Janssen Research & Development*

Non-interventional Post-authorization Safety Study - Protocol

A Post-authorization Safety Study to Evaluate the Incidence of and Risk Factors for Severe and Fatal Infusion-related Reactions in Participants Treated with Daratumumab (Intravenous or Subcutaneous)

Protocol 54767414NAP4001

JNJ-54767414 (daratumumab)

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Study not registered

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

1. PASS INFORMATION

Title:	**A Post-authorization Safety Study to Evaluate the Incidence of and Risk Factors for Severe and Fatal Infusion-related Reactions in Participants Treated with Daratumumab (Intravenous or Subcutaneous)**
Protocol version:	0.3
Date of last version of the protocol:	12 April 2022
EU PAS Register no:	Study not registered
Active substance (International nonproprietary name common name):	Daratumumab
Pharmaco-therapeutic group (Anatomical Therapeutic Chemical Code):	L01XC24
Medicinal product(s):	Darzalex/Darzalex Faspro
Product reference:	EMEA/H/C/004077
Procedure number:	European Medicines Agency or national procedure number(s) if applicable: EU/1/16/1101/001_ Darzalex 20 mg/ml (5 ml) EU/1/16/1101/002_ Darzalex 20 mg/ml (20 ml) EU/1/16/1101/004_ Darzalex 1800 mg (15 ml)
Name of Marketing Authorization Holder(s)	Janssen Biotech, Inc.
Joint PASS	No
Research question and objectives	This single-arm, prospective observational study aims to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) infusion-related reactions (IRRs) in participants treated with intravenous (IV) or subcutaneous (SC) daratumumab for the treatment of multiple myeloma (MM) in the clinical practice setting and characterize potential risk factors.
Country(-ies) of study	United States of America (USA) plus additional countries not yet identified.
Author	PPD, Janssen Research & Development, LLC

2. MARKETING AUTHORIZATION HOLDER

Name of Marketing Authorization Holder:	Janssen Biotech, Inc.
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Qualified Person Pharmacovigilance:

Name:	Dr. Laurence Oster-Gozet, PharmD, PhD
Signature:	[electronic signature appended at the end of this document]
Date:	[electronic signature appended at the end of this document]

3. RESPONSIBLE PARTIES

Principal Participating Physician:	PPD, MD, Medical Director, Global Medical Affairs, Janssen Research & Development, LLC
Coordinating Investigator:	Not applicable
Contact person for this protocol:	PPD, MD, Medical Director, Global Medical Affairs, Janssen Research & Development, LLC
E-mail address or telephone number of contact person:	PPD

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AMENDMENTS AND UPDATES

Neither the participating investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor and will follow the review and approval process in accordance with local regulations.

There are no amendments for this protocol.

4. ABSTRACT

Protocol Title: A Post-authorization Safety Study to Evaluate the Incidence of and Risk Factors for Severe and Fatal Infusion-related Reactions in Participants Treated with Daratumumab (Intravenous or Subcutaneous) (2.0, 12 July 2022)

Sponsor's Responsible Medical Officer: PPD, Janssen Research & Development, LLC (Main Author)

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

Background and Rationale

Daratumumab is a first-in-class, human immunoglobulin G1 kappa monoclonal antibody (mAb) that specifically binds to the cell surface molecule cluster of differentiation (CD)38. Daratumumab is being developed for the treatment of multiple myeloma (MM) and other malignancies.

Infusion-related reactions (IRRs) are a common adverse event (AE) during daratumumab treatment, especially for participants receiving intravenous (IV) daratumumab.

The rationale for this study is CCI conducting a prospective, observational, single-arm study to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants with MM treated with IV or subcutaneous (SC) daratumumab. The study will inform on potential risk factors for IRRs during daratumumab use and potential mitigation strategies. Based on these results, Janssen may be able to identify subgroups of participants using daratumumab who are at a higher risk of IRRs and potentially develop more detailed, targeted guidance for mitigation in higher risk subpopulations. Given the difficulty of identifying IRRs in structured electronic health records and CCI concerns about missing risk factor data in structured electronic health records, Janssen proposed a prospective study with a pre-defined electronic case report form (eCRF).

In this protocol, the term 'IRRs' refers to both systemic administration-related reactions for participants receiving daratumumab SC and systemic IRRs for participants receiving daratumumab IV. Severe IRRs from the United States Prescribing Information (USPI) include hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.[3,5] Other signs and symptoms of IRRs may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision. Local injection-site reactions (eg, bruising, edema at injection site) are not considered IRRs.

Research Question and Objectives

This single-arm, prospective observational study aims to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants treated with IV or SC daratumumab for the treatment of MM in the clinical practice setting and to attempt to identify potential risk factors.

Objective(s) and Measure(s) of Interest

Objectives	Measures of Interest
To assess the overall incidence of IRRs (all grades and Grades 3 to 5) in participants with MM receiving the first 3 administrations of daratumumab IV/SC and the attribution of the IRR to daratumumab IV/SC.	IRR occurrence, toxicity grade, seriousness, outcome, action taken.

Objectives	Measures of Interest
To describe the baseline and treatment characteristics of participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Baseline participant characteristics before first infusion.
To document the type and timing of pre- and post-administration medications/care used in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Type and timing of pre- and post-administration medications/care used in participants with MM receiving the first 3 administrations of daratumumab IV/SC.
To describe the administration characteristics in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	For daratumumab IV: diluted volume of infusion, infusion start/stop date/time, time from infusion start to first signs/symptoms of Grades 3 to 5 IRRs. For daratumumab SC: volume of injection, injection start/stop date/time, time from injection to first signs/symptoms of Grades 3 to 5 IRRs.
To identify risk factors (baseline and demographic characteristics and infusion/injection characteristics) for incident Grades 3 to 5 IRRs (overall and separately by Grades 3 to 4 and Grade 5) after the first 3 administrations of daratumumab in participants with MM.	Odds ratio of Grades 3 to 5 IRR for baseline and administration risk factors.
To describe signs/symptoms of IRRs in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Signs and symptoms by grade.

IRR=infusion-related reaction; IV=intravenous; MM=multiple myeloma; SC=subcutaneous.

Study Design

This is a prospective, observational, single-arm, multicenter study to assess the incidence of and risk factors for severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants with MM during or following the first 3 administrations of daratumumab in a clinical practice setting in accordance with approved local labeling.

Setting and Participant Population

Participants included in this non-interventional study will receive daratumumab IV or SC for the first time for the treatment of MM in a clinical practice setting in accordance with approved local labeling. The decision to start treatment with daratumumab is made independent of this study.

Data collection will commence when a participant signs an informed consent form (ICF) and will continue until (but not include) the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab, in accordance with the Data Collection Schedule.

Baseline data on demographics, medical history, and disease characteristics will be collected before the first infusion or injection of daratumumab. During the first 3 weekly administrations of daratumumab, data on the infusion or injection characteristics will be recorded. IRRs that occur up to but not including the fourth administration of daratumumab will also be captured in the eCRF. Clinical manifestations of IRRs and post-medications or care administration will be recorded for participants experiencing an IRR, regardless of grade.

The study will be considered completed with the last visit for the last participant in the study.

Variables

The Data Collection Schedule summarizes the frequency and timing of data collection in this non-interventional study. The principal investigator and site personnel will be trained on the expectations of collecting accurate data.

The following variables will be collected in the eCRF at enrollment and/or during or following each administration of daratumumab:

- Demographic data (at enrollment only)
- Disease characteristics (at enrollment only)
- Medical history (at enrollment only)
- Laboratory values (the most recent values available prior to administration of daratumumab, in accordance with standard of care)
- Current daratumumab treatment
- Other medications (at enrollment only)
- Pre-medication for daratumumab treatment (during or following each administration of daratumumab only)
- Post-medication for daratumumab treatment (during or following each administration of daratumumab only).

Evaluation of Safety

For the prospective observational study, all AEs and special situations following exposure to daratumumab are to be recorded in the eCRF and the participant's source records, regardless of seriousness or causality. Adverse event collection should start with the first use within the study of daratumumab and will apply to all AEs, regardless of seriousness, that occur up to but not including the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab, in accordance with the Data Collection Schedule.

Data Sources

The primary data source for this study will be the medical record of each participant with MM who has provided a signed participation agreement/ICF.

Source documentation should be in participants' medical records for all data entered into the eCRF. In addition, source documentation should be available for the following to confirm data collected in the eCRF for this study: participant identification, eligibility and study identification; date of signed participation agreement/ICF; date of and reason for end of study. The author of any entry in the source documents should be identifiable.

