Janssen Research & Development *

Clinical Protocol

An Open Label, Phase 2 Study to Evaluate Efficacy and Safety of Daratumumab in Relapsed or Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma

Protocol 54767414LYM2001; Phase 2
Amendment-1

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	Issue Date
Original Protocol	12 January 2015
Amendment 1	19 January 2016

Amendments below are listed beginning with the most recent amendment.

Amendment-1 (19 January 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To optimize candidate screening potential, elaborate on Indirect Antiglobulin (Coombs) Testing (IAT) during the Screening Phase due to the risk of daratumumab interference with IAT, as well as make updates throughout the protocol to align with the other daratumumab protocols.

Applicable Section(s)	Description of Change(s)
Rationale: Changes were made to the subject inclusion criteria to increase candidate screening without compromising study objectives.	
Synopsis; Subject Population, 4.1 Inclusion Criteria #2, MCL	The MCL prior line restriction of 2 to 5 lines of prior therapy was changed to at least 2 prior lines of therapy, with no upper limit.
Synopsis, Overview of Study Design, Biomarkers evaluation; Table 1 Time and Events Schedule, Tumor sample; 3.1 Overview of Study Design; 4.1 Inclusion Criteria #4; 9.1.2 Screening Phase; 9.5 Biomarkers	To ease sample collection for the CD38 assay plus paired sample. Subjects must have available archival or fresh tumor tissue or both for CD38 assay.

Applicable Section(s)	Description of Change(s)
Synopsis, Primary Objective, Hypothesis, and Overview of Study Design; 1.3 Overall Rationale for the Study; 2.1 Objectives, Primary Objective; 2.2 Hypothesis; 3.1 Overview of Study Design; Figure 1; Table 3; 3.2 Study Design Rationale, 1); 4.1 Inclusion Criteria #4; 9.1.2 Screening Phase; 11.2 Sample size determination; 11.3.1 Primary Efficacy Endpoint; 11.9 Interim analysis	Stage 2 will allow for enrollment of subjects with all levels of CD38 expression. Changed CD38 expression level for subset of Stage 2 to <50% throughout. Removed CD38 positive subjects from text throughout.
Synopsis, Subject Population; 4.1 Inclusion Criteria #2, MCL	Changed “ibrutinib” to “Bruton’s tyrosine kinase (BTK) inhibitor”
4.2 Exclusion Criteria #3	Subject history of malignancy was reduced to be less strict from 5 years before screening period to 3 years. The minimal risk of recurrence was reduced from 3 years to 2 years.
4.2 Exclusion Criteria #5	Subjects with a history of Hepatitis C should not be excluded if the viral load becomes negative with modern therapy.
4.2 Exclusion Criteria #10	Added emergent use of steroids at screening stage (100 mg prednisone per day or equivalent for up to 7 days).
Rationale: Due to risk of daratumumab interference with IAT testing, text was removed from Prohibitions and Restrictions and added to Sec 9.5 Safety Evaluations to be consistent to other daratumumab protocols.	
4.3 Prohibitions and Restrictions	Removed the text pertaining to daratumumab interference with indirect antiglobulin testing (IAT) from here as this information is provided in Section 9.5 Safety Evaluations.
9.5 Safety Evaluations	Updated text on daratumumab interference with indirect antiglobulin testing (IAT) to align with other daratumumab protocols.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the timing of daratumumab PK and Immunogenicity sample collections and PK parameters.	
Time and Events Schedule Overview	Modified Laboratory Assessments for Daratumumab PK sampling in End-of-Treatment and Follow-up Phase: Added 1 week window for PK collections
9.3.2 Analytical Procedures	Text removed: ~~All samples collected and received up to the time of the primary study endpoint analysis (first bioanalysis) are planned to be analyzed for immunogenicity (when applicable) and serum daratumumab concentration as indicated by Table 1. The final bioanalysis is planned to include all serum daratumumab concentration (pharmacokinetics) and immunogenicity samples that become available after the previous analysis. Adjustments to bioanalysis timing may be made if it is later determined that the timing for data needed to facilitate crucial decision-making differs from these two planned efforts. However, data from each round of bioanalysis will be considered final and samples will not be reanalyzed in any subsequent efforts.~~
9.3.3 Pharmacokinetic Parameters; 11.4 Pharmacokinetic Analyses	Removal of PK parameters to be tested CL, V. Definitions for C_{min} and C_{max} for added.
9.4 Pharmacokinetic/ Pharmacodynamic Evaluations	Removal of section as text is duplicated in Sec 11.6.
11.5 Immunogenicity Analyses	Text added "In addition, subjects who are positive for antibodies to daratumumab will also be listed."
Rationale: Miscellaneous updates made to clarify or add consistency.	
Synopsis, Overview of Study Design and Efficacy Evaluations; Table 1 Time and Events Schedule; 3.1 Overview of Study Design; 9.2.1 Evaluations; 10.2 Discontinuation of Study Treatment	Disease evaluations were restated in weeks not cycle times. The follow text regarding the timing of disease evaluations was added. **After first dose, disease evaluations will occur every 8 weeks for the first 3 evaluations, then every 16 weeks for the next two evaluations and then every 24 weeks thereafter.**
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 9.1.4 Follow-up Phase	Clarification made for end of cohort. The end of the ~~study~~ **cohort** for each NHL subtype is defined as 18 months after the last subject in the particular NHL subtype receives the first dose of daratumumab.
Table 1; 6 Dosage and Administration	Clarification to give a 1 day window within-cycle (Cycles 1-6) to accommodate site or subject logistics.
6. 3.2 Postinfusion Medication	Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or ~~salbumatol~~ **salmeterol** ± inhaled corticosteroids for subjects with COPD).

Applicable Section(s)	Description of Change(s)
6.4.1 Daratumumab-Related Toxicity Management; Footnote added to Table 4	Edits made to clarify dose delays and adjustments. Text added: "If a dose is delayed on Day 1of a cycle, then the dates of all the subsequent doses should be adjusted. However, if a within-cycle dose is delayed, then the dates of the subsequent doses should not be adjusted."
9.1.1 Overview; 16.1 Study Specific-Design Considerations	Clarifications made to total estimated blood volumes.
9.2.1.3 PET Scan	Clarification made to add "per investigator discretion" and remove "and relapse from CR".
Attachment 1: Revised Response Criteria for Response Assessment	Clarified site for no response or stable disease of "Target nodes/nodal masses, extranodal lesions" to be consistent with the Revised Response Criteria for Response Assessment
9.5 Safety Evaluations	Blood type, RhD tests added
9.5 Safety Evaluations, Vital Signs	Text was removed that was contradictory to the eCRF. ~~Only vital signs associated with an AE will be entered in the eCRF;~~
Synopsis, Overview of Study Design; 4.1 Inclusion Criteria #4; 9.1.2 Screening Phase; 9.4 Biomarkers	Clarified that the CD38 IHC test is "investigational and under development".
7. Treatment Compliance	Added "and postinfusion" medications for clarity. A subject diary may be used to document any pre- **and post- infusion** medications taken at home.
Rationale: Clarification made to the Follow-up Phase.	
Table 1, Time and Events Schedule	During Follow-up Phase, 8 weeks post PD collection of ECOG was removed as it is not necessary.
Table 1, Time and Events Schedule; 9.1.4 Follow-up Phase	Added window of +/- 2 weeks for Follow-up Phase and changed 4 months to 16 weeks.
Rationale: To increase the strength of our primary endpoint analysis.	
Synopsis, Statistical Methods; 11.3.1 Primary Efficacy Endpoint	For each NHL subtype, an estimate of the ORR was changed from 90% to 95% for the two-sided exact confidence interval.
Rationale: Hypokalemia increases the risk of QT elongation in ECG.	
4.3 Prohibitions and Restrictions	Added: 2. Subjects with persistent hypokalemia (eg, serum potassium <3.5 mM after proper treatment) need to be monitored for the potential of QTc prolongation.

Applicable Section(s)	Description of Change(s)
Rationale: To align language to be consistent with other daratumumab protocols, IB, and new template text.	
1.2 Daratumumab	Revised text: For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (Daratumumab IB). 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.
4. Subject Population	If there is a question about the inclusion or exclusion criteria below, the investigator ~~should~~ **must** consult with the appropriate sponsor representative **and resolve any issues** before enrolling a subject in the study. **Waivers are not allowed.**
4.1 Inclusion Criteria, #6 g)	Changed calculated creatinine clearance of ≥30 mL/min.
4.1 Inclusion Criteria, #9, 4.2 Exclusion Criteria #11	Changed text that men should not donate sperm for 3 months after receiving study drug. Women should not become pregnant within 3 months after last dose of daratumumab, or man should not father a child within 3 months after last dose of daratumumab.
Synopsis, Subject Population; 4.1 Inclusion Criteria #2, DLBCL	Clarified text to **subjects with relapsed or refractory disease who have not received HDT and ASCT and are ineligible for HDT/ASCT due to comorbidities**
4.2 Exclusion Criteria, #7c)	Modify the language of "screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec " as "screening 12-lead ECG showing a baseline QT interval as corrected QTc>470 msec"
4.2 Exclusion Criteria, NOTE	Revised 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.** See Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.
4.3 Prohibitions and Restrictions	New text: 1. Subjects agree to follow the contraceptive requirements as noted in the inclusion criteria.
6.4.1 Daratumumab-Related Toxicity Management	Changed Grade 3 or higher neutropenia with infection to "any grade"
8.3 Prohibited Therapies	The maximum dose of prednisone allowed was increased to **≥20 mg/day of prednisone or its equivalent per day for more than 7 days during study, unless reviewed/approved by medical monitor**).~~(>10 mg prednisone per day or equivalent for over 7 days)~~
12.3.3 Pregnancy	~~Any subject who becomes pregnant during the study must promptly discontinue further study treatment.~~ **If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the sponsor.**
17.5 Case Report Form Completion	Text regarding corrections to eCRFs updated.

Applicable Section(s)	Description of Change(s)
Rationale: Optional endoscopy at baseline added as CRs must be confirmed with endoscopy if the lymphoma originated from or involved the GI tract at diagnosis.	
Table 1 Time and Events Schedule Overview; 9.2.1.5 Endoscopy (new)	Endoscopy added. New section added: CRs must be confirmed with endoscopy examination if the lymphoma originated from or involved the GI tract at diagnosis.
Rationale: To reflect current practice, updated management of infusion-related reactions section to indicate that the infusion will be paused (not interrupted or slowed down) if an infusion-related reaction occurs.	
6.3.3 Management of Infusion-Related Reactions	If an infusion-related reaction develops, then the infusion should be **paused** ~~temporarily interrupted or slowed down~~.
Rationale: Removal of the term "legally acceptable representative" to address IRB concerns that for those adults who lack capacity to consent should be excluded.	
4.1 Inclusion Criteria #10, 9.5 Safety Evaluations (Adverse Events); 10.2 Discontinuation of Study Treatment;15.2.3 Informed Consent; 16.2.4 Privacy of Personal Data	Removal of "legally acceptable representative" throughout the protocol.
Rationale: Beta 2 microglobulin (β2M) was added because it is an important lymphoma biomarker for tumor burden as well as prognosis.	
Table 1 Time and Events Schedule Overview; 9.5 Safety Evaluations; 11.3.1 Primary Efficacy Endpoint	Beta 2 microglobulin was added to the Time and Events Schedule and safety analyses. Statistical methods for beta 2 microglobulin were added.

