.

Attachment 6: Revised Response Criteria for Response Assessment[12]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi; No extralymphatic sites of disease
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if inderterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites from baseline; When a lesion is too small to measure on CT, assign 5mm×5mm as the default value; When no longer visible, 0×0mm; For a node > 5mm× 5mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

Response and Site	PET-CT–Based Response	CT-Based Response
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from virtually determined nadir	PPD progression: An individual target (nodal or extranodal) must be abnormal with: Node >1.5 cm in LDi or extranodal lesion>1.0 cm in any axis; Increase by≥50% from PPD nadir and An increase in LDi or SDi from nadir: ≥0.5 cm for lesions≤2 cm ≥1.0 cm for lesions>2 cm In the setting of splenomegaly, the splenic length must increase by>50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node >1.5 cm in LDi; A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma; Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Response and Site	PET-CT–Based Response	CT-Based Response

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, short diameter, the widest part of the lesion perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake≤mediastinum; 3, uptake>mediastinum but≤liver; 4, uptake moderately> liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

INVESTIGATOR AGREEMENT

JNJ-54767414 Daratumumab
Clinical Protocol 54767414NKT2001 Amendment 4

INVESTIGATOR AGREEMENT

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

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study 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): Ming Qi; MD, PhD

Institution: Janssen Research & Development

Signature: _____ PPD _____ Date: 24 January 2019
(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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Approved, Date: 24 January 2019