The type and level of detail of source data available for a participant should be consistent with that commonly recorded at the participating site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the participating investigator before the study.

Race and ethnicity data will be recorded directly into the eCRF and the eCRF will be considered source documentation for these data points.

Study Size

A quantitative approach was used to estimate the sample size needed for enrollment based on methods reported by van Smeden et al. and Riley et al.[22,23,25]

Assuming a 3.5% incidence in the real world, 1000 participants will provide an exact Clopper-Pearson 95% confidence interval (CI) of (0.024, 0.048), with a half width of 0.012, for the incidence rate of severe and fatal IRRs.

Data Analysis

All analyses will be performed based on the safety analysis set, which is defined as all participants receiving at least 1 administration of daratumumab IV or SC formulation.

Risk factors for IRRs will be assessed using a logistic regression model. Independent variables will include those potential predictor variables examined. Dependent variables will be a binary variable representing whether or not the participant experienced any IRR (1=yes, 0=no) or a severe or fatal IRR (1=yes, 0=no) in the first 3 administrations of daratumumab. Each independent variable will be tested through its univariate logistic regression model. Independent variables meeting inclusion criteria will be included in a full multivariate logistic regression model for further risk factor selection using backward selection approach. Sensitivity analysis using forward, stepwise or subset selections will be explored to help identify the risk factors. During the model selection process, multicollinearity will be examined.

The number and percentage of participants with at least 1 IRR will be calculated for all toxicity grades combined as well as by the maximum toxicity grade. The number and percentage of participants with IRRs following the first, second and third daratumumab administration will be presented based on the onset date/time of the IRR signs/symptoms. The time from the daratumumab administration to the onset of each IRR will be summarized for all IRRs, and by the first, second and third daratumumab administration, separately.

The signs/symptoms of IRRs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All summaries of the signs/symptoms will be based on treatment-emergent events, which are defined as any event considered an IRR that occurs after the start of the first administration of daratumumab through the data collection follow-up time up to but not including the fourth administration of daratumumab. The IRR sign/symptoms will be summarized overall, by MedDRA system organ class (SOC) and preferred term (PT), by toxicity grade, and by the 3 daratumumab administrations based on onset date/time.

Where appropriate, additional summaries, listings, datasets, or narratives will be provided, eg, deaths, serious signs/symptoms, and other treatment-emergent AEs reported, etc. The number of patients who died due to any cause and the cause of death will be summarized.

Milestones

Milestone	Planned Date
Start of data collection	Q4 2022
End of data collection	January 2026
Registration in the EU PAS register	To be confirmed
Interim report #1	January 2024
Interim report #2	January 2025
Final report of study results	July 2026

DATA COLLECTION SCHEDULE

	Enrollment Visit (up to 3 weeks prior to administration of daratumumab)	Daratumumab Administration #1			Daratumumab Administration #2			Daratumumab Administration #3			End of Study
		Pre	During	After	Pre	During	After	Pre	During	After	
Participant Information											
Participant consent[a]	X										
Selection criteria	X										
Demographics	X										
Medical history	X										
Disease characteristics	X										
Prior treatment regimens	X										
Current disease status	X										
Concomitant medication	X		X			X			X		
Product Under Study											
Treatment regimen with daratumumab[b]			X			X			X		
Route of daratumumab administration			X			X			X		
Outcomes											
IRRs (grade and clinical manifestations)			X	X		X	X		X	X	X
Other adverse events[c]		X	X	X	X	X	X	X	X	X	X
Laboratory values[d]	X	X			X			X			
IRR Prevention and Care											
Pre-medication and care		X			X			X			
Post-medication and care			X	X		X	X		X	X	
Infusion or Injection Characteristics											
Marketed drug batch/lot number			X			X			X		
Infusion or injection volume			X			X			X		
Infusion or injection start/stop date/time			X			X			X		
Presence of change of infusion rate			X			X			X		
Study Completion/Withdrawal											
End-of-study											X[e]

eCRF=electronic case report form; ICF=informed consent form; IRR=infusion-related reaction.

[a] Before the start of data collection in this study, all participants (and/or a legally acceptable representative where applicable) must sign a participation agreement/ICF allowing source data verification in accordance with local requirements and sponsor policy; the participation agreement/ICF may be obtained at or before enrollment.

[b] If treatment with daratumumab is delayed for longer than 1 week since the previous administration, the reason for the delay will be collected (eg, adverse event, participant choice, supply issues).

[c] All adverse events and special situations following exposure to daratumumab are to be recorded in the eCRF, regardless of seriousness or causality. Adverse event collection should start with the first use of daratumumab within the study and will apply to all adverse events that occur up to but not including the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab.

[d] Laboratory values: the most recent values available prior to administration of daratumumab, in accordance with standard of care.

[e] When an enrolled participant completes or withdraws from the study, or is lost to follow-up, the participating investigator will complete the end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s).

5. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Start of data collection	Q4 2022
End of data collection	January 2026
Registration in the EU PAS register	To be confirmed
Interim report #1	January 2024
Interim report #2	January 2025
Final report of study results	July 2026

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADR	adverse drug reaction
AE	adverse event
CD	cluster of differentiation
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DRB	Designated Regulatory Body
eCRF	electronic case report form
eDC	electronic data capture
EU	European Union
FDA	US Food and Drug Administration
FOIA	Freedom of Information Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
NCI	National Cancer Institute
PAS	post-authorization study
PASS	post-authorization safety study
PQC	product quality complaint
PT	preferred term
SAE	Serious adverse event
SOC	system organ class
SC	subcutaneous
US(A)	United States of America
USPI	United States Prescribing Information

Definition of Term(s)

Study	The term “study” indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
PASS	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

6. BACKGROUND AND RATIONALE

6.1. Background

Daratumumab is a first-in-class, human immunoglobulin G1 kappa monoclonal antibody (mAb) that specifically binds to the cell surface molecule cluster of differentiation (CD)38. Daratumumab is being developed for the treatment of multiple myeloma (MM) and other malignancies. Daratumumab binds CD38-expressing cells with high affinity in a variety of hematological malignancies, including myeloma, lymphomas, and leukemias, as well as other cell types and tissues with various expression levels.

Daratumumab by intravenous (IV) infusion is currently approved in over 90 countries worldwide as a treatment for MM. Daratumumab subcutaneous (SC) was developed to provide several potential benefits for both patients and healthcare providers. Shorter administration time of 3 to 5 minutes (compared with 4 to 7 hours for IV infusion) and the lower rate of infusion-related reactions (IRRs) give additional flexibility and reduction in treatment burden to the patient, as well as reducing healthcare professional time spent on administration. The smaller administration volume for daratumumab SC reduces the risk of volume overload in patients with cardiac or renal insufficiency. Daratumumab SC is currently approved in the United States (US) and European Union (EU), and is either approved or under review in a number of other countries worldwide.

Please see the local label for additional information.[3-5]

6.2. Infusion-related Reactions

In this protocol, the term 'IRRs' refers to both systemic administration-related reactions for participants receiving daratumumab SC and systemic IRRs for participants receiving daratumumab IV. Severe IRRs from the USPI include hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.[3,5] Other signs and symptoms of IRRs may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision. Local injection-site reactions (eg, bruising, edema at injection site) are not considered IRRs.

The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 defines an IRR as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances."[17] Biologic therapies, like mAbs, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions. These acute effects have been grouped as 'infusion reactions'.[8] There is no agreed-upon definition for IRRs, therefore, additional information is needed to define these types of AEs, including timing, duration, and specific signs and symptoms observed upon administration of a therapeutic protein product. Signs/symptoms of IRRs are categorized into different grades of severity based on NCI CTCAE Version 5.0.[17]

IRRs are a common AE during daratumumab treatment, especially for participants receiving daratumumab IV. Table 1 presents the proportion of participants in different randomized

daratumumab clinical trials experiencing IRRs. In all daratumumab IV clinical trials listed in the most recent daratumumab USPI (monotherapy and combination: N=2,066), IRRs occurred in 37% of participants with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions.[3] The median time to onset was 1.5 hours (range: 0 to 73 hours). Apart from the 13% of participants experiencing IRRs in daratumumab SC monotherapy for relapsed or refractory MM (COLUMBA trial),[15] no other trial with daratumumab SC has observed >10% of participants with an IRR. As described in the USPI for daratumumab SC, in a pooled safety population of 898 patients with MM (n=705) or light chain amyloidosis (n=193), either as monotherapy or as part of a combination therapy, 9% of patients experienced an IRR.[5] IRRs occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days).