Applicable Section(s)	Description of Change(s)
Rationale: Update tumor lysis syndrome text added to align with other daratumumab protocols and provide additional detailed information for tumor lysis syndrome diagnosis and management.	
8.1.1 Therapy for Tumor Lysis Syndrome	~~Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, are highly recommended. It is also recommended that high-risk subjects, ie, those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion).~~ Text updated: The symptoms for tumor lysis syndrome should be monitored. Subjects with more than 1 of the factors listed below are considered to be at increased risk of tumor lysis syndrome and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms, including blood chemistry. Uric acid-lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric® [Adenuic™, febuxostat] with or without rasburicase per the drug product package inserts. 1. Serum creatinine ≥1.5 x ULN or calculated creatinine clearance <60 mL/min 2. Uric acid ≥450 µmol/L or 7.5 mg/dL 3. Bulky disease (eg, lymph node >10 cm or massive splenomegaly) 4. Elevated LDH >2 x ULN
Rationale: Since this study is in relapsed/refractory setting, chest x rays are not necessary for all subjects, unless clinically indicated.	
Table 1 Time and Events Schedule Overview; 9.1.2 Screening Phase	Chest x rays were removed from the Time and Events Schedule.
Rationale: Updated text reflects most recent screening data in clinical study.	
3.2 Study Design Rationale	This subset of subjects **may** represent ~~about~~ **up to** 50%, 30% and **60%** ~~30%~~ of population with MCL, DLBCL and FL, respectively. If a low overall response rate is observed in this subset of subjects, it is highly unlikely that there exists a practical subset of subjects based on CD38 expression level in which a clinically meaningful overall response rate can be observed.
Rationale: Since the study may include subjects that have taken BTK inhibitors, a washout period for BTK inhibitors was added.	
4.2 Exclusion Criteria #2, h) new	h) for the MCL cohort, BTK inhibitors within 1 week or 5 half-lives, whichever is longer
Rationale: Subject wallet (study) cards were corrected.	
12.3.1 All Adverse Events; 15 Study-Specific Materials	Removed "Blood antigen profile" and replaced with **Blood type, Rh, and IAT or phenotyping result collected before first daratumumab dose**
Rationale: Additional risk benefit language added for the investigational CD38 IHC Assay.	
16.1.1 CD38 IHC Assay (New Section added)	New risk benefit language for the investigational CD38 IHC assay to included false positives and false-negative results.

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 Evaluate Efficacy and Safety of Daratumumab in Relapsed or Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. CD38 is also expressed in subtypes of non-Hodgkin's lymphoma (NHL), warranting further investigation of daratumumab in NHL.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The study will evaluate daratumumab separately in three relapsed or refractory NHL subtypes: mantle cell lymphoma (MCL), diffuse large B cell lymphoma (DLBCL), and follicular lymphoma (FL). There are two main objectives:

- To assess overall response rate (ORR, including complete response [CR] and partial response [PR]), of daratumumab in subjects with NHL.
- To evaluate association between ORR and CD38 expression level in order to determine a threshold for CD38 expression level in each NHL subtype, above which daratumumab activity is enhanced.

Secondary Objectives

For each subtype of NHL, the secondary objectives are:

- To assess the duration of response (DoR), progression-free survival (PFS), and overall survival (OS)
- To assess time to response
- To assess and correlate the CD38 expression level with DoR, PFS, and OS
- To assess pharmacokinetics of daratumumab
- To assess immunogenicity of daratumumab
- To assess the safety profile of daratumumab

Exploratory Objectives

- To explore biomarkers, in addition to CD38 expression level, predictive of response to daratumumab

Hypothesis

For each subtype of NHL, analyses will be conducted on the overall population and on the CD38 enriched population (only subjects with CD38 expression level above a threshold to be determined via statistical inference). There is one hypothesis for each population. Daratumumab is considered active per subtype if at least one of the null hypotheses is rejected:

For MCL

- For the overall population, ORR is at least 35% (versus a null hypothesis of at most 20%)
- For the enriched population, ORR is at least 40% (versus a null hypothesis of at most 20%)

For DLBCL

- For the overall population, ORR is at least 30% (versus a null hypothesis of at most 15%)
- For the enriched population, ORR is at least 40% (versus a null hypothesis of at most 15%)

For FL

- For the overall population, ORR is at least 50% (versus a null of at most 30%)
- For the enriched population ORR is at least 60% (versus a null of at most 30%).

OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, Phase 2 study in subjects at least 18 years of age with tumors in MCL, DLBCL, or FL. Approximately 210 subjects may be enrolled, with up to 100 subjects planned for MCL and up to 55 subjects each for DLBCL and FL.

This study will be conducted and analyzed separately for each subtype of NHL. A biomarker adaptive threshold design is implemented that enables testing of the overall population and the establishment of a biomarker-defined enriched population simultaneously. Two stages are planned.

Stage 1 of the study is designed to provide a preliminary assessment of activity at an early stage. Since CD38 expression level may be associated with daratumumab activity, Stage 1 will enroll subjects who have tumors where at least 50% of the cells are CD38 positive as determined by the CD38 test currently under development. This requirement seeks to mitigate the possibility that a low response rate observed in Stage 1 might be due to low levels of CD38 expression. The selection of the 50% cutoff is based on the existing CD38 expression level data in these NHL subtypes as well as practical considerations.

At the end of Stage 1, which is expected to be 6 months after the last subject is enrolled in each NHL subtype, or earlier if emerging data allows, an interim analysis will be conducted. The purpose of the interim analysis is to evaluate efficacy and safety data in Stage 1. The efficacy assessment will be focused on ORR. If the futility criteria as defined in the protocol are met, an NHL subtype may be terminated. Alternatively, if the futility criteria are not met and if supported by the totality of the Stage 1 data, Stage 2 for that NHL subtype may be opened for accrual. If the required number of responses (eg, 5 responders out of 20 enrolled subjects in MCL) is observed prior to completion of enrollment in Stage 1, Stage 2 may be opened immediately upon completion of enrollment to Stage 1, if supported by the totality of data.

Stage 2, if opened, is designed to further evaluate safety and efficacy as well as to determine a threshold for CD38 expression that is associated with enhanced daratumumab activity. Therefore, Stage 2 will allow for enrollment of subjects with all levels of CD38 expression. However, to mitigate the possibility that a low response may be observed due to low levels of CD38 expression in enrolled subjects, the number of Stage 2 subjects with CD38 expression level <50% will be capped within each NHL subtype.

The target number of subjects in each stage by CD38 expression level is shown in the table below.

Type of NHL	Number of Subjects			
	Stage 1 CD38 expression level [b] ≥50%	Stage 2 (optional)		Overall
		CD38 expression level [a] <50%	CD38 expression level [b] ≥50%	Total
MCL	20	≤30	≥50	**100**
DLBCL	15	≤20	≥20	**55**
FL	15	≤20	≥20	**55**

a. These subjects have tumors where <50% of the cells are positive for CD38 by immunohistochemistry.
b. These subjects have tumors where ≥50% of the cells are positive for CD38 by immunohistochemistry.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days prior to Cycle 1, Day 1. Prior to enrollment, subjects are required to provide tumor tissue to determine CD38 expression level by immunohistochemistry (IHC) at a central laboratory. An additional fresh biopsy should be obtained whenever possible even if an archival sample is provided. The Treatment Phase will extend from Cycle 1, Day 1 until study drug discontinuation. After first dose, disease evaluations will occur every 8 weeks for the first 3 evaluations, then every 16 weeks for the next two evaluations and then every 24 weeks thereafter. Subjects will be treated until disease progression, unacceptable toxicity, or other reasons as listed in the protocol.

The Follow-up Phase will begin once a subject discontinues study drug, and will continue until death, loss to follow up, consent withdrawal for study participation, or end of study, whichever occurs first.

An interim analysis for futility will be conducted in each NHL subtype no later than 6 months from when the last subject is enrolled in Stage 1 in that NHL subtype. If Stage 2 is expanded for a particular NHL subtype, the primary analysis will be performed at 6 months after the last subject is enrolled in Stage 2.

The end of the cohort for each NHL subtype is defined as 18 months after the last subject in the particular NHL subtype receives the first dose of daratumumab. After each NHL subtype completes the study, the sponsor will ensure that subjects, who are currently on treatment and receiving benefit, as determined by the investigator, will continue to receive daratumumab. The end of the study is defined as the completion of all three NHL subtypes.

Assessment of tumor response and disease progression will be conducted by investigators in accordance with the Cheson 2014 response criteria. Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. 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 pharmacokinetics, immunogenicity, biomarkers and pharmacodynamics parameters.

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age, have histologically confirmed diagnosis of MCL, DLBCL, or FL and measurable disease, centrally determined expression levels of CD38, and an ECOG performance status score of 0 or 1. Key criteria for each NHL subtype:

MCL:

- pathologically verified diagnosis of MCL based on local pathology report, AND
- relapsed or refractory disease after at least 2 prior lines of therapy, including at least one cycle of a Bruton's tyrosine kinase (BTK) inhibitor therapy and documented PD during or after BTK inhibitor treatment or subjects who could not tolerate BTK inhibitor (ie, discontinued BTK inhibitor due to adverse events [AEs])

DLBCL:

- pathologically confirmed diagnosis of non-transformed DLBCL, AND
- relapsed or refractory disease; for those subjects who have not received HDT/ASCT and are not eligible for HDT/ASCT due to comorbidities

FL:

- pathologically confirmed diagnosis of FL of Grade 1, 2, or 3a according to World Health Organization criteria without pathological evidence of transformation, AND
- relapsed disease after at least two prior systemic therapies including one anti-CD20 containing combination regimen

DOSAGE AND ADMINISTRATION

Daratumumab (16 mg/kg) will be administered by 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.

EFFICACY EVALUATIONS/ENDPOINTS

After the first dose, disease evaluations will be performed every 8 weeks (±7 days) in the first 6 months (Week 9 ±7 days, Week 17 ±7 days, Week 25 ±7 days, followed by every 16 weeks ±7 days [Weeks 41 and 57], and thereafter every 24 weeks [±14 days] until PD). These assessments will be conducted until disease progression, withdrawal of consent from study participation, or the end of study.

The determination of disease status will be assessed by the investigator based on the Revised Criteria for Response Assessment (Cheson 2014). Identical methodology should be used for disease assessment at screening and throughout the course of the study.

Radiological and PET scans should be performed and collected according to instructions from the independent imaging laboratory. A central review of the response assessments may be performed if deemed necessary.

The major efficacy endpoint, ORR, is defined as the proportion of subjects who achieve CR or PR.

Secondary efficacy endpoints are:

- 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 (or relapse for subjects who experience CR). For those subjects who are still without progression/relapse, DoR will be censored at the last adequate tumor assessment.
- PFS is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse 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.

- 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.
- 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) is first documented. For non-responders, it will be censored at the date of progressive disease/relapse or the date of the last adequate disease assessment, whichever comes first.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

For all subjects, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to Time and Events Schedule. At specified timepoints, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

BIOMARKER EVALUATIONS

During screening, subjects will be required to provide archived tumor samples for assessment of CD38 expression based on the CD38 investigational IHC test performed at the central laboratory. An additional fresh biopsy should be obtained whenever possible even if an archival sample is provided. Fresh tumor samples can be either lymph node excision or core needle biopsy; fine needle aspirates are not acceptable.

In addition to evaluating CD38 expression, archived biopsy samples and/or fresh may be evaluated 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, Gene Expression Profiling [GEP], quantitative RT-PCR, or RNA-seq) to determine if specific mutations or transcriptomic profiles (translocations, deletions, inversions, genes involved in B-cell signaling pathways, 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, CD59 expression will be measured by IHC in a designated laboratory as an exploratory biomarker. CD59 is a complement inhibitory protein and can contribute to resistance to complement-dependent cytotoxicity, which may be important for daratumumab response.

Whole blood samples will be utilized for immunophenotyping, (performed by flow cytometry or mass cytometry/time-of-flight mass spectrometry [CyTOF]) which includes analysis of natural killer cells, T cells, and B cells as well as other potential immune cell subpopulations.

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 (IL-1, IL-6, TNFα, IFNγ, tryptase), and exploratory proteomics.