Table 1: Randomized Daratumumab IV/SC Multiple Myeloma Trials in Which Participants Experienced an IRR by Grade

Trial	Indication	Regimen	Any IRR (%)	Grades 3 to 4 IRR (%)
MAIA[11]	NDMM (no ASCT)	Dara IV, lenalidomide, dexamethasone (DRd)	41	<3
ALCYONE[14]	NDMM (no ASCT)	Dara IV, bortezomib, melphalan, prednisone (D-VMP)	28	5
CASSIOPEIA[16]	NDMM (ASCT)	Dara IV, bortezomib, thalidomide, dexamethasone (D-VTd)	35	<4
POLLUX[6]	RRMM	Dara IV, lenalidomide, dexamethasone (DRd)	48	5
CASTOR[18]	RRMM	Dara IV, bortezomib, dexamethasone (DVd)	45	9
COLUMBA[15]	RRMM	Dara IV or Dara SC Monotherapy	34 (IV) 13 (SC)	5 (IV) 2 (SC)
APOLLO[7]	RRMM	Dara SC, pomalidomide, dexamethasone (DPd)	5	0

ASCT=autologous stem-cell transplantation; Dara=daratumumab; IRR=infusion-related reaction; IV=intravenous; NDMM=newly diagnosed multiple myeloma; RRMM=relapsed or refractory multiple myeloma; SC=subcutaneous.

For participants receiving daratumumab, severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, and pulmonary edema.[3] Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, and throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms are wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.[3] These signs/symptoms can become more severe and may require hospitalization. Severe (Grades 3 to 4) IRRs occurred in <3% to 9% of trial participants receiving daratumumab IV, with <1% of participants experiencing a Grades 3 to 4 IRR at Week 2 or subsequent infusions.

No fatal (Grade 5) IRRs have been observed in registrational clinical trials of daratumumab IV or SC. Using spontaneous reports, reporting rates of fatal IRRs was estimated as 1.4 per 10,000 user-years of daratumumab IV as of April 2021.

6.3. Overall Rationale for the Study

The rationale for this study is CCI [redacted] by conducting a prospective, observational, single-arm study to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants with MM treated with IV or SC daratumumab. The study will inform on potential risk factors for IRRs during daratumumab use and potential mitigation strategies. Based on these results, Janssen may be able to identify

subgroups of participants using daratumumab who are at a higher risk of IRRs, and potentially develop more detailed, targeted guidance for mitigation in higher risk subpopulations. Given the difficulty of identifying IRRs in structured electronic health records and CCI concerns about missing risk factor data in structured electronic health records, Janssen proposed a prospective study with a pre-defined electronic case report form (eCRF).

7. RESEARCH QUESTION AND OBJECTIVES

This single-arm, prospective observational study aims to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants treated with IV or SC daratumumab for the treatment of MM in the clinical practice setting and to attempt to identify potential risk factors.

Objective(s) and Measure(s) of Interest

Objectives	Measures of Interest
To assess the overall incidence of IRRs (all grades and Grades 3 to 5) in participants with MM receiving the first 3 administrations of daratumumab IV/SC and the attribution of the IRR to daratumumab IV/SC.	IRR occurrence, toxicity grade, seriousness, outcome, action taken.
To describe the baseline and treatment characteristics of participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Baseline participant characteristics before first infusion.
To document the type and timing of pre- and post-administration medications/care used in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Type and timing of pre- and post-administration medications/care used in participants with MM receiving the first 3 administrations of daratumumab IV/SC.
To describe the administration characteristics in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	For daratumumab IV: diluted volume of infusion, infusion start/stop date/time, time from infusion start to first signs/symptoms of Grades 3 to 5 IRRs. For daratumumab SC: volume of injection, injection start/stop date/time, time from injection to first signs/symptoms of Grades 3 to 5 IRRs.
To identify risk factors (baseline and demographic characteristics and infusion/injection characteristics) for incident Grades 3 to 5 IRRs (overall and separately by Grades 3 to 4 and Grade 5) after the first 3 administrations of daratumumab in participants with MM.	Odds ratio of Grades 3 to 5 IRR for baseline and administration risk factors.
To describe signs/symptoms of IRRs in participants with MM receiving the first 3 administrations of daratumumab IV/SC.	Signs and symptoms by grade.

Objectives	Measures of Interest

IRR=infusion-related reaction; IV=intravenous; MM=multiple myeloma; SC=subcutaneous.

Refer to Section 8.7 for statistical aspects of measures of interest.

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overview of Study Design

This is a prospective, observational, single-arm, multicenter study to assess the incidence of and risk factors for severe (Grades 3 to 4) and fatal (Grade 5) IRRs in participants with MM during or following the first 3 administrations of daratumumab in a clinical practice setting in accordance with approved local labeling.

Prior to data collection, all potential participants and/or a legally acceptable representative where applicable must sign a participation agreement/informed consent form (ICF) allowing source data verification in accordance with local requirements and sponsor policy.

Participants' decision to take part in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. All aspects of treatment decisions and clinical management of participants will be in accordance with clinical practice and at the discretion of the treating investigator.

Only data available within routine clinical practice will be collected in this study. Routine clinical practice is considered to be care for patients with MM in an oncology clinic where care decisions are made between the patient and the investigator. Care decisions, including decisions about treating with daratumumab, should not be influenced by external factors or enrollment in the study, and should reflect the local standard of care. No additional testing, diagnostics, monitoring or procedures should be conducted outside of what would be performed in the clinic.

8.1.2. Rationale for Study Design Elements

The prospective observational design facilitates collection of a sufficient quantity of defined variables, where available in clinical practice, to address the study objectives. To avoid potential bias in participant selection, each participating investigator should enroll eligible participants in a consecutive manner (ie, in the order in which they are assessed for eligibility). All participants who meet the selection criteria should be offered enrollment in the study.

8.2. Setting and Participant Population

8.2.1. Study Setting and Duration

At the inclusion visit, the participant's eligibility for inclusion into the study will be determined by the participating investigator based on prespecified inclusion/exclusion criteria. Once consent is obtained, data collection at enrollment will include demographic data (including age, gender, race/ethnicity), medical history/comorbidities, baseline disease characteristics (including type of myeloma and International Staging System stage), height, body weight, and Eastern Cooperative

Oncology Group performance status. This will be followed by data collection during daratumumab IV or SC therapy in routine clinical practice as specified below and in the Data Collection Schedule.

Participants included in the prospective non-interventional study will receive daratumumab IV or SC for the first time for the treatment of MM in a clinical practice setting in accordance with approved local labeling. Daratumumab IV and SC and pre- and post-medications used for treating IRRs will not be provided by the sponsor and participants will not be reimbursed for purchasing any treatments that they need to treat their pathology. The decision to start treatment with daratumumab is made independent of this study.

Data collection will commence when a participant signs an ICF equivalently and will continue until (but not include) the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab, in accordance with the Data Collection Schedule.

Baseline data on demographics, medical history, and disease characteristics will be collected before the first infusion or injection of daratumumab. During the first 3 weekly administrations of daratumumab, data on the infusion or injection characteristics will be recorded. IRRs that occur up to but not including the fourth administration of daratumumab will also be captured in the eCRF. Clinical manifestations of IRRs and post-medications or care administration will be recorded for participants experiencing an IRR, regardless of grade.

A participant will be considered to have completed the study if they have data collection completed until the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab.

When an enrolled participant completes or withdraws from the study, the participating investigator will complete an end-of-study form for the individual participant and provide a specific date for the end-of-study observation. When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF.

If a participant is lost to follow-up, every reasonable effort should be made (within clinical practice) by personnel at the participating site to contact the participant and determine the reason for discontinuation. The measures taken to follow up should be documented. In the event that the status of the participant cannot be determined, and the participant is considered to be lost to follow-up, an end-of-study form for the individual participant will be completed and a specific date for the last observation will be provided.

A participant will be withdrawn from further documentation in this study for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up

- Discontinuation of daratumumab IV or SC before the third administration (switching from daratumumab IV to daratumumab SC will not be considered a discontinuation)
- Death.

All treatment decisions will be made at the discretion of the treating investigator. Starting or stopping therapies for MM during the observation period will only impact data collection for the remaining administrations of the first 3 administrations of daratumumab.