SAFETY EVALUATIONS

Safety will be measured by AEs, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

STATISTICAL METHODS

For each NHL subtype, an estimate of the ORR will be presented along with a two-sided 95% exact confidence interval. In addition, the biomarker adaptive threshold method of Jiang (2007)[16] will be utilized to select a threshold for CD38 expression level. The threshold is used to define an enriched subpopulation above which the daratumumab activity is enhanced. The number and percentage of subjects falling into each response category will be descriptively tabulated. Duration of response will be provided descriptively using the Kaplan-Meier method for responders only.

Progression-free survival and OS will be analyzed using the Kaplan-Meier method, and the comparison between the above- and below-threshold subpopulations will be made using log-rank test and Cox regression.

Table 1: Time And Events Schedule Overview

	Notes	Screening Phase within 28 days before Cycle 1 Day 1	Treatment Phase Day 1 of each cycle (4-week cycles)	EOT within 30 days of last dose	FU Phase Q16 weeks +/- 2 weeks
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.					
Procedures					
Informed consent	ICF must be signed before any study-related procedures are performed and may be more than 28 days prior to C1D1.	X			
Eligibility criteria		X			
Demography/ Medical History		X			
FEV1 test	Subjects with COPD	X			
Tumor sample	If a fresh biopsy (lymph node excision or core needle biopsy) is taken, then it should be done within 28 days of C1D1. Archived sample (slides or tumor block) can be acquired more than 28 days prior to C1D1. For subjects with MCL a copy of the pathology report must be sent to the sponsor. CD38 assessment by IHC performed centrally; enrollment only after defined CD38 criteria are met.	X			
ECOG	Obtain prior to any other study procedures planned for the same day.	X	C1D1, C3D1, D5D1, C7D1, thereafter every 12 wks		16 wks post PD
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before Cycle 1 Day 1	X	C3D1, C6D1	X	
Physical examination	Height at screening only	X	symptom and disease directed exam as clinically indicated		
Vital signs, weight		X	Please see Table 2 for details.		
Lymphoma B symptoms	Review and record (fevers, night sweats, weight loss)	X	X	X	
Blood type and Indirect Antiglobulin Test (IAT)	ABO, Rh, and IAT		predose C1D1		

	Notes	Screening Phase within 28 days before Cycle 1 Day 1	Treatment Phase Day 1 of each cycle (4-week cycles)	EOT within 30 days of last dose	FU Phase Q16 weeks +/- 2 weeks
Laboratory Assessments					
Pregnancy test	serum or urine, women of childbearing potential only, within 14 days of C1D1	X	As clinically indicated	X	
Hematology		X	Please see Table 2 for details.	X	
Serum chemistry		X	Please see Table 2 for details.	X	
β2-microglobulin		X			
Biomarker sample	Whole blood samples for plasma and PBMC biomarker assessments and for immunophenotyping		C1D1, C2D1, and C6D1 predose	X	
Daratumumab PK	On dara infusion days, 1 sample is to be collected before (window -2 hrs) and 1 sample immediately after (window +2 hrs) end of infusion. Samples to be sent to central laboratory.		C1D1, C3D1, C5D1, C7D1, C11D1, C15D1	4 wks (+/- 1 wk) and 8 wks (+/- 1 wk) after last daratumumab dose	
Daratumumab immunogenicity	No additional sample needed for planned timepoints; will be taken from PK sample.		C1D1 predose If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.	4 wks (+/- 1 wk) and 8 wks (+/- 1 wk) after last daratumumab dose	
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule. Refer to Section 9.2 for details on efficacy evaluations.					
CT or MRI imaging (neck, chest, abdomen, and pelvis)	Acceptable for screening if performed as part of SOC within 42 days before Cycle 1 Day 1. 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 stored at a central lab.	X	Week 9 ±7 days, Week 17 ±7 days, Week 25 ±7 days (8 weeks since previous image) Week 41±7 days and Week 57 ±7 days (16 weeks since previous image) Thereafter every 24 wks (±14 days) until PD (24 weeks since previous image) The same methodology should be used throughout the study.		
FDG-PET scan (skull base to the proximal femur)	Acceptable for screening if performed as part of SOC within 42 days before Cycle 1 Day 1. All scans will be collected and stored at a central lab	optional	if positive PET at screening, at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction)		
Bone marrow aspirate/biopsy	Acceptable for screening if performed as part of SOC within 42 days before Cycle 1 Day 1.	optional	required to confirm CR (all lymphoma subtypes), regardless of whether aspirate/biopsy was performed at screening		
Endoscopy	Only subjects with diagnosis of lymphoma with GI involvement	optional	CRs must be confirmed with endoscopy if the lymphoma originated from or involved the GI tract at diagnosis.		

	Notes	Screening Phase within 28 days before Cycle 1 Day 1	Treatment Phase Day 1 of each cycle (4-week cycles)	EOT within 30 days of last dose	FU Phase Q16 weeks +/- 2 weeks
Subsequent therapy					X
Other new malignancy					X
Survival					X
Ongoing Subject Review					
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug			
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug			

Abbreviations: AE=adverse event; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; ECG=electrocardiogram; EOT= End-of-Treatment; FEV= Forced Expiratory Volume (in 1 second); FU=follow-up; IAT=indirect antiglobulin test; ICF=informed consent form; IHC=immunohistochemistry; MCL=mantle cell lymphoma; MRI=magnetic resonance imaging; PBMC= peripheral blood mononuclear cell ; PET=positron emission tomography; PK=pharmacokinetics; PD= disease progression; Q16 weeks=every 16 weeks; SAE=serious adverse event; SIPPM=site investigational product procedures manual; SOC=standard of care; Wk=week

Table 2: Time And Events Schedule, Dose Administration

	Notes	Cycle 1 and Cycle 2				Cycle 3-Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
Hematology	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 timepoints, as clinically indicated. To be done by local lab. Refer to Section 9.5 for parameters to be tested.	X	X	X	X	X	X	X	X
Clinical Chemistry		X				X		X	X
Weight	If a subject's weight changes by more than 10% from baseline, the dose study treatment will be re-calculated	X				X		X	
Vital Signs	Vital signs (blood pressure, temperature, pulse) measured in sitting position. On Cycle 1 Day 1: immediately before the start of dara 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. For all other infusions, vital signs will be measured immediately before infusion start and at end of dara infusion.	X	X	X	X	X	X	X	
Study Drug Administration									
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. Administer pre- and postinfusion medications as per Section 6.	X	X	X	X	X	X	X	

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BTK	Bruton's tyrosine kinase
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
DLBCL	diffuse large B cell lymphoma
DoR	duration of response
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
FdG	fluoro-deoxyglucose
FEV	forced expiratory volume
FL	follicular lymphoma
GCP	Good Clinical Practice
hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
IAT	indirect antiglobulin test (also known as indirect Coombs test)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
MCL	mantle cell lymphoma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PD	disease progression
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PQC	Product Quality Complaint
PR	partial response
RBC	red blood cell
R-CHOP	rituximab + CHOP
R-DHAP	rituximab, dexamethasone, high-dose cytarabine, and cisplatin

R-Hyper-CVAD	rituximab + hyper-CVAD
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
SAE	serious adverse event
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
ULN	upper limit of normal
VGPR	very good partial response
VR-CAP	bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone

1. INTRODUCTION

1.1. Background

The non-Hodgkin's lymphomas (NHLs) are a diverse group of blood cancers that originate from lymphocytes. They can occur at any age and are often manifested by enlarged lymph nodes, fever, and weight loss. There are many different types of NHLs. Clinically, there are aggressive and indolent types of NHL. These NHLs can be formed from either B-cells (>90%) or T-cells (<10%) or rarely natural killer (NK) T cells. Prognosis and treatment depend on the stage and type of disease.

1.1.1. Diffuse Large B-cell Lymphoma (DLBCL)

The most common histological subtype of NHL is Diffuse Large B-Cell Lymphoma (DLBCL) which accounts for approximately 30% to 58% of all new cases diagnosed annually worldwide (Tilly 2010)[25]. Standard chemotherapy treatment consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab. A randomized study of CHOP versus rituximab-CHOP (R-CHOP) was performed in 398 newly diagnosed DLBCL patients, 60 to 80 years of age (Coiffier 2002)[4]. The rate of complete response (CR) was significantly higher in the group that received R-CHOP compared with the group that received CHOP alone (76% vs. 63%; p=0.005). With a median follow-up of 2 years, event-free survival (EFS) was 57% in the R-CHOP group and 38% in the CHOP group. Results from the 10-year analysis confirmed the benefit of the addition of rituximab to CHOP (10-year progression-free survival [PFS]: 36.5% vs. 20% for R-CHOP and CHOP, respectively; 10-year OS: 43.5% vs. 27.6%, respectively) (Coiffier 2010)[6]. Despite high response rates with an anthracycline-containing regimen such as R-CHOP, approximately one-third of patients with DLBCL have refractory disease or will relapse. A variety of combination cytotoxic chemotherapy regimens are used in the relapsed / refractory setting. Two commonly used regimens are R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin). The CORAL study (Collaborative Trial in Relapsed Aggressive Lymphoma, Gisselbrecht 2010)[11] compared the R-ICE and R-DHAP regimens in relapsed patients with DLBCL followed by high-dose chemotherapy-autologous stem cell transplantation (HD-ASCT) after an induction response. The study showed similar 3-year EFS and OS rates for the 2 induction regimens; however, subjects previously treated with rituximab had an OS of 40% compared with 66% for subjects with no prior rituximab treatment. Subjects whose disease progressed less than 12 months after diagnosis compared with more than 12 months also had significantly lower response rates (46% vs. 88%, respectively; p<0.001), indicating a poor prognosis for those patients who relapse early following rituximab-containing first-line therapy. Although subjects who underwent ASCT had longer PFS (3-year PFS=39%) compared with subjects who did not receive ASCT (14%; p<0.001), only 50% of subjects were able to undergo ASCT. Therefore, given the limited options for salvage therapy in the relapsed/refractory setting, additional therapies are urgently needed to improve outcomes in relapsed/refractory DLBCL.

1.1.2. Follicular Lymphoma (FL)

Follicular lymphoma (FL) is the second most common NHL and comprises approximately 20% to 33% of all NHL cases (Anderson 1998)[1]. Follicular lymphoma is characterized by an indolent

clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients (Relander 2010)[24]. This translocation results in the overexpression of BCL2 protein, a member of a family of proteins that inhibits apoptosis (Freedman 2012)[10]. Transformation of FL to an aggressive lymphoma, most commonly the clonally related DLBCL, occurs at a rate of 3% per year and is associated with substantial morbidity and mortality (Relander 2010)[24], including rapid progression of lymphadenopathy, extranodal disease, B symptoms (fever, drenching night sweats, and weight loss >10%), and elevated serum lactate dehydrogenase (LDH) (Freedman 2012)[10]. In patients with early-stage FL (Stage I or II), radiation therapy is associated with 10-year progression-free survival (PFS) rates of 45% to 60%, and is considered to represent a curative treatment in this otherwise incurable disease with conventional modalities (Jacobson 2012)[15]. Advanced-stage FL (Stage III or IV) is incurable with conventional chemotherapy, even if combined with radiotherapy (Relander 2010)[24]. Historically, median survival has ranged from 6 to 10 years. Responsiveness to therapy and duration of response (DoR) both decline with repeated treatments when relapsed, particularly after documented transformation of FL to a more aggressive histology lymphoma, with death generally resulting from the disease (Montoto 2007)[18]. Idelalisib (Zydelig) was recently approved by the FDA to treat relapsed FL in patients who have received at least two prior systemic therapies, which defines a population with unmet medical needs. The safety and efficacy of Zydelig in patients with FL was evaluated in a single-arm, multicenter clinical trial which included 72 patients with follicular B-cell non-Hodgkin lymphoma who had relapsed within 6 months following rituximab and an alkylating agent and had received at least 2 prior treatments. The results showed that overall response rate (ORR) was 54% (CR 8% and partial response (PR) 46%). The median DoR range was between 1-15 months.

1.1.3. Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma (MCL) is an incurable subtype of NHL that was recognized as a unique clinicopathologic entity in the 1990s (Harris 1994)[12]. It is often said to incorporate the worst aspects of both the aggressive and indolent lymphomas. The disease progresses quickly, like the aggressive lymphomas, but it is incurable, like the indolent lymphomas. The unique characterization at the molecular level is the overexpression of the cell cycle regulator protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene, B-cell leukemia/lymphoma-1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer with subsequent overexpression of cyclin D1 (Harris 1994; Van Den Berghe 1979; Williams 1992)[12,26,27]. Current initial therapy for the treatment of MCL includes CHOP or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper-CVAD). The FDA also approved in October 2014 the use of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) as frontline treatment for patients with MCL. The use of R-CHOP in previously untreated patients resulted in an ORR of 96%, including CR of 48% (Howard 2002)[14]. Once the disease has progressed after first-line therapy, the prognosis for patients with MCL is dismal. Although the treatment of patients with relapsed or refractory MCL requires the use of aggressive therapies, there is currently no consensus regarding a standardized approach for treating this population. In the relapsed/refractory setting, temsirolimus (Torisel®) was approved in the European Union (EU),

bortezomib was approved by the FDA (ORR 31% and median DoR 9.3 months, n=155) for treatment of MCL patients who have received at least 1 prior therapy, and lenalidomide was approved by the FDA (ORR 26%, and median DoR 16.6 months, n=134) for treatment of MCL patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. Patients treated with temsirolimus (175/75-mg) had significantly longer PFS than those treated with investigator choice (median PFS 4.8 vs. 1.9 months; hazard ratio=0.44; p=0.0009). The ORR in the temsirolimus (175/75-mg) group was 22% (CR 2%). Median OS was 12.8 months, which was not significantly different from that of the investigator choice group (9.7 months) (Hess 2009)[13]. Ibrutinib (Imbruvica) is a BTK inhibitor approved (FDA 2013 and EU 2014) as a single agent for treatment of patients with MCL who have at least one prior therapy. The study from a single-arm open-label trial of 111 MCL showed that ORR was 65.9% (CR17.1% and PR48.6%). The median DoR was 17.5 months. The median time to response was 1.9 months. However, there are still about 35% of patients who either do not respond to ibrutinib or cannot tolerate ibrutinib due to treatment related toxicity.

1.2. Daratumumab

Daratumumab is a fully human IgG1κ monoclonal antibody that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38 in a variety of hematological malignancies including multiple myeloma, lymphoma, and leukemia.

Daratumumab induces lysis of CD38-expressing tumor cells, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of complement proteins, NK cells, and macrophages, respectively (de Weers 2011, Overdijk 2013)[7,22].

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

1.2.1. Nonclinical Studies

Preliminary pharmacodynamic studies suggest that daratumumab utilizes multiple effector cell functions, resulting in immune mediated killing of CD38-expressing tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary CD38-expressing multiple myeloma cells, CDC occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011)[7]. Daratumumab-induced ADCC is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011)[7]. Daratumumab has also been shown to induce ADCP in the presence of macrophages within 4 hours in vitro (Overdijk 2013)[22]. Further, in vitro studies indicated that daratumumab inhibited the cyclase activity of CD38 and stimulated the CD38 hydrolase activity (Study No. GMB 3003-013).

Studies on proliferation of and release of cytokines in human blood cells have indicated that daratumumab does not exert target-specific agonistic activity. The cytokine release observed is mainly caused by the Fc-portion of IgG1 and comparable to that of approved therapeutic antibodies already in clinical use. Specific binding of daratumumab was detected in multiple tissues of both human and chimpanzee origin.

1.2.1.1. Toxicology

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, daratumumab infusions and thrombocytopenia. Anemia was observed in cynomolgus monkeys. The binding affinity of daratumumab is significantly higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. The effect on platelets and red blood cells was reversible.

Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in both chimpanzees and cynomolgus monkeys. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

1.2.2. Clinical Studies

No clinical studies with daratumumab have been conducted in NHL. Preliminary data from 5 ongoing clinical studies on multiple myeloma are summarized below. For further details and the most up-to-date information, please refer to the Daratumumab IB.

As of 31 July 2014, approximately 300 subjects with multiple myeloma have been treated across 5 ongoing clinical studies of daratumumab: Studies GEN501, GEN503, 54767414MMY1001, 54767414MMY1002, and 54767414MMY2002 (hereafter referred to as MMY1001, MMY1002, and MMY2002, respectively). Single-agent daratumumab has been administered to 232 subjects in Studies GEN501, MMY1002, and MMY2002; 41 subjects have been treated with daratumumab in combination with lenalidomide and dexamethasone in Study GEN503, and 25 subjects have been treated with daratumumab in combination with VELCADE-containing regimens (VELCADE-dexamethasone [VD], VELCADE-thalidomide-dexamethasone [VTD], VELCADE-melphalan-prednisone [VMP]) and pomalidomide-dexamethasone [Pom-dex] in Study MMY1001. In addition, as of the clinical cutoff date, 16 subjects have been randomized in Study 54767414MMY3003 (MMY3003), a Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma.

1.2.2.1. Clinical Pharmacokinetics

Pharmacokinetic (PK) data are available from Study GEN501 Part 1. The doses ranged from 0.005 to 24 mg/kg. The PK profile was consistent with target mediated disposition (TMD) with rapid target-related clearance at low doses and slower clearance at higher doses. Following long-term treatment, clearance may decrease as the tumor burden decreases. The preliminary PK data

in Studies GEN501 Part 2 and MMY2002 are consistent with the PK profile obtained in GEN501 Part 1. Preliminary PK data from Study GEN503 show that following both the first dose and multiple repeated doses, the PK profile of daratumumab in combination with lenalidomide and dexamethasone is similar to what was observed in Study GEN501 following the same dose and schedule. The data suggest that lenalidomide and dexamethasone do not affect the PK profile of daratumumab.

1.2.2.2. Preliminary Efficacy

Preliminary efficacy data for Study GEN501 Parts 1 and 2 were presented at the 2013 and 2014 American Society of Clinical Oncology (ASCO) Annual Meetings, respectively. As the study is still ongoing, and data reconciliation activities are underway, the data should be considered preliminary. Among 12 subjects treated with daratumumab in Part 1 at doses ≥ 4mg/kg, 5 partial responders (PRs) and 3 minimal responders (MRs) were observed. Seven (7) of these subjects had a 50 to 100% concomitant reduction in bone marrow plasma cells. Among 29 subjects treated with 8 mg/kg daratumumab in Part 2, 3 subjects (10%) had a PR; the response rate was 10%. Among 20 subjects treated with 16 mg/kg, 2 subjects (10%) had a CR, 1 subject (5%) had a very good partial response (VGPR), and 4 subjects (20%) had a PR; the response rate was 35%.

1.2.2.3. Safety and Tolerability

In general, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 151 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage of subjects with a reported IRR was identical (49%) to what was observed across all treated subjects. The most frequently reported AEs (reported in ≥5% of subjects) reported as IRRs were rhinitis allergic (8%), cough (7%), and nasal congestion (6%). Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs (1% each).

Across all ongoing studies, bronchospasm was reported in 10 subjects. Early in daratumumab development, in Study GEN501, 2 cases of bronchospasm were reported 24-48 hours following the second full-dose infusion of daratumumab. With the exception of those 2 cases, which had a delayed onset, all other reported bronchospasm events occurred following the first dose. All of the events occurring during the infusion period resolved quickly after standard treatments were administered. The daratumumab infusion was restarted, and no new onset of bronchospasm occurred. Most of the subjects who experienced bronchospasm had underlying respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], and others).

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) other than IRR were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

1.3. Overall Rationale for the Study

The CD38 target in NHL has been intensively studied in both preclinical models as well primary tumors. Quantitative flow cytometry analysis of 16 NHL cell lines showed that CD38 expression levels varied among cell lines, but the majority (81%, n=13/16) had >1000 CD38 receptors per cell (Doshi 2014)[8]. Of 80 MCL subjects studied, CD38 expression was found in 32 (94%) of 34 subjects with tumors in peripheral lymphadenopathy, and 16 (48%) of 33 subjects with tumors without lymphadenopathy (Orchard 2003)[21]. In another study with 17 typical MCL subjects, the median CD38 expression was 89% in tumor by flow cytometry analysis (Espinet 2014)[9]. A panel of 99 primary DLBCL tumors was screened for CD38 staining using an established immunohistochemistry (IHC) method. Staining score and intensity were defined by semi-quantitative parameters. Forty-seven percent of tumors had CD38 expression (any grade). About 30% of tumors had CD38 expression in over 50% of cells at any grade, and about 20% of tumors had CD38 expression in over 50% of cells at a staining score of 2+ or 3+. In another DLBCL study, CD38 expression after ibrutinib treatment was sequentially monitored (n=23) by flow cytometry in every cycle for up to 6 cycles. The results showed that subjects with high CD38 level maintained CD38 expression during therapy (unpublished data). By using the established IHC methodology described above, a panel of 20 primary FL tumors was studied. Seventy-five percent of tumors had CD38 expression at any grade. About 30% of tumors had CD38 expression in over 50% of cells at any grade, and about 21% of tumors had CD38 expression in over 50% of cells with a staining score of 2+ or 3+. These data suggest that a significant portion of NHL express CD38. Based on these observations, it is hypothesized that daratumumab may show clinical activity in NHL subjects whose tumors express CD38.

Daratumumab induces tumor cell lysis through immune effector functions such as CDC, ADCC, 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. These data suggest that a threshold of CD38 expression is required for daratumumab-induced CDC and ADCC although the specific threshold for CD38 expression required for clinical response needs to be established in a clinical study. Furthermore, emerging data from a clinical study of daratumumab in multiple myeloma reveal a trend for correlation between CD38 expression and clinical response (Nijhof 2014)[19]; however, other factors, possibly

disease-related, may also influence daratumumab activity. Since MCL, DLBCL, and FL are distinct diseases, it is conceivable that different threshold levels of CD38 expression may be required for robust daratumumab activity in each of the NHL subtypes.

In an in vivo mouse xenograft model established with Burkitt's lymphoma line NAMALWA, treatment with daratumumab in combination with CHOP resulted in significant tumor growth inhibition (47%, $p < 0.001$) compared to the control group on day 26. In a DLBCL in vivo mouse xenograft model established with SU-DHL-6 line, treatment with daratumumab either alone or in combination with CHOP also caused significant tumor growth inhibition (55% and 63%, respectively, $p<0.01$). In a human tumor xenograft model (tumor from a subject with DLBCL) in which 80% of tumor cells had CD38 expression at a score of 3+ measured by IHC, treatment with daratumumab in combination with CHOP or R-CHOP induced complete tumor regression. The tumors did not regrow even after as few as 3 doses of daratumumab. At the end of study (day 60), the mice in the combination treatment groups were still tumor free compared to daratumumab alone, CHOP alone or R-CHOP alone. These data suggest that daratumumab significantly inhibits tumor growth or induces long-term tumor regression in xenograft tumor models that express CD38 (Doshi 2014)[8].

Given these compelling preclinical data as well as the molecular epidemiological survey, this proof-of-concept Phase 2 study was designed to assess the overall response rate and safety of daratumumab in relapsed or refractory MCL, DLBCL, and FL where there are significant unmet medical needs.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The study will evaluate daratumumab separately in three relapsed or refractory NHL subtypes: MCL, DLBCL, and FL. There are two main objectives:

- To assess overall response rate (ORR, including CR and PR), of daratumumab in subjects with NHL.
- To evaluate association between ORR and CD38 expression level in order to determine a threshold for CD38 expression level in each NHL subtype, above which daratumumab activity is enhanced.