Additionally, a participant will be withdrawn from further documentation in this study for any of the following reasons:

- The participating investigator (or treating investigator where different) believes that it is in the best interest of the participant to stop treatment (eg, due to IRRs or any other AE)
- The participant develops a medical condition that requires concomitant therapy with a drug listed as prohibited in the respective product information (approved label)

If a participant discontinues treatment before the end of the observational period, the end-of-treatment and follow-up assessments should be documented.

Participants who are subsequently enrolled in another non-Janssen-sponsored clinical study do not need to be withdrawn from this non-interventional study. It is accepted that data collection in this observational study may be restricted by confidentiality agreement terms and/or conditions of another concurrent clinical study. However, where permitted, start and end dates and type of therapy administered during any other clinical study should be recorded. When the other clinical study is complete, full data collection for this non-interventional study may resume.

The study will be considered completed with the last visit for the last participant in the study. Participating sites will be closed upon study completion. Further details of study completion and termination procedures are presented in Annex 1.12.

8.2.2. Selection Criteria

At each site, the investigator will determine the eligibility of participants for data collection in this study based on the selection criteria described below. If there is a question about any of the selection criteria, the participating investigator should consult with the appropriate sponsor representative before enrolling the participant. To avoid potential selection bias, all eligible participants should be offered enrollment for data collection in the study. Eligible participants who sign the participation agreement/ICF will sequentially enrolled into the study.

Each potential participant must satisfy the following criteria to be eligible for data collection in this study:

1. Participant must be aged at least 18 years or legal age of consent in the jurisdiction that the study is conducted.

2. Participants must be starting daratumumab treatment for the first time in accordance with the approved label.

3. Participant (and/or a legally acceptable representative where applicable) must sign a participation agreement/ICF allowing source data verification in accordance with local requirements.

Potential participants who meet any of the following criteria will not be eligible for this study:

1. Participant has prior use of daratumumab or CD-38 antibody.
2. Participant has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the start of the study or the first data collection time point.
3. Participant is currently enrolled in an interventional study.

8.3. Variables

The Data Collection Schedule summarizes the frequency and timing of data collection in this non-interventional study. The principal investigator and site personnel will be trained on the expectations of collecting accurate data. Data collection sources for variable collection are defined in Section 8.4.

8.3.1. Covariates Collected at Baseline and During or Following Each Daratumumab Administration

The following variables will be collected in the eCRF at the enrollment visit.

Table 2: Covariates Collected at the Enrollment Visit

Category	Variable	Definition
Demographics	Age	Age in years
	Gender	Male or Female
	Race	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White (Caucasian); Other
	Ethnicity	Hispanic, Non-Hispanic
	Height	Height in meters
	Weight	Weight in kg
Disease characteristics	Date of diagnosis for indication	[Investigator specify]
	Investigator-assessed ISS stage	[Investigator specify]
	ECOG score	[Investigator specify]
	Bone marrow plasma cell percentage	[Investigator specify]
Medical history	Newly diagnosed vs relapsed/refractory	[Investigator specify newly diagnosed or relapsed/refractory]
	Previously diagnosed conditions (ever diagnosed)	With start/stop date: • History of hypersensitivity or anaphylaxis • History of hypersensitivity, anaphylaxis, injection site reactions, and/or IRRs due to a drug • History of transfusion-related reactions to, during or after stem cell transplant • Heart failure • Prior myocardial infarction – Severity

Category	Variable	Definition
		• Hypertension • Hypotension
		• Peripheral vascular disease • Asthma • Chronic obstructive pulmonary disease • Cerebrovascular disease • Connective tissue disease • Stomach ulcers • Liver disease – Severity (mild, moderate, severe) • Diabetes • Hemiplegia • Renal disease – Stage • Cancer (excluding non-melanoma skin cancer) – Site – Presence of metastasis • Dementia • Migraine (including severity and annual frequency) • HIV or HIV/AIDS • Other [Investigator specify]
Laboratory values (the most recent values available prior to administration of daratumumab, in accordance with standard of care)	Total white blood cell count Absolute neutrophil count Platelet counts Total red blood cell count Hemoglobin	• Provide test date • Units=$\times 10^9$ cells/liter • Provide test date • Units=$\times 10^9$ cells/liter • Provide test date • Units=$\times 10^9$ platelets/liter • Provide test date • Units=$\times 10^9$ cells/liter • Provide test date • Units=g/dL
Current daratumumab treatment	Route of administration for daratumumab	• IV • SC
Other medications	Other treatments currently used or used in the prior 30 days	• Corticosteroids (excluding those used to treat MM) • Respiratory drugs • Anti-allergy drugs • Cardiovascular drugs • Other monoclonal antibodies

AIDS=acquired immunodeficiency syndrome; ECOG=Eastern Cooperative Oncology Group; HIV=human immunodeficiency virus; IRR=infusion-related reaction; ISS=International Staging System; IV=intravenous; MM=multiple myeloma; SC=subcutaneous.

The following variables will be collected during or following each administration, in line with the Data Collection Schedule.

Table 3: Covariates Collected During or Following Each Daratumumab Administration

Category	Variable	Definition
Pre-medications for daratumumab treatment	Drugs administered	With time given before daratumumab administration: • Corticosteroids (methylprednisolone, dexamethasone) • Histamine receptor antagonists (diphenhydramine) • Leukotriene receptor antagonists (montelukast) • Paracetamol • Other [Investigator specify]
Post-medication for daratumumab treatment	Drugs administered	With time given after daratumumab administration: • Corticosteroids (methylprednisolone, dexamethasone) • Other [Investigator specify]

Category	Variable	Definition
Current daratumumab treatment	Route of administration for daratumumab	• IV • SC
	Dose	[Investigator specify]
	Batch lot number	[Investigator specify]
	Injection volume	[Investigator specify]
	Injection start/stop time and date	[Investigator specify]
Laboratory values (the most recent values available prior to administration of daratumumab, in accordance with standard of care)	Total white blood cell count	• Provide test date • Units=$\times 10^9$ cells/liter
	Absolute neutrophil count	• Provide test date • Units=$\times 10^9$ cells/liter
	Platelet counts	• Provide test date • Units=$\times 10^9$ platelets/liter
	Total red blood cell count	• Provide test date • Units=$\times 10^9$ cells/liter
	Hemoglobin	• Provide test date • Units=g/dL

IV=intravenous; SC=subcutaneous.

8.3.2. Daratumumab IV or SC Use for Multiple Myeloma – Primary Therapy

The primary therapy for this study will be newly administered daratumumab therapy (of any type, either IV or SC). Administration will be provided as part of routine clinical practice and will not be influenced by enrollment in the study. For each of the first 3 administrations of daratumumab, the investigator will specify the date and time of administration and whether the formulation is IV or SC.

According to the label for daratumumab, the first 4 administrations are given weekly. If treatment with daratumumab is delayed for longer than 1 week since the previous administration, the reason for the delay will be collected (eg, AE, participant choice, supply issues).

8.3.3. Evaluation of IRRs

As stated in Section 8.3.5 (Evaluation of Other Safety Events), all AEs will be entered into the eCRF by the investigator, including their start and stop time and date. The capture of data on IRRs will be more detailed than for other AEs. In this protocol, the term 'IRRs' refers to both systemic administration-related reactions for participants receiving daratumumab SC and systemic IRRs for participants receiving daratumumab IV. Local injection-site reactions (eg, bruising, edema at injection site) are not considered IRRs.

The IRR signs/symptoms will be captured in the eCRF from medical records and, when necessary, from the patient and/or other healthcare providers at a subsequent care visit in case an IRR occurs outside of the study sites. An eCRF form will be used for the trained investigator to identify the IRR signs/symptoms, their severity, and any hospitalization or intensive care services required to treat them. The responsible investigator will review the patient's IRR signs/symptoms that have been entered into the eCRF and confirm whether they are due to an IRR, and attributable to daratumumab, based on their expert clinical knowledge.

A list of key IRR signs/symptoms will be provided to investigators (Annex 4, Table 6). These IRR signs/symptoms were selected based on those listed in or analogous to those in the USPI.[3,5] Severe IRR signs/symptoms from the USPI include hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of IRRs include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision. The IRR signs/symptoms corresponding to the MedDRA PTs of other IRR signs/symptoms that are considered medically important are also included in the list (narrow scope PTs in the Standardized MedDRA Query of hypersensitivities plus the PTs of dyspnoea, hypertension, hypotension, hypoxia, pulmonary oedema, and wheezing).

Investigators will be asked to classify IRR symptom severity using NCI CTCAE Version 5.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/NCIt_CTCAE_5.0.xlsx). When no specific CTCAE grading is available for a symptom, the investigator will be asked to use the general grading for the corresponding MedDRA SOC. The IRR signs/symptom with the most severe grading will be used to define severity of the IRR.

If the investigator observes a sign/symptom of an IRR that is not provided in Annex 4, they can use this sign/symptom and assess the grading using NCI CTCAE Version 5.0. The IRR severity will be defined by the most severe symptom occurring before the subsequent daratumumab administration. If a fatal event occurs, the investigator should characterize the IRR as fatal rather than severe.

Although most IRRs were observed within 48 hours of daratumumab administration in clinical trials, the study will capture all IRR symptoms occurring until the subsequent administration (usually within 7 days) to allow for potential delayed presentation of symptoms.

The outcome of an IRR and the action taken with daratumumab will be recorded. The investigator will indicate whether the IRR is considered a serious AE (SAE) and whether it led to hospitalization or prolonged hospitalization. If the event requires hospitalization, the admittance and discharge dates will be provided.

In order to assess the reliability of the IRR outcome, a sample of 25 to 50 patients will be selected from certain sites.[9,10] Two independent physicians will individually classify whether a selected patient did or did not have an IRR and the grade of any IRR using CTCAE grading. Each physician will be blinded to the other physician's assessment. The Cohen's kappa statistic will be calculated to assess inter-rater reliability in classifying IRRs and severity. This assessment will be further specified in the statistical analysis plan.

8.3.4. Mortality

Deaths due to any cause will be captured from medical records and from other healthcare professionals and caregivers in the 30-day period (early discontinuation prior to the fourth dose) or 7-day period (follow-up until the fourth dose only) following the last administration of daratumumab for the study. Investigators will assess whether deaths are due to IRRs.

8.3.5. Evaluation of Other Safety Events

Adverse Events and Adverse Drug Reactions

For the prospective observational study, all AEs and special situations following exposure to daratumumab are to be recorded in the eCRF and the participant's source records, regardless of seriousness or causality. Adverse event collection should start with the first use within the study of daratumumab and will apply to all AEs, regardless of seriousness, that occur up to but not including the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab, in accordance with the Data Collection Schedule.

Section 10 provides further details of safety data collection and reporting procedures.

Clinical Laboratory Tests

Only available hematology and/or serum chemistry results that are obtained as part of the participant's usual standard of care will be collected.

Other Safety Evaluations

Body Weight: The body weight of the participant will be documented when measured per clinical practice at the participating site. Body mass index will be calculated using the participant's baseline height and weight.

8.4. Data Sources

The primary data source for this study will be the medical record of each participant with MM who has provided a signed participation agreement/ICF. To avoid selection bias, participants who meet the eligibility criteria and who sign the participation agreement/ICF are sequentially enrolled into the study. Source documentation should be in participants' medical records for all data entered into the eCRF. In addition, source documentation should be available for the following to confirm data collected in the eCRF for this study: participant identification, eligibility and study identification; date of signed participation agreement/ICF; date of and reason for end of study. The author of any entry in the source documents should be identifiable.

The type and level of detail of source data available for a participant should be consistent with that commonly recorded at the participating site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the participating investigator before the study.

Race and ethnicity will be recorded directly into the eCRF, and the eCRF will be considered source documentation for these data points.

8.5. Study Size

A quantitative approach was used to estimate the sample size needed for enrollment based on methods reported by van Smeden et al. and Riley et al.[22,23,25]

Assuming a 3.5% incidence in the real world, 1000 participants will provide an exact Clopper-Pearson 95% confidence interval (CI) of (0.024, 0.048), with a half width of 0.012, for the incidence rate of severe and fatal IRRs (Table 4).

Table 4: Exact Clopper-Pearson 95% CIs for Sample Size of 1000

Anticipated Severe/Fatal IRR Incidence	Exact Clopper-Pearson 95% CIs	Actual Width of CIs
0.02	(0.012, 0.031)	0.019
0.035	(0.024, 0.048)	0.024
0.05	(0.037, 0.065)	0.028
0.10	(0.082, 0.120)	0.038

CI=confidence interval; IRR=infusion-related reaction.

The calculations examined scenarios where the incidence of severe and fatal IRRs ranged from 2% to 10% depending on the primary daratumumab formulation used in the population. Based on the percentages of severe IRRs observed in daratumumab clinical trials, it is anticipated that the average percentage of patients experiencing severe IRRs during daratumumab IV and SC use in ideal trial settings would be approximately 5% and 1%, respectively. However, in the real-world setting, a broader patient population may be treated with daratumumab, including patients with underlying cardiac and respiratory conditions that would have excluded them from clinical trials. Furthermore, in the real-world setting, infusion rates may not mirror the strict clinical trial rates and may therefore lead to more rapid infusion of daratumumab, which can increase the risk of IRR. Additionally, not all pre-infusion medications may be given, which may increase the potential for IRR and severe IRR. Lastly, patients may not be monitored as stringently during an infusion which may lead to a delayed detection of IRR and, as a result, a more severe IRR. Therefore, patients with MM receiving daratumumab in real-world clinical settings could have a higher risk for severe or fatal IRRs. A conservative estimate is that estimates of severe/fatal IRR in the real world are double the average percentage of severe IRRs observed in clinical trial settings for daratumumab IV and SC, resulting in a real-world severe/fatal IRR percentage of 10% and 2% for each respective mode of administration. These estimated outcome proportions should be considered alongside the increasing use of daratumumab SC versus IV in the planned study countries. In Q4 2021, in the planned study countries, 16% of patients had initiated daratumumab IV, while 84% of patients had initiated daratumumab SC. Together, the average of 84% of patients receiving daratumumab SC with a 2% risk of developing severe/fatal IRR risk and 16% of patients receiving daratumumab IV with a 10% risk of developing severe/fatal IRR risk results in an overall approximate 3.5% risk of developing a severe/fatal IRR.

Given the predicted 2% to 10% range of incidence for severe and fatal IRRs, sample size was estimated assuming a margin of error or mean absolute prediction error ≤0.05 based on recommendations from Riley et al.[23] Additionally, the estimated sample size was explored for a logistic regression when 5, 10, and 15 predictors were considered. This sample size calculation used parameters from simulations conducted by van Smeden et al.[25] Table 5 provides the suggested sample sizes given the different proportions of severe and fatal IRR, predictor count, and mean absolute prediction error in the estimate. Given a 3.5% incidence of severe/fatal IRRs in new daratumumab users, a prediction model with 10 predictors will have an acceptable 2% mean absolute prediction error in a sample of approximately 1000 patients.

Table 5: Estimated Sample Size Produced Across Different Counts of Predictors and Mean Absolute Prediction Errors

Mode of Administration	Anticipated Severe/Fatal IRR Incidence	Number of Predictor Parameters	Mean Absolute Prediction Error	Sample Size	Severe/Fatal IRR Count
Daratumumab SC use	0.02	5	0.05	67	1
	0.02	5	0.03	171	3
	0.02	5	0.02	360	7
	0.02	10	0.05	127	3
	0.02	10	0.03	325	6
	0.02	10	0.02	684	14
	0.02	15	0.05	185	4
	0.02	15	0.03	473	9
	0.02	15	0.02	996	20
Mixed use of 16% daratumumab IV and 84% daratumumab SC	0.035	5	0.05	87	3
	0.035	5	0.03	223	8
	0.035	5	0.02	470	16
	0.035	10	0.05	166	6
	0.035	10	0.03	424	15
	0.035	10	0.02	893	31
	0.035	15	0.05	241	8
	0.035	15	0.03	617	22
	0.035	15	0.02	1300	46
Daratumumab IV use	0.1	5	0.05	144	14
	0.1	5	0.03	368	37
	0.1	5	0.02	775	77
	0.1	10	0.05	273	27
	0.1	10	0.03	699	70
	0.1	10	0.02	1472	147
	0.1	15	0.05	398	40
	0.1	15	0.03	1017	102
	0.1	15	0.02	2143	214

IRR=infusion-related reaction; IV=intravenous; SC=subcutaneous.
Calculations based on the predicted values having a small mean error (+/- 0.5 margin of error) This calculation takes into consideration various characteristics of the prediction development dataset, including number of predictor parameters and outcome proportions. Parameters used to calculate the estimated sample size come from simulations by van Smeden et al, 2019.[25]

Annex 5 provides additional sample size estimates considering precise estimation of the outcome risk, a target shrinkage factor of 0.9, and a Nagelkerke R^2 of 0.05.[23]

In addition to the sample size, the study enrollment will also require that US study populations include approximately 15% from minority and/or underserved populations (eg, Black/African-American, Asian, Hispanic). Diversity will be actively monitored.