Secondary Objectives

For each subtype of NHL, the secondary objectives are:

- To assess the DoR, PFS and OS
- To assess time to response
- To assess and correlate the CD38 expression level with DoR, PFS and OS
- To assess pharmacokinetics of daratumumab

- To assess immunogenicity of daratumumab
- To assess the safety profile of daratumumab

Exploratory Objective

- To explore biomarkers, in addition to CD38 expression level, predictive of response to daratumumab

2.2. Hypothesis

For each subtype of NHL, analyses will be conducted on the overall population and on the CD38 enriched population (only subjects with CD38 expression level above a threshold to be determined via statistical inference). There is one hypothesis for each population. Daratumumab is considered active per subtype if at least one of the null hypotheses is rejected:

For MCL

- For the overall population, ORR is at least 35% (versus a null hypothesis of at most 20%)
- For the enriched population, ORR is at least 40% (versus a null hypothesis of at most 20%)

For DLBCL

- For the overall population, ORR is at least 30% (versus a null hypothesis of at most 15%)
- For the enriched population, ORR is at least 40% (versus a null hypothesis of at most 15%)

For FL

- For the overall population, ORR is at least 50% (versus a null of at most 30%)
- For the enriched population ORR is at least 60% (versus a null of at most 30%).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label, multicenter, Phase 2 study in subjects at least 18 years of age with MCL, DLBCL, or FL. Approximately 210 subjects may be enrolled, with up to 100 subjects planned for MCL and up to 55 subjects each for DLBCL and FL.

This study will be conducted and analyzed separately for each subtype of NHL. A biomarker adaptive threshold design (Jiang, 2007)[16] is implemented that enables testing of the overall population and the establishment of a biomarker-defined enriched population simultaneously. Two stages are planned.

Stage 1 of the study is designed to provide a preliminary assessment of activity at an early stage. Since CD38 expression level may be associated with daratumumab activity, Stage 1 will enroll subjects who have tumors where at least 50% of the cells are CD38 positive. This requirement seeks to mitigate the possibility that a low response rate observed in Stage 1 might be due to low levels of CD38 expression. The selection of the 50% cutoff is based on the existing CD38 expression level data in these NHL subtypes as well as practical considerations.

At the end of Stage 1, which is expected to be 6 months after the last subject is enrolled in each NHL subtype, or earlier if emerging data allows, an interim analysis will be conducted. The purpose of the interim analysis is to evaluate efficacy and safety data in Stage 1. The efficacy assessment will be focused on ORR. The futility criteria for each NHL subtype are defined in Section 11.9 and provided in Figure 1. If the futility criteria are met, an NHL subtype may be terminated. Alternatively, if the futility criteria are not met and if supported by the totality of the Stage 1 data, Stage 2 for that NHL subtype may be opened for accrual. If the required number of responses (eg, 5 responders out of 20 enrolled subjects in MCL as shown in Figure 1), is observed prior to completion of enrollment in Stage 1, Stage 2 may be opened immediately upon completion of enrollment to Stage 1, if supported by the totality of data.

Stage 2, if opened, is designed to further evaluate safety and efficacy as well as to determine a threshold for CD38 expression that is associated with enhanced daratumumab activity. Supported by the preliminary activity observed in Stage 1, Stage 2 will enroll any subject in each NHL subtype. To mitigate the possibility that a low response may be observed due to low levels of CD38 expression in enrolled subjects, the number of Stage 2 subjects with CD38 expression level <50% will be capped within each NHL subtype.

The target number of subjects in each stage by CD38 expression level is shown in Table 3.

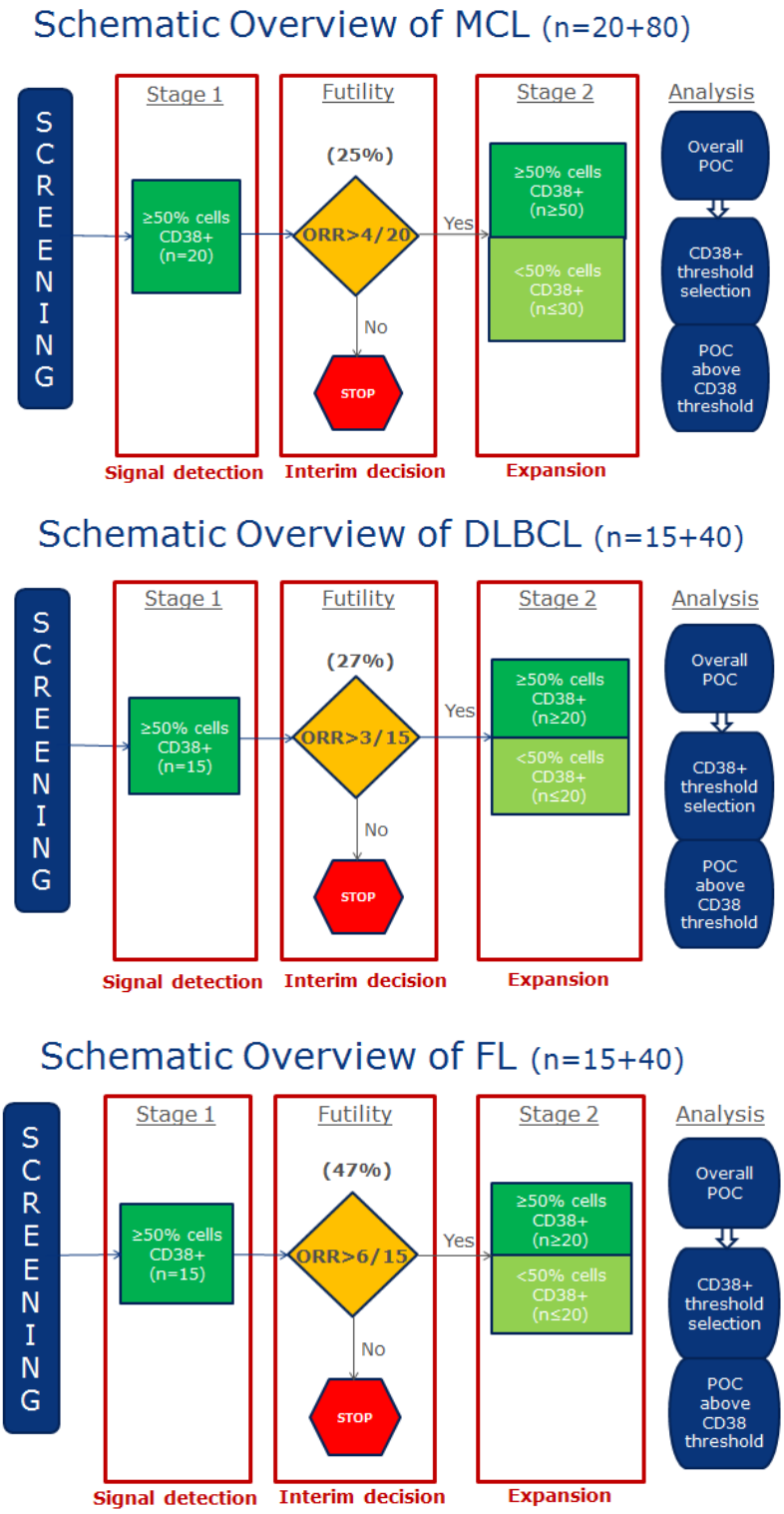
Table 3: Number of Subjects Enrolled

Type of NHL	Number of Subjects			
	Stage 1	Stage 2 (optional)		Overall
	CD38 expression level [b] ≥50%	CD38 expression level [a] <50%	CD38 expression level [b] ≥50%	Total
MCL	20	≤30	≥50	**100**
DLBCL	15	≤20	≥20	**55**
FL	15	≤20	≥20	**55**

DLBCL=diffuse large B cell lymphoma ; FL=follicular lymphoma; MCL= mantle cell lymphoma
a. These subjects have tumors where <50% of the cells are positive for CD38 by immunohistochemistry.
b. These subjects have tumors where ≥50% of the cells are positive for CD38 by immunohistochemistry.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; MCL= mantle cell lymphoma; POC=proof-of-concept

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days prior to Cycle 1, Day 1. Prior to enrollment, subjects are required to provide tumor tissue to determine CD38 expression level by immunohistochemistry (IHC) at a central laboratory. An additional fresh biopsy should be obtained whenever possible even if an archival sample is provided. The Treatment Phase will extend from Cycle 1, Day 1 until study drug discontinuation. Subjects will be treated until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2. After first dose, disease evaluations will occur every 8 weeks for the first 3 evaluations, then every 16 weeks for the next two evaluations and then every 24 weeks thereafter.

The Follow-up Phase will begin once a subject discontinues study drug, and will continue until death, loss to follow up, consent withdrawal for study participation, or end of study, whichever occurs first.

An interim analysis for futility will be conducted in each NHL subtype no later than 6 months from when the last subject is enrolled in Stage 1 in that NHL subtype. If Stage 2 is expanded for a particular NHL subtype, the primary analysis will be performed at 6 months after the last subject is enrolled in Stage 2.

The end of the cohort for each NHL subtype is defined as 18 months after the last subject in the particular NHL subtype receives the first dose of daratumumab. After each NHL subtype completes the study, the sponsor will ensure that subjects who are currently on treatment and receiving benefit, as determined by the investigator, will continue to receive daratumumab. The end of the study is defined as the completion of all three NHL subtypes.

Assessment of tumor response and disease progression will be conducted by investigators in accordance with the Cheson 2014[3] response criteria (see Attachment 1). Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Measures to prevent IRRs will include preinfusion medication with methylprednisolone, acetaminophen (or paracetamol), and an antihistamine before each daratumumab infusion. Blood samples will be drawn for assessment of pharmacokinetics, immunogenicity, biomarkers and pharmacodynamics parameters.

3.2. Study Design Rationale

Rationale for Design, Dose, and Primary Endpoint

A biomarker adaptive threshold design (Jiang, 2007)[16] is implemented which combines the evaluation of the ORR of daratumumab in all subjects with the establishment and validation of a threshold for CD38 expression level, which will be used to define an enriched subpopulation. In addition, an early interim futility analysis is to be performed within each NHL subtype.

The study is designed to address two questions for each NHL subtype:

1) if daratumumab is sufficiently active in the overall population of all subjects, and

2) if a threshold value for CD38 expression at baseline can be defined, above which daratumumab produces robust clinical activity

Furthermore, within each NHL type, an early interim analysis is incorporated. The purpose of Stage 1 is to assess the preliminary activity of daratumumab in each NHL subtype, thus providing the opportunity for an early futility check.

It is hypothesized that an unknown threshold of CD38 expression may exist for enhanced daratumumab activity. As such, an *a priori* cutoff for CD38 expression level should be selected for Stage 1 subjects in order to mitigate the possibility that a low response rate observed in Stage 1 could be attributed to low CD38 expression levels in the enrolled subjects, thus improving the reliability of the interim futility decision. It is therefore required that Stage 1 subjects, for all three NHL subtypes, should have a CD38 expression level of at least 50% at baseline. The selection of this 50% expression level, while relatively subjective, is based on the following considerations.

1) This subset of subjects is presumably more likely to respond to daratumumab treatment than those subjects with a majority of tumor cells not expressing CD38.

2) This subset of subjects may represent up to 50%, 30% and 60% of the population with MCL, DLBCL and FL, respectively. If a low ORR is observed in this subset of subjects, it is highly unlikely that there exists a practical subset of subjects based on CD38 expression level in which a clinically meaningful ORR can be observed.

An established dose regimen of 16 mg/kg weekly for 8 weeks, 16 mg/kg every 2 weeks for 16 weeks, and then 16 mg/kg every 4 weeks until disease progression was selected because it maximally saturates the target (ie, CD38) using the principles of target mediated drug disposition tested in the multiple myeloma setting with manageable toxicity profile.

The primary efficacy endpoint of ORR (CR+PR) will be assessed according to the Cheson 2014[3] response criteria. Additional endpoints will include response duration and overall survival (and others). Durable and objective response rates have been accepted by regulatory authorities as reasonably likely to predict clinical benefit.

Rationale for Pharmacokinetic, Immunogenicity, and Biomarker Evaluations

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

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 during the Follow-up Phase 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.

Biomarkers collected in this study will evaluate tumor CD38 levels as a predictive marker of response. Exploratory analysis of CD59 expression from previous studies has indicated that high expression of CD59 might be predictive of lower or lack of response to daratumumab. Therefore, samples collected in this study will evaluate both CD38 and CD59 expression levels by IHC. Specific immune cell subtypes (NK cells, T cells, and B cells) will be analyzed to evaluate the effects of daratumumab on immune cells. This will provide information on potential prognostic markers in NHL to better understand these diseases, as well as potential markers that predict response to daratumumab.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before Cycle 1 Day 1.

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 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Subject must be at least 18 years of age (and satisfying the legal age of consent in the jurisdiction in which the study is taking place).

2. Criterion modified as per Amendment-1

   2.1 Diagnosis and prior treatment for each NHL subtype as defined below:

   MCL:

   - pathologically verified diagnosis of MCL based on local pathology report (please refer to Section 9.1.2), AND
   - relapsed or refractory disease after at least 2 prior lines of therapy, including at least 1 cycle of BTK inhibitor therapy and documented PD during or after BTK inhibitor treatment or subjects who could not tolerate BTK inhibitor (ie, discontinued BTK inhibitor due to AEs)

DLBCL:

- pathologically confirmed diagnosis of non-transformed DLBCL, AND
  - relapsed or refractory disease; for those subjects who have not received HDT/ASCT are not eligible for HDT/ASCT due to comorbidities

FL:

- pathologically confirmed diagnosis of FL of Grade 1, 2, or 3a according to World Health Organization (WHO) criteria without pathological evidence of transformation, AND
- relapsed disease after at least two prior systemic therapies including one anti-CD20 containing combination regimen

3. At least 1 measurable site of disease as described in Section 9.2.1.1.

4. Criterion modified as per Amendment-1

   4.1 Subjects must have available archival or fresh tumor tissue or both to submit to a central laboratory for CD38 assay. Expression of CD38 is measured by immunohistochemistry on fresh or archived tumor sample by central assessment using a CD38 investigational IHC assay under development:

   - Stage 1: subjects whose tumors are ≥50% positive for CD38
   - Stage 2: subject has <50% CD38+ or > 50% CD38+ depending on the distribution of CD 38 expression of enrolled subjects during Stage 2 (see Table 3). The sponsor will advise on which eligibility criterion is permitted during the enrollment period.

5. Subject must have an ECOG performance status score of 0 or 1 (refer to Attachment 2)

6. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a) hemoglobin ≥7.5 g/dL (≥5 mmol/L) without transfusion support within 7 days before the lab test;

   b) absolute neutrophil count (ANC) ≥0.75 x 10^9/L (ie, ≥750/ µL);

   c) platelet count ≥50 x 10^9/L without transfusion support within 7 days of test;

   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) Criterion modified as per Amendment-1

      g1) creatinine determined by serum creatinine levels ≤1.5 x ULN or a calculated creatinine clearance of ≥30 mL/min (see Attachment 3 for Cockcroft-Gault formula)

7. Criterion modified as per Amendment-1

7.1 Women of childbearing potential must be practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject) during and after the study (3 months after the last dose of any component of the treatment regimen). Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. During the study and for 3 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

8. Criterion modified as per Amendment-1

8.1 A woman of childbearing potential must have a negative serum or urine pregnancy test within 14 days before commencing treatment. Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously.

9. Criterion modified as per Amendment-1

9.1 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 last dose of any component of the treatment regimen. The exception to this restriction is that if the subject's female partner is surgically sterile, a second method of birth control is not required.

10. Criterion modified as per Amendment-1

10.1 Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

4.2. Exclusion Criteria

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

1. Known central nervous system lymphoma.

2. Prior anti-tumor therapy including (all times measured prior to start of study drug):

   a) nitrosoureas within 6 weeks
   b) chemotherapy within 3 weeks
   c) therapeutic antibodies within 4 weeks
   d) radio- or toxin-immunoconjugates within 10 weeks
   e) radiation therapy within 2 weeks
   f) investigational agents within 3 weeks, unless antibody this should be within 4 weeks
   g) Daratumumab or other anti-CD38 therapies

   Criterion modified as per Amendment-1

   h) for the MCL cohort, BTK inhibitors within 1 week or 5 half-lives, whichever is longer

3. Criterion modified as per Amendment-1

   3.1 Subject has a history of malignancy (other than NHL) within 3 years before the screening period (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, non-muscle invasive bladder cancer (papillary neoplasms of low malignant potential and primary non-invasive tumors), or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 2 years).

4. a) Subject has known COPD with a Forced Expiratory Volume in 1 second (FEV1) < 50% predicted normal. Note that FEV1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV1 <50%

   b) Subject has known moderate or severe persistent asthma within 2 years (see Attachment 4: NHLBI table of asthma severity), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

5. Criterion modified as per Amendment-1

   5.1 Subject is known to be seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or known to have a history of hepatitis C (except for those with Sustained Virologic Response [SVR]). SVR is defined as aviremia 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection (Pearlman 2011).[23]

6. Subject has any concurrent medical or psychiatric condition or disease (eg, autoimmune disease, active systemic disease, myelodysplasia) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

7. Subject has clinically significant cardiac disease, including:

   a) myocardial infarction within 1 year before the screening period, or an 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) Criterion modified as per Amendment-1

      b1) uncontrolled cardiac arrhythmia (NCI CTCAE Version 4 Grade ≥3) or clinically significant ECG abnormalities

   c) Criterion modified as per Amendment-1
      c1) screening 12-lead ECG showing a baseline QT interval as corrected QTc >470 msec

8. Subject has known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure).

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

10. Criterion modified as per Amendment-1

    10.1 Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). 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 the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited therapies, as per Section 8.3, during screening with the exception of an emergency use of a short course of corticosteroids (equivalent of prednisone 100 mg/day for a maximum 7 days) before enrollment.

11. Criterion modified as per Amendment-1

    11.1 Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of daratumumab. Or, subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of daratumumab.

12. Subject has used an invasive investigational medical device within 4 weeks before the screening period or is currently enrolled in an interventional investigational study.

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. See Section 17.4, 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. For restrictions related to concomitant medications, please refer to Section 8.3.

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

2. Subjects with persistent hypokalemia (eg, serum potassium <3.5 mM after proper treatment) need to be monitored for the potential of QTc prolongation.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

After determination of eligibility, subjects will be enrolled to the study. No randomization will be used in this study.

Blinding

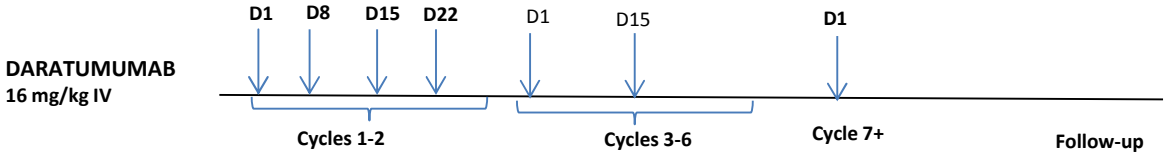
As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Daratumumab is to be administered as described in Figure 2. Each cycle is 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 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



6.1. 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.

6.2. Daratumumab Administration

Daratumumab (16 mg/kg) will be administered by 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. After the end of the study, the sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment.

Each subject's dose will be calculated based on the subject's weight at baseline rounded to the nearest kilogram at screening. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the SIPPM. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.3.

Every effort should be made to keep subjects on the planned dosing schedule. Time windows for daratumumab administration are outlined in Table 1. In instances of daratumumab-related toxicity management, time windows for daratumumab administration are outlines in Table 4.

As noted in Table 2, 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 immediately before the start of 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.

6.3. Guidelines for Prevention of Infusion Reactions

6.3.1. Preinfusion Medication

On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg IV approximately 1 hour prior to daratumumab infusion or orally (PO)
- An antihistamine (diphenhydramine or equivalent) 25-50 mg IV approximately 1 hour prior to daratumumab infusion or PO
- 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 [see Attachment 5 for conversion table]. IV administration is preferred, but oral steroids may be substituted if IV administration is not available.

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours prior to the infusion.

6.3.2. Postinfusion Medication

For the prevention of delayed IRRs, all subjects will receive corticosteroid orally (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). 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 a FEV1 <80% or subjects with 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)
- 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 an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after 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 a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject is taking postinfusion medications and experiences no major IRRs, then these medications may be stopped after 4 full doses, at the investigator's discretion.

6.3.3. 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 infusion reactions 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 infusion-related reaction develops, then the infusion should be paused. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen (paracetamol), antihistamine, or corticosteroids. 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 infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

6.3.3.1. Infusion-Related Events of Grade 1 or Grade 2

If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased 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 the onset, then the subject must be withdrawn from treatment.

6.3.3.2. Infusion-Related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

6.4. Dose Delays and Dose Modification

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

6.4.1. Daratumumab-Related Toxicity Management

Refer to Section 6.3 for details on management of IRRs. If any of the following criteria are met, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

1) Grade 4 hematologic toxicity
2) Grade 3 thrombocytopenia with bleeding
3) Febrile neutropenia
4) Neutropenia with infection, of any grade

5) Grade 3 or higher nonhematologic 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

If a daratumumab administration does not commence within the prespecified window (Table 4) 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 4: 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)	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

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

Doses of daratumumab 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. However, if a within-cycle dose is delayed, then the dates of the subsequent doses should not be adjusted.

Any adverse event 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 pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.4.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 4) 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. TREATMENT COMPLIANCE

Daratumumab will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). A subject diary may be used to document any pre- and post- infusion medications taken at home. Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. 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 the following concomitant medications will be collected in the 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: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, antihistamines and other medications targeting postinfusion systemic reactions, and any anticancer therapy (including radiation). Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

In addition to the mandatory preinfusion medications outlined in Section 6.3.1, the following therapies are recommended.

8.1.1. Therapy for Tumor Lysis Syndrome

The symptoms for tumor lysis syndrome should be monitored. Subjects with more than 1 of the factors listed below are considered to be at increased risk of tumor lysis syndrome and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms, including blood chemistry. Uric acid-lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric® [Adenuic™, febuxostat] with or without rasburicase per the drug product package inserts.

1. Serum creatinine ≥1.5 x ULN or calculated creatinine clearance <60 mL/min
2. Uric acid ≥450 µmol/L or 7.5 mg/dL
3. Bulky disease (eg, lymph node >10 cm or massive splenomegaly)
4. Elevated LDH >2 x ULN

8.1.2. Prophylaxis for Pneumocystis Carinii

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

8.1.3. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation may be used at the discretion of the investigator.

8.2. 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:

- 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.

8.3. Prohibited Therapies

During Cycle 1, the prophylactic use of hematopoietic growth factors is prohibited.

Vaccination with live attenuated vaccines is prohibited. Concurrent radiation therapy is prohibited while on study.

Concomitant administration of any other antineoplastic therapy for the intention of treating NHL not defined in the study protocol is prohibited, including medications that target CD38.

Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for NHL, including systemic corticosteroids (≥20 mg/day of prednisone or its equivalent per day for more than 7 days during study, unless reviewed/approved by medical monitor) (other than those given for IRRs as described in Section 6.3.2) is prohibited.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, and safety measurements applicable to this study.

Blood collections for pharmacokinetic assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints 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 total blood volume to be collected is estimated at about 20 mL (about 1.5 tablespoons) for screening tests, 215 mL (about 1 cup) for Cycles 1-7, 20 mL (about 1.5 tablespoons) at subsequent cycles, and 36 mL (about 2 tablespoons) at the End-of-Treatment Visit and the post treatment visits. This includes laboratory assessments associated with, safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. 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 the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Table 1. Screening procedures will be performed within 28 days before Cycle 1 Day 1; however, results of tests (such as radiologic tests; ECG; or bone marrow aspirate/biopsy) performed up to 6 weeks (42 days) before Cycle 1 Day 1 as routine standard of care for the subject's disease can be used.