8.6. Data Management

Participating sites will enter data into the case report form using electronic data capture (eDC) via an internet browser-based interface. The eCRF will direct the site regarding which data are required for collection. Participating sites will be trained on the use of the eDC system. Data collected should be recorded accurately, legibly and promptly for each participant during the study. Further details of eCRF completion procedures are presented in Annex 1.8.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a site visit log that will be kept at the participating site. Further details of monitoring procedures are presented in Annex 1.9.

The signs/symptoms of IRRs and other AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

8.7. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the Statistical Analysis Plan.

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be summarized using frequency and percentage.

Covariates will be operationalized for analysis in multiple ways according to clinical input. Continuous variables may be categorized according to clinically meaningful cut points. Binary and categorical variables will be explored as indicator variables. Specific variable definitions will be detailed in the Statistical Analysis Plan.

8.7.1. Main Summary Measures

8.7.1.1. Analysis Data Sets

All analyses will be performed based on the safety analysis set, which is defined as all participants receiving at least 1 administration of daratumumab IV or SC formulation. A subgroup analysis will also be conducted by daratumumab formulation (IV or SC) to support hypothesis generation; however, sample size may be insufficient to calculate precise estimates.

8.7.1.2. Data Summary

The number and percentage of participants with at least 1 IRR will be calculated for all toxicity grades combined as well as by the maximum toxicity grade. If a participant reports multiple IRRs with different toxicity grades, the maximum toxicity grade will be counted for the by-grade summary.

The number and percentage of participants with IRRs following the first, second and third daratumumab administration will be presented based on the onset date/time of the IRR signs/symptoms. Denominators for the percentages will vary according to the number of participants receiving that injection/infusion.

The time from the daratumumab administration to the onset of each IRR will be summarized for all IRRs, and by the first, second and third daratumumab administration, separately.

All demographic data, baseline disease characteristics, prior treatment characteristics, and medical history will be summarized. Daratumumab treatment duration, and pre- and post-administration medications/care will also be summarized. The Charlson comorbidity score will also be calculated using the Quan updated weights[1,19] and summarized.

All summaries of the signs/symptoms will be based on treatment-emergent events, which are defined as any event considered an IRR that occurs after the start of the first administration of daratumumab through the data collection follow-up time up to but not including the fourth administration of daratumumab. The IRR sign/symptoms will be summarized overall, by MedDRA SOC and PT, by toxicity grade, and by the 3 daratumumab administrations based on onset date/time.

Where appropriate, additional summaries, listings, datasets, or narratives will be provided, eg, deaths, serious signs/symptoms, and other treatment-emergent AEs reported, etc. The number of patients who died due to any cause and the cause of death will be summarized.

8.7.2. Main Statistical Methods

8.7.2.1. Risk Factor Assessment

The number and percentage of patients with IRRs and severe/fatal IRRs will be summarized by levels of each categorical predictor. The risk difference among the levels of each predictor will be summarized. Details of these variables and their levels will be provided in the Statistical Analysis Plan.

Risk factors for IRRs will be assessed using a logistic regression model. Independent variables will include those potential predictor variables listed in Section 8.3. Dependent variables will be a binary variable representing whether or not the participant experienced any IRR (1=yes, 0=no) or a severe or fatal IRR (1=yes, 0=no) in the first 3 administrations of daratumumab. Each independent variable will be tested through its univariate logistic regression model. An independent variable with a 2-sided p-value <0.2 will be included in a full multivariate logistic regression model. A reduced model will be developed through backward selection by dropping effects that are not significant at a 2-sided 0.1 level of significance one at a time, starting with the highest p-value. Sensitivity analysis using forward, stepwise or subset selections will be explored to help identify the risk factors. If deemed necessary, additional machine learning approaches such as LASSO or Elastic Net logistic regression will be explored and the c-statistics will be compared to the backward selection model.

During the model selection process, multicollinearity will be examined. To keep or remove a variable from the multivariable model, Akaike Information Criterion and/or Bayesian Information Criterion for the goodness-of-fit of the model will be taken into account. Participants will be clustered within sites and observations in the same site can be correlated. To account for participants' nesting effect to their study sites, a multilevel logistic regression will be tested with a 2-level hierarchical structure, with participants being the first level unit and the study sites being the second level unit as random effect.[24] The study site will be tested for its statistical significance. If it is not a statistically significant factor, the nesting effect will be removed from the final model. In the event of convergence failure of a logistic regression model, the root cause will be investigated. Solutions will include but are not limited to the following:[1]

1. Use of exact logistic regression estimates (this is useful when the number of IRRs is small)

2. Use of penalized maximum likelihood estimates

3. Reduction of the levels of a categorical variable if the variable is the cause of convergence failure

4. Combination of 2 categorical variables into 1 in case of empty cells for the number of IRR events

5. Leaving the convergence failure as it is, testing a predictor by taking twice the positive difference in the log-likelihoods from the models with and without the predictor

6. Adaption of Bayesian estimation with a prior distribution on the regression coefficients.

The odds ratio and 95% CIs of each predictor will be estimated from the final model.

Details of the model development process will be addressed in the Statistical Analysis Plan.

8.7.3. Missing Values

The missing data mechanism will be assessed for the predictor variables of IRRs. For the initial logistic regression analysis, if the percentage of missingness is greater than 30%, the predictor variable, either continuous or categorical, will be excluded from the analysis. For categorical predictors with missing observations (10% to 30% missingness), a missing category will be created. For categorical predictors with missing observations (<10% missingness), a complete case will be used for univariate analysis. For continuous predictors with missing observations (<30% missingness), a complete case will be used for univariate analysis.

Sensitivity analyses with multiple imputation will be conducted for those variables for which missingness is considered at random, regardless of the percentage missing. This method is considered appropriate for reducing bias even when the proportion of missingness is large.[13]

8.7.4. Interim Analysis

There will be no interim analysis planned. As described in Section 5, 2 interim reports are planned:

Interim report #1	January 2024
Interim report #2	January 2025

The participant count, participant characteristics and incidence of severe and fatal IRRs up until approximately 2 months prior to the interim report due dates will be provided.

8.8. Quality Control

Procedures to ensure the accuracy and reliability of data will include the selection of qualified investigators and appropriate participating sites, review of data collection procedures with the participating investigator and site personnel before the study, and periodic monitoring visits and/or remote monitoring by the sponsor (see Section 8.6). Written instructions for the handling, storage, and shipments of samples obtained in clinical practice will be provided where appropriate.

Guidelines for eCRF completion will be provided and reviewed with the participating site personnel before the start of the study (see Annex 1.8). The sponsor will review eCRFs for accuracy and completeness during monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the participating 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.

The participating investigator and/or site will maintain all eCRFs and source documentation that support the data collected for each participant, as well as all study documents specified by the applicable regulatory requirement(s) (see Annex 1.3). The participating investigator and/or site will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 5 years after the completion of the final study report, but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the participating investigator and/or site as to when these documents no longer need to be retained. Further details of record retention policies are provided in Annex 1.11.

Representatives of the sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and/or company policy. Similar procedures may also be conducted by a regulatory body. Further details of on-site audit policies are presented in Annex 1.10.

8.9. Limitations of the Research Methods

In the real-world setting, the proportion of participants using SC versus IV daratumumab for the treatment of MM, as well as the incidence of IRRs, are not known. It is, therefore, difficult to predict the sample size required to assess the risk of severe and fatal IRRs in the clinical practice setting and characterize potential risk factors.

Variables used as potential predictors in the risk factor analysis may not be available in the participant's medical record, especially for the medical history variables. Entering investigators will be asked to fill in the eCRF with additional variables if they believe data may be missing.

Repeated measures will not be assessed in the logistic regression prediction model exploring risk factors. Only the first IRR will be considered as an outcome. Therefore, the risk factor results will only apply to the first IRR that the participant experiences while on daratumumab.

Participants may be lost to follow-up or discontinue daratumumab after the first administration, which could be related to the IRR. Entering investigators will be asked to contact surviving participants to determine why they discontinued daratumumab in the first 3 administrations, which will be described in the report.

9. PROTECTION OF HUMAN SUBJECTS

Where appropriate, as required by local regulations, this study will be undertaken only after the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) has given full approval of

the final protocol, any applicable amendments, and the participation agreement/ICF, and the sponsor has received a copy of this approval (see Annex 1.4).

Prior to data collection, all participants (and/or a legally acceptable representative where applicable) must sign a participation agreement/ICF allowing source data verification in accordance with local requirements and sponsor policy (see Annex 1.5). Potential participants will be told that their consent to allow collection of information within the context of this non-interventional study is entirely voluntary and may be withdrawn at any time. Participants will be informed of the observational nature of the study, that the sponsor only intends to collect information and follow the course of treatment in the clinical practice setting, and that their participation in the study does not involve invasive procedures outside of the recommendations in the local label. Only participants who are fully able to understand the nature of the study and provide their consent voluntarily will be enrolled.

Personal data collected from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, and must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Annex 1.7).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information.

10.1. Definitions and Classifications

10.1.1. Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), 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 based on International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. The phrase "a reasonable possibility" means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires in-patient 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 other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent 1 of the other outcomes listed above.

Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an AE will be determined by whether or not it is listed in the applicable reference safety information.[3,4,5]

NOTE: Unlistedness of an event is only relevant for the sponsor's reporting obligations, but is not determining reporting requirements of the participating investigator to the sponsor or Marketing Authorization Holder.

Product Quality Complaint

A product quality complaint (PQC) is any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or drug delivery system.

10.1.2. Attribution Definitions

Assessment of Causality

The causal relationship to treatment is determined by an investigator and should be used to assess all AEs. The causal relationship can be 1 of the following:

Related

There is a reasonable causal relationship between administration of the product under study and the AE.

Not Related

There is not a reasonable causal relationship between administration of the product under study and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.1.3. Severity Criteria

The severity for all AEs, including IRRs, will be assessed using NCI CTCAE Version 5.0.

10.2. Special Situations

Special situations for a Janssen product under study that require reporting and/or safety evaluation by Janssen include:

- Overdose of a product
- Exposure to a product from breastfeeding
- Suspected abuse/misuse of a product
- Inadvertent or accidental exposure to a product
- Any failure of expected pharmacological action (ie, lack of effect) of a product
- Unexpected therapeutic or clinical benefit from use of a product
- Medication error, intercepted medication error, or potential medication error involving a Janssen medicinal product (with or without participant exposure to the Janssen medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

These safety events may not meet the definition of an AE; however, from a policy perspective, they are treated in the same manner as AEs.

10.3. Procedures

In this non-interventional study, daratumumab (IV and SC) is the Janssen product under study.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) AEs and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities (see country-specific attachments). All collected AEs will be summarized in the final study report.

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

10.3.1. All Adverse Events

Adverse Events Systematically Collected (Solicited Adverse Events)

All AEs and special situations following exposure to daratumumab are to be systematically recorded in the eCRF and the participant's source records, regardless of seriousness or causality. Adverse event collection should start with the first use within the study of daratumumab and will apply to all AEs, regardless of seriousness, that occur up to but not including the fourth administration of daratumumab or 30 days after the last dose if the participant does not receive all 4 administrations of daratumumab, in accordance with the Data Collection Schedule. All AEs recorded following exposure to daratumumab should be assessed by the participating investigator to document their opinion concerning the relationship of the event to daratumumab; the causal relationship of the AE must be recorded in the eCRF. An AE will be considered as an ADR if there is at least a reasonable possibility of a causal relationship (see Section 10.1.2). Where necessary, the sponsor and/or participating investigator will report non-serious ADRs to the local health authorities following applicable requirements.

Any event that meets the definition of an SAE (see Section 10.1.1) should be reported as an SAE according to the requirements in Section 10.3.2.

All AEs should be followed up in accordance with clinical practice, regardless of seriousness. This follow-up should be recorded in the participants' source records and documented according to sponsor instructions.

Adverse Events Not Systematically Collected (Spontaneous Adverse Events)

For AEs and special situations that are not systematically collected (eg, for a medicinal product other than the product under study) and where the participating investigator considers there is at least a reasonable possibility of a causal relationship to a medicinal product (ie, spontaneous ADRs), the participating investigator is requested to notify the manufacturer of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible.

For ADRs and special situations related to non-studied Janssen products, it is requested to report the event directly to the local sponsor (see country-specific attachments).

Where available, reports of spontaneous ADRs will be summarized in the clinical study report.

10.3.2. Serious Adverse Events

All SAEs following exposure to a Janssen product under study should be reported directly by the participating investigator, within 24 hours of them becoming aware, to the local sponsor (see country-specific attachments) using a Serious Adverse Event Report Form (or local equivalent).

For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure(s) planned before entry into the study (should be documented in the eCRF). Note: Hospitalizations that were planned before the start of data collection, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported in the eCRF if they fulfill the SAE definition (refer to Section 10.1.1). Since a fatal outcome is part of the study outcomes, AEs with fatal outcome will only be recorded as serious in the eCRF and should not be reported as an SAE.

10.3.3. Pregnancy

All reports of pregnancy occurring in temporal association with the administration of a Janssen product under study must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using a Serious Adverse Event Form.

As this is an observational study, it is recommended that participating investigators follow the guidance in the approved local product labels for daratumumab regarding discontinuation of therapy in participants who become pregnant during the study. If a participant becomes pregnant during the study, data specified in the Data Collection Schedule that is collected as part of the participant's standard-of-care will continue to be recorded in the eCRF for the applicable time points.

Because the effect of the Janssen product under study on sperm is unknown, pregnancies in partners of male participants exposed to a Janssen product under study will be reported by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

10.3.4. Special Situations

Special situations for a Janssen product under study should be recorded in the eCRF. Any special situation that meets the criteria of an SAE should be recorded on a Serious Adverse Event Report Form and reported to the local sponsor within 24 hours of them becoming aware of the event.

10.3.5. Product Quality Complaints

A PQC may have an impact on the safety and effectiveness of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, 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.

All initial PQCs involving a Janssen product must be reported to the local sponsor by the participating site personnel within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs for a Janssen product are listed on the contact information page(s), which is/are provided separately.

If the defect for a Janssen product is combined with an SAE, the study-site personnel must report the PQC to the local sponsor according to the SAE reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor, which will contain data collected from all study sites that participated in the study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Participant identifiers will not be used in the 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 participating investigator) shall be the property of the sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.13.

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

Title	Reference No	Date
None		

Annex 1.2: Information to be Provided to Participating Investigators

The participating investigator will be provided with the following supplies:

- Summary of Product Characteristics Package Insert for daratumumab, if required by local regulations
- eDC Manual
- Sample participation agreement/ICF.

Annex 1.3: Regulatory Documentation

Regulatory Approval/Notification

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

Required Prestudy Documentation

The following documents must be provided to the sponsor before starting the study:

- Protocol and amendment(s), if any, signed and dated by the participating investigator
- Where appropriate, as required by local regulations, a copy of the dated and signed written IEC/IRB approval of the protocol, amendments, participation agreement/ICF, and any recruiting materials
- Where appropriate, as required by local regulations, a copy of the dated and signed written Designated Regulatory Body (DRB) approval of the protocol, protocol amendments, participation agreement/ICF, and any other recruiting materials. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee
- Where appropriate, as required by local regulations, the name and address of the DRB (with a statement that it is organized and operates according to applicable laws and regulations). If a participating investigator or a member of the participating site personnel is a member of the DRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote or opinion of the study
- Regulatory authority approval or notification, if applicable
- Documentation of the qualifications (eg, curriculum vitae) of the participating investigator, where appropriate
- Any other documentation required by local regulations.

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

- Signed and dated clinical trial agreement, which includes the financial agreement.

Annex 1.4: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

Before the start of data collection, the participating 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, protocol amendments
- Sponsor-approved participation agreement/ICF (and any other written materials to be provided to the participants)
- Participating investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding name of the sponsor, institutional affiliations, other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligation.