Pathological Confirmation of Diagnosis

Diagnosis of MCL must be verified by the sponsor from the local pathology report. This diagnosis report must include expression of either cyclin D1 in association with other relevant markers (eg, CD20 and CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization, or polymerase chain reaction. The report containing this information must be sent to sponsor for confirmation of the diagnosis prior to enrollment.

If possible, local pathology report for diagnosis of FL will be collected. The report should include expression of B-cell lymphoma 2 (Bcl-2) in association with other relevant markers (eg, CD10 and CD19) or evidence of t(14;18) as assessed by cytogenetics, fluorescent in situ hybridization, or polymerase chain reaction.

If possible, local pathology report for diagnosis of DLBCL will also be collected. The report should include: a) histologic documentation of no significant follicular or low grade component; b) evidence of positive B-cell lineage, and c) documentation of a sufficient large cell component or increased Ki67-defined proliferative rate.

Determination of CD38 Expression

Before enrollment to the study, subjects will be required to provide tumor samples for assessment of CD38 expression. Subjects are strongly encouraged to provide both fresh and archival tumor tissue for this study. Where feasible, a fresh lymph node biopsy (excision or core needle biopsy) should be collected. An investigational IHC assay currently under development will be used by the central laboratory to determine CD38 expression levels. Only subjects who

fulfill the eligibility criteria, including tumors with ≥50% cells CD38 positive for Stage 1 and tumors <50% cells CD38 positive or ≥50% cells CD38 positive for Stage 2, will be considered for participation in the study. An ICF for CD38 screening only may be obtained separately from the full study ICF.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Table 1. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

End-of-Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur within 30 days (+7 day window) after the last dose of all study treatments. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on adverse events and concomitant medications that occur up to 30 days after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject discontinues study treatment. Subjects who discontinue before disease progression (for other reasons such as an AE) must continue to have their regularly scheduled scans according to the Table 1 until confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow up, or the end of the study for that NHL subtype. After disease progression is documented, follow-up will occur at least every 16 weeks (±2 weeks). Subsequent anticancer therapy, second primary malignancies, and survival status will be recorded.

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

The end of the cohort for each NHL subtype is defined as 18 months after the last subject in the particular NHL subtype receives the first dose of daratumumab. After completion of an NHL subtype, the sponsor will ensure that subjects who are currently on treatment and receiving benefit, as determined by the investigator, will continue to receive daratumumab. The end of the study is defined as the completion of all three NHL subtypes.

9.2. Efficacy

9.2.1. Evaluations

After the first dose, disease evaluations will be performed every 8 weeks (±7 days) in the first 6 months (Weeks 9, 17, 25), followed by every 16 weeks (±7 days) for the next 6 months (Weeks 41 and 57), and thereafter every 24 weeks (±14 days). These assessments will be conducted until disease progression, withdrawal of consent from study participation, or the end of study.

The determination of disease status will be assessed by the investigator based on the Revised Criteria for Response Assessment (Cheson 2014)[3], provided in Attachment 1. Identical methodology should be used for disease assessment at screening and throughout the course of the study.

Radiological and PET scans should be performed and collected according to instructions from the independent imaging laboratory. A central review of the response assessments may be performed if deemed necessary.

For all subjects, as soon as disease progression is confirmed by local assessment, the sponsor should be informed immediately.

9.2.1.1. Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions. Measurement must be determined by local imaging evaluation. All other sites of disease are considered assessable, but not measurable. 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, clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease 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 measurable lesions should be from as disparate regions of the body as possible.

All other sites of disease will be considered assessable. 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. In addition, if more than 6 sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

9.2.1.2. Radiographic (CT/MRI) Assessments

During the study, disease response will be assessed using CT scans with IV contrast of the neck (only if neck lymph nodes are involved, in which case full neck views must be obtained), 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.

A separate CT scan and PET scan are preferred but, if the only available modality is combined/dual PET/CT scanner, then the CT portion of a PET/CT may be used in lieu of a dedicated CT.

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 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.

9.2.1.3. Positron Emission Tomography (PET Scan)

FDG-PET is important for the complete assessment of response and progression in subjects with FL. Whole body FDG-PET scans (skull base to the proximal femur) should be done at screening, per investigator discretion. For subjects who are PET-positive at baseline, PET scans will be done at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction).

Assessment of PET results is based on published criteria (Juweid 2007)[17]. Visual assessment is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

9.2.1.4. Bone Marrow Assessment

An optional bone marrow biopsy, with or without aspirate, at Screening to document bone marrow involvement with lymphoma may be obtained at the investigator's discretion. A bone marrow biopsy obtained as routine standard of care may be used instead if taken up to 42 days before first dose of study drug. If bone marrow aspirate is obtained, determination of bone marrow involvement may be confirmed by flow cytometry. However, 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 either flow cytometry or immunohistochemistry (IHC), if warranted, to confirm the presence or absence (complete remission) of lymphoma. If bone marrow involvement can be confirmed with morphology, IHC need not be done if this is not part of a study-site standard practice.

9.2.1.5. Endoscopy

CRs must be confirmed with endoscopy examination if the lymphoma originated from or involved the GI tract at diagnosis.

9.2.2. Endpoints

9.2.2.1. Primary Endpoint

Overall response rate is defined as the proportion of subjects who achieve CR or PR.

9.2.2.2. Major Secondary Endpoints

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 (or relapse for subjects who experience CR). For those subjects who are still without progression/relapse, DoR will be censored at the last adequate tumor assessment.

PFS is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse 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.

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.

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) is first documented. For non-responders, it will be censored at the date of progressive disease/relapse or the date of the last adequate disease assessment, whichever comes first.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For all subjects, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to Table 1. At specified timepoints, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic 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 timepoint.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility.

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

9.3.3. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. Pharmacokinetic endpoints include:

- Minimum observed concentration (C_{min})
- Maximum observed concentration (C_{max})

If sufficient data are available, then other pharmacokinetic parameters may be calculated.

9.3.4. Immunogenicity Assessments (Antibodies to Daratumumab)

Serum from venous blood samples collected from all subjects will be assessed for the generation of antibodies to daratumumab (immunogenicity) according to Table 1. Daratumumab concentration is also evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. 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.

Additionally, blood samples should also be collected at the final visit from subjects who are discontinued from treatment. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

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.

9.4. 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 Table 1.

Determination of CD38 and CD59 Expression:

During screening, subjects will be required to provide tumor samples for assessment of CD38 expression based on central testing using investigational IHC methodology under development (Section 9.1.2). An additional fresh biopsy should be obtained whenever possible even if an archival sample is provided. Fresh tumor samples can be either lymph node excision or core needle biopsy; fine needle aspirates are not acceptable.

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 in B-cell signaling pathways, 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, CD59 expression will be measured by IHC in a designated laboratory as an exploratory biomarker. CD59 is a complement inhibitory protein and can contribute to resistance to CDC, which may be important for daratumumab response.

Companion Diagnostic:

The tumor sample will be collected, tested for CD38 expression by investigational IHC test under development, and stored in order to potentially develop a companion diagnostic in parallel to the clinical study. Additional biopsy material may be requested if the initial sample is determined to be insufficient for all evaluations.

Immunophenotyping:

Previous daratumumab clinical studies in multiple myeloma 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 or 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 multiple myeloma 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 RNA profiling (RNA-seq, gene expression profiling) or methylation assessment to evaluate novel technologies for immune profiling in whole blood, and to compare these methodologies to standard flow cytometry. These assessments will be evaluated for association with clinical response.

Plasma samples may be analyzed for proteins associated with disease progression or daratumumab response, including complement proteins, sCD38, proteins indicative of infusion reaction (IL-1, IL-6, TNFα, IFNγ, tryptase), and exploratory proteomics. Analyses will determine whether specific proteins are associated with daratumumab response.

9.5. Safety Evaluations

Safety will be measured by adverse events, 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. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint 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 adverse events should be evaluated by the investigator according to the standard practice, if clinically indicated.

Adverse Events

Adverse events (with the exception of progression of NHL) will be reported by the subject (or, when appropriate, by a caregiver, or surrogate) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology 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 adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The tests below will be performed by the local laboratory unless otherwise noted.

- Hematology Panel

  -hemoglobin
  -white blood cell (WBC) count with absolute neutrophils and lymphocytes
  -platelet count

- Serum Chemistry Panel

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

Pregnancy Testing

For women of childbearing potential only: serum or urine pregnancy test at screening and as clinically indicated.

Blood Type, Rh, and Indirect Antiglobulin Testing (IAT)

Blood Type, Rh, 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 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/RhD typing. CD38 is expressed at very

low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a 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. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015)[2].

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

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

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

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB.

β2-microglobulin

Baseline Beta-2 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 6.3.2 for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG)

ECGs will be performed as specified in Table 1. 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 Table 1 and Table 2. 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.

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 Table 2. Abnormalities will be recorded in the appropriate sections of the eCRF. ECOG performance status (Attachment 2) 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 any other study procedures planned for the same day.

9.6. Sample Collection and Handling

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 Table 1 for the timing and frequency of all sample collections.

For samples collected for the central laboratory, sample dates and times must be recorded on the laboratory requisition form. Further 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.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, **this will not result in automatic withdrawal of the subject from the study**. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in Table 1. If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in Table 1.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) 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 treatment
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for NHL
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.3.3
- The subject's dose of daratumumab is held for more than 4 weeks (Cycle 1 to Cycle 6) or 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, after consultation with the sponsor and review of safety and efficacy, continuation is agreed upon
- The subject experiences disease progression (please see below). Relapse from CR is not considered as disease progression

A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of lymphoma.

The primary reason for discontinuation of study treatment is to be recorded in the eCRF.

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- The study investigator or sponsor, for any reason, stops the study or stops the subject's participation in the study

Before 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. Study treatment 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, assessments outlined in the End-of-Treatment Visit should be obtained.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). 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.

11. STATISTICAL METHODS

Efficacy and safety analyses will be performed separately for each of the three NHL subtypes (MCL, DLBCL, FL). In addition, safety data across the NHL subtypes may be combined together for analysis at the end of the study when appropriate.

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.

11.1. 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, standard deviation, 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.

11.2. Sample Size Determination

Within each subtype of NHL, a biomarker adaptive threshold design (Jiang 2007)[16] is to be utilized, which allows identification of a biomarker threshold based on data analysis in parallel with the statistical testing of the ORR for proof-of-concept. That is, the proof-of-concept could be established either in the overall population or in the subpopulation of subjects as identified by the biomarker (CD38 expression level) threshold. In order to provide an early futility check within each NHL subtype, a two-stage procedure is also incorporated, which will be detailed later.

Given that there are two potential pathways for proof-of-concept and the inherent multiple testing issues associated with the selection of the biomarker threshold, per the recommendation by Jiang (2007)[16], the powering for MCL will be based on the overall population with an overall alpha of 0.04, which preserves the power of the overall test while providing a reasonable power against a strong subset effect at the same time with the remaining alpha of 0.01. Since further randomized Phase 2 proof-of-concept studies in combination with other agents are likely required for DLBCL and FL, an alpha of 0.05 is used for the overall population in these two subtypes.

In Stage 1, a total of 50 subjects will be enrolled for all 3 NHL types combined. In Stage 2, a maximum of 160 subjects may be enrolled if all three tumor types are expanded, bringing the maximal sample size to 210 with all tumor types combined.

For MCL, the null hypothesis is that the ORR is at most 20%, and the alternative hypothesis is that the ORR is at least 35% for all subjects, or at least 40% for those subjects whose CD38 expression level is above a to-be-determined level. These are based on the fact that some recent approvals in previously treated MCL were based on an ORR of approximately 31% for bortezomib and 26% for lenalidomide. Up to 100 MCL subjects with positive CD38 expression may be enrolled. Seventy (70) of those must have tumors with 50% or more cells positive for CD38 expression at baseline in order to rule out that any lack of activity is mostly due to low CD38 expression level in the enrolled subjects.