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding those that are purely administrative, with no consequences for data collection), and the participation agreement/ICF, 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 participating 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 those that are purely administrative, with no consequences for data collection)
- Revision(s) to the participation agreement/ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB
- Reports of AEs that are serious, unlisted/unexpected, and temporally associated with the product under study
- New information that may adversely affect the safety of the participants or the conduct of the study
- Report of deaths of participants under the participating investigator's care
- Notification if a new investigator is responsible at the participating site

- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding those that are purely administrative, with no consequences for data collection), the amendment and applicable revisions to the participation agreement/ICF must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

Annex 1.5: Participant Consent

The participation agreement/ICF that is/are used must be reviewed and approved in accordance with local regulations, applicable regulatory requirements and sponsor policy, and must be in a language that the participant can read and understand. The participation agreement/ICF must be signed before collection of any participant data.

Before enrollment in the study, the participating investigator or an authorized member of the participating site personnel must explain to potential participants their involvement in the study and data protection (see Section 9). Participants will be informed that their participation is entirely voluntary and that they may withdraw consent for data collection at any time. They will also be informed that choosing not to participate in this study will not affect the standard of care the participant will receive. Finally, they will be told that the participating investigator will maintain a participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the participation agreement/ICF the participant is authorizing such access, including permission to obtain information about his/her survival status, and agrees to allow the participating investigator to re-contact the participant to obtain information about his/her survival status.

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

If the participant 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 participation agreement/ICF after the oral consent of the participant is obtained.

Annex 1.6: Participant Identification and Enrollment

The participating investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor and participating site contact for completeness. The participant identification and enrollment log will be treated as confidential and will be filed by the participating investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled for data collection in the study, the date seen and age at initial informed consent will be used.

Where applicable, the participating investigator should also complete a participant screening log, which documents all participants who were seen to determine eligibility for data collection in the study.

Annex 1.7: Participant Data Protection

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

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

The participant has the right to request through the participating investigator access to his/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.

Annex 1.8: Case Report Form Completion

Case report forms are provided for each participant in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed from the source documents onto an eCRF by personnel at each participating site, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a participant visit.

The participating 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 participating investigator or other authorized participating site personnel. If necessary, queries will be generated in the eDC tool. The participating investigator or participating site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Personnel at each participating site can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- The manager of the participating site can generate a query for resolution by the personnel at that site
- Clinical data manager can generate a query for resolution by the participating site personnel.

Annex 1.9: Monitoring

At the first postinitiation visit, the monitor will compare the data entered into the eCRFs with the source documents. 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 participating site personnel and are accessible for verification by the sponsor/participating-site contact. If electronic records are maintained at the participating site, the method of verification must be discussed with the site personnel.

Direct access to source documentation 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 participating site personnel. The sponsor expects that, during monitoring visits, the relevant participating 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 participating investigator on a regular basis during the study to provide feedback on the study conduct.

Annex 1.10: On-site Audits

Any audits conducted by the sponsor at a participating site will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Participant privacy must, however, be respected. The participating investigator and participating site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Annex 1.11: Record Retention

If the responsible participating 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 participating 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 participating investigator and/or site must permit access to such reports.

Annex 1.12: Study Completion/Termination

The final data from the participating site will be sent to the sponsor (or designee) after completion of the final data collection time point at that site.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor.

A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

The participating investigator may initiate 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 participating site by the sponsor or participating investigator may include but are not limited to:

- Failure of the participating investigator to comply with the protocol, requirements of the local health authorities, or the sponsor's procedures
- Inadequate recruitment of participants by the participating investigator.

The participating investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Annex 1.13: Use of Information and Publication

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

The participating investigator understands that the information obtained 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 obtained to be used, the participating investigator is obligated to provide the sponsor with all data obtained in the study.

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 participating 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 the primary (multicenter) data and information without approval from the participating investigator. The participating investigator has the right to publish data specific to the associated participating site after the primary data are published. If a participating 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 participating 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 participating investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, participating investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual 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.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
1.1.2 The objectives of the study?	☐	☐	☐	
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☐	☐	☐	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☐	☐	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☐	☐	☐	
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☐	☐	☐	
2.2.2 Age and sex?	☐	☐	☐	
2.2.3 Country of origin?	☐	☐	☐	
2.2.4 Disease/indication?	☐	☐	☐	
2.2.5 Co-morbidity?	☐	☐	☐	
2.2.6 Seasonality?	☐	☐	☐	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	
3.4 Is sample size considered?	☐	☐	☐	
3.5 Is statistical power calculated?	☐	☐	☐	

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☐	☐	☐	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, participant interview including scales and questionnaires, vital statistics, etc)	☐	☐	☐	
4.1.3 Covariates?	☐	☐	☐	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☐	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☐	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☐	☐	☐	
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☐	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	
7.4 Does the protocol address other limitations?	☐	☐	☐	

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☐	☐	
8.2 Is the choice of statistical techniques described?	☐	☐	☐	
8.3 Are descriptive analyses included?	☐	☐	☐	
8.4 Are stratified analyses included?	☐	☐	☐	
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☐	
8.5.2 Effect modifiers?	☐	☐	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☐	
8.6.2 Effect modification?	☐	☐	☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
9.2 Are methods of quality assurance described?	☐	☐	☐	
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☐	
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, participant recruitment)	☐	☐	☐	
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☐	☐	☐	
9.5.2 Any progress report?	☐	☐	☐	
9.5.3 End of data collection?	☐	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☐	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	
9.7 Are communication methods to disseminate results described?	☐	☐	☐	
9.8 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☐	
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
10.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

ANNEX 3: PRIOR CANCER THERAPY – GUIDANCE REGARDING LINE OF TREATMENT

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.[20,21]

ANNEX 4: MEDICALLY IMPORTANT IRR SIGNS/SYMPTOMS

Table 6: List of Potential Medically Important IRR Signs/Symptoms

MedDRA SOC	PTs
Cardiac disorders	• Atrial fibrillation • Atrial flutter • Atrioventricular block complete • Atrioventricular block first degree • Cardiac arrest • Chest pain - cardiac • Circulatory collapse • Conduction disorder • Cyanosis • Hypersensitivity myocarditis • Kounis syndrome • Myocardial infarction • Palpitations • Paroxysmal atrial tachycardia • Sinus bradycardia • Sinus tachycardia • Supraventricular tachycardia • Ventricular arrhythmia • Ventricular fibrillation • Ventricular tachycardia
Eye disorders	• Acute myopia • Angle closure glaucoma • Blepharitis allergic • Choroidal effusion • Conjunctival oedema • Conjunctivitis allergic • Corneal oedema • Eye allergy • Eye swelling • Eyelid oedema • Giant papillary conjunctivitis • Oculomucocutaneous syndrome • Periorbital oedema • Periorbital swelling • Scleral oedema • Scleritis allergic • Swelling of eyelid

MedDRA SOC	PTs
Gastrointestinal disorders	• Bloating • Diarrhoea • Dry mouth • Dyspepsia • Dysphagia • Epiglottic oedema • Gastrointestinal pain • Gingival oedema • Gingival swelling • Intestinal angioedema • Lip oedema • Lip swelling • Mouth swelling • Nausea • Oedema mouth • Palatal oedema • Palatal swelling • Swollen tongue • Tongue oedema • Vomiting
General disorders and administration site conditions	• Chills • Circumoral oedema • Circumoral swelling • Death NOS • Oedema limbs • Oedema trunk • Face oedema • Fatigue • Fever • Generalized oedema • Limbal swelling • Localized oedema • Malaise • Neck oedema • Non-cardiac chest pain • Shock • Shock symptom • Sudden death NOS • Swelling face
Immune system disorders	• Allergic oedema • Allergic pharyngitis • Allergic reaction • Allergic respiratory disease • Allergic respiratory symptom • Allergic sinusitis • Allergic stomatitis • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylaxis • Angioedema • Anti-neutrophil cytoplasmic antibody positive vasculitis • Arthritis allergic • Atopic cough • Atopy • Cytokine release syndrome • Drug hypersensitivity • Drug reaction with eosinophilia and systemic symptoms • Eosinophilic granulomatosis with polyangiitis • Hypersensitivity • Immune thrombocytopenia • Type I hypersensitivity • Type II hypersensitivity

MedDRA SOC	PTs
	• Type III immune complex mediated reaction • Type IV hypersensitivity reaction
Injury, poisoning and procedural complications	• Administration related reaction • Infusion related hypersensitivity reaction • Infusion related reaction
Investigations	• Forced expiratory volume decreased • Vital capacity abnormal
Musculoskeletal and connective tissue disorders	• Arthralgia • Myalgia
Nervous system disorders	• Cognitive disturbance • Depressed level of consciousness • Dizziness • Encephalitis allergic • Encephalopathy