For DLBCL, the null hypothesis is that the ORR is at most 15%, and the alternative hypothesis is that the ORR is at least 30% for all subjects, or at least 40% for those subjects whose CD38 expression level is above a to-be-determined level. These were based on the clinical observation that relapsed DLBCL subjects who are not eligible for HDT/ASCT have a very poor prognosis and no established therapeutic options.

For FL, the null hypothesis is that the ORR is at most 30%, and the alternative hypothesis is that the ORR is at least 50% for all subjects, or at least 60% for those subjects whose CD38 expression level is above a to-be-determined level. These are based on the published ORRs of idelalisib (54%, which was the basis of an accelerated approval is the U.S.) and rituximab monotherapy (49%, Coiffier 2011)[5].

For both DLBCL and FL, 55 subjects may be enrolled. Thirty-five (35) of those must have tumors with 50% or more cells positive for CD38 expression at baseline in order to rule out that any lack of activity is mostly due to low CD38 expression level in the enrolled subjects.

The trial will be carried out in two stages within each NHL subtype, as in a Simon's two-stage design. Each NHL subtype, independent of the other subtypes, may be discontinued after Stage 1 due to futility. To exclude the possibility that an observed low response rate is due to low CD38 expression level at baseline, the trial will enroll sufficient number of subjects with tumors where ≥50% of cells are CD38 positive in both stages. The detailed procedure will proceed as follows.

For MCL, Stage 1 will accrue 20 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 4 responses overall), no further expansion is planned. Otherwise, an additional 80 subjects will be enrolled to Stage 2; at least 50 of these subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 85% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.04.

For DLBCL, Stage 1 will accrue 15 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 3 responses overall), no further expansion is planned. Otherwise, an additional 40 subjects will be enrolled to Stage 2; at least 20 of these subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 80% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.05.

For FL, Stage 1 will accrue 15 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 6 responses overall), no further expansion is planned. Otherwise, an additional 40 subjects will be enrolled to Stage 2; at least 20 of these subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 80% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.05.

At the end of the study, all available data for each particular NHL subtype will be analyzed to determine a CD38 expression threshold for that subtype, which will be used to define an enriched population, via statistical inference.

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Endpoint

For each NHL subtype, an estimate of the ORR will be presented along with a two-sided 95% exact confidence interval. In addition, the biomarker adaptive threshold method of Jiang (2007)[16] will be utilized to select a threshold for CD38 expression level. The threshold is used to define an enriched subpopulation above which the daratumumab activity is enhanced. The number and percentage of subjects falling into each response category will be descriptively tabulated.

For each NHL subtype, a test for the null hypothesis in all subjects is to be combined with the establishment and validation of a CD38 expression threshold level, which is to be used to identify a sensitive subpopulation, using the biomarker adaptive threshold method (Jiang 2007).[16] Specifically, for a threshold value of c, a log-likelihood ratio statistic, *S(c)*, will be obtained is used to test the null hypothesis in the subset of subjects with CD38 expression level above *c*. Then a maximally selected test statistic will be defined as

$$T=\max\{S(0)+R,\max_{c>0}[S(c)]\}$$

Here, *R* is specified to be a constant 2.2, which is equal to the difference between the 95th and 80th percentiles from the chi-squared distribution with 1 degree of freedom and provides an optimal ability to detect a subset effect without compromising the overall effect power. Due to the inherent multiple testing issue and the complexity in constructing the test statistic, a bootstrap resampling method will be used to perform the test at an overall level of 0.05 for each NHL subtype. Similarly, the confidence intervals for the CD38 threshold value will also be obtained for each NHL subtype via bootstrapping.

The correlation between ORR and baseline tumor burden related variables (eg, beta-2 microglobulin) will be explored, as appropriate.

11.3.2. Secondary Efficacy Endpoints

Duration of response will be provided descriptively using the Kaplan-Meier method for responders only.

Progression-free survival and OS will be analyzed using the Kaplan-Meier method, and the comparison between the above- and below-threshold subpopulations will be made using log-rank test and Cox regression.

11.4. Pharmacokinetic Analyses

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

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listings. 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 timepoint and pharmacokinetic parameters of daratumumab. C_{min} is defined as the concentration observed immediately before infusion and C_{max} is defined as the concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling time point. Other pharmacokinetic parameters may also be summarized.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab may be performed 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.

11.5. Immunogenicity Analyses

The incidence of antibodies to daratumumab will be summarized for all subjects who receive at least one dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab. In addition, subjects who are positive for antibodies to daratumumab will also be listed.

11.6. 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. If performed, details and results of the analysis will be presented in a separate report.

11.7. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab, as well as to gain deeper understanding of NHL. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance [ANOVA], or

survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with clinical parameters will identify responsive (or resistant) subgroups in addition to immune cells, genes and pathways attenuated following treatment with daratumumab.

Natural killer cells, as a potential pharmacodynamic measure, will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by NHL subtype, dose, or clinical response. Data from CD38 testing by investigational IHC assay underdevelopment will be used for enrollment purposes, as well as correlated to overall clinical response to establish a potential threshold of CD38 expression that can be used for future subject selection. As this is an open-label study without a control treatment, statistical analyses will be done to aid in the understanding of the results. 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

11.8. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. All reported adverse events with onset during the Treatment Phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

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 post treatment 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 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). Clinically relevant changes (i.e. causing a treatment intervention or need for

concomitant therapy) will be also recorded on the adverse event eCRF. All other lab abnormalities need not be recorded as adverse events.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized and listed.

Vital Signs

Descriptive statistics of temperature and blood pressure (systolic and diastolic) values and changes from baseline will be summarized.

11.9. Interim Analysis

Within each NHL subtype, an interim analysis will be performed. The main purpose of the interim analysis is futility assessment based on ORR. In case of low ORR taking into consideration of CD38 expression level, an individual NHL subtype may be terminated for futility. The detailed futility stopping guideline is as follows.

1) For MCL, if at least 5 out of 20 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated. For DLBCL, if at least 4 out of 15 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated. For FL, if at least 7 out of 15 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated.

2) For MCL, if at most 4 out of 20 subjects have achieved CR or PR after Stage 1, consider terminating MCL for futility. For DLBCL, if at most 3 out of 15 subjects have achieved CR or PR after Stage 1, consider terminating DLBCL for futility. For FL, if at most 6 out of 15 subjects have achieved CR or PR after Stage 1, consider terminating FL for futility.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not

related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

  *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product Reference Safety Information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information included in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

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

12.2. 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. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 24 mg/kg, then it will be considered as overdose in this study
- 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 exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breast-feeding

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events 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 treatment, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received subsequent treatment with therapeutic intent for lymphoma during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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

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

Subjects (or their designees, if appropriate) will 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
- Subject name
- Blood type, Rh, and IAT or phenotyping result collected before first daratumumab dose (as described in Section 9.5)

12.3.2. Serious Adverse Events

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

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

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study 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 a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of daratumumab, then the hospitalization should not be reported as a serious adverse event.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the sponsor.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

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

14.2. Packaging

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

14.3. 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.

14.4. Preparation, Handling, and Storage

All study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The 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.

Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration. Refer to the Investigational Product Procedures Manual or equivalent document for details regarding dose preparation, storage, and handling of diluted solutions.

14.5. 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 study drug administered 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, or used returned study drug for destruction, 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. 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.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- eCRF completion guidelines
- Sample ICF
- Subject wallet card indicating blood type, Rh, and IAT or phenotyping result before first daratumumab dose

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with IRRs; see Section 6.3 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.

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

The total blood volume to be collected is estimated at about 20 mL (about 1.5 tablespoons) for screening tests, 215 mL (about 1 cup) for Cycles 1-7, 20 mL (about 1.5 tablespoons) at subsequent cycles, and 36 mL (about 2 tablespoons) at the End-of-Treatment Visit and the post treatment visits (see Section 9.1.1). This includes laboratory assessments associated with, safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. These blood volumes are not burdensome and fall within the normal range of a single blood donation.

16.1.1. CD38 IHC Assay

The archived biopsy samples were originally taken prior to the clinical study as part of the subject's non-Hodgkin's lymphoma disease clinical work-up or management. The archived biopsy tissue is then sent to the central laboratory for CD38 status determination. 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.

The risks to MCL, DLBCL, FL subjects whose tumors are tested by the Dako CD38 IHC pharmDx involves potential misclassification with respect to CD38 expression status.

- False-negative assay result- if the test returns a false-negative result at patient screening, the patient would be excluded from the clinical study. Patients with relapsed or refractory MCL, DLBCL, or FL would be treated as per the local practice or entered into another clinical study. Since the efficacy of daratumumab is yet to be proven in these patient populations, the impact of a false-negative result is believed to be minimal.

- False-positive assay result- if the test returns a false-positive result during patient screening, the outcome is that the subject would be entered in the clinical study and treated with daratumumab. Considering the absence of approved SOC treatment in the US for relapsed or refractory MCL, DLBCL, or FL, the overall risk to the subject with a false-positive result is expected to be low.

Further, in the Simon 2-stage design of the clinical study protocol, a futility analysis will be performed to evaluate efficacy and safety data at the end of Stage 1. If the futility criteria are met, an NHL subtype may be terminated and further subject exposure, inclusive of those who might have had false-positive test results, will be limited. Similarly, the number of Stage 2 subjects with CD38 expression level <50% will be capped within each NHL subtype, including those who might have had false-positive test results, to mitigate the possibility that a low response may be observed due to low levels of CD38 expression.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)

- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study 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). Furthermore, where required, progress reports/written summaries of the study status will be submitted to the IRB/IEC annually, or more frequently if requested.

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. An ICF for CD38 screening may be obtained separately from the full study ICF. 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, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

When prior consent of the subject is not possible is not available, 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.

16.2.4. Privacy of Personal Data

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

collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. 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/immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

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

Samples 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 lymphoma, to understand differential drug responders, and to develop tests/assays related to daratumumab and lymphoma. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care, must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study treatment administration information;

and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

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

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- 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.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in CRF. All CRF 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 CRF are accurate and correct.

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

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRFs 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. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the electronic Data Capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, 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.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, 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 eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

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

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

17.8. Monitoring

The sponsor will 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 eCRFs with the hospital or clinic records (source documents, eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed for each NHL subtype approximately 18 months after the last subject receives the first dose of daratumumab in that NHL subtype. The end of the study is defined as the completion of all three subtypes. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding 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 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 eCRF 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. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors 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. The results of each NHL subtype may be published separately from the others. 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 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the 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.

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ATTACHMENT 1: REVISED RESPONSE CRITERIA FOR RESPONSE ASSESSMENT (CHESON 2014)

Refer to full manuscript (Cheson 2014)[3] for details.

Response	Site	PET-CT-Based Response	CT-Based Response
Complete	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a] with or without a residual mass on 5PS[2] 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
	Non measured lesion	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 determinate, IHC negative
Partial	Lymph nodes and extralymphatic sites	Partial metabolic response	Partial remission (all of the following)
		Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	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

Response	Site	PET-CT-Based Response	CT-Based Response
	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	Target nodes/nodal masses, extranodal lesions	No metabolic response	Stable disease
		Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non measured lesion	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 disease	Progressive disease requires at least 1 of the following
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and 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
	Non measured 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 any axis 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

Response	Site	PET-CT-Based Response	CT-Based Response
			attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

a: 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).

b: 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.

ATTACHMENT 2: ECOG PERFORMANCE STATUS SCALE

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken 1982[20]

ATTACHMENT 3: CALCULATED CREATININE CLEARANCE

Cockcroft-Gault formula:

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

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

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

- serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL).

ATTACHMENT 4: ASTHMA GUIDELINES

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 any day	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: CONVERSION TABLE FOR GLUCOCORTICOSTEROID DOSE

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

INVESTIGATOR AGREEMENT

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

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Nushmia Khokhar, Senior Director Clinical Research

Institution [redacted] Janssen Research & Development

Signature: [redacted] Date: 19 JAN 2016
(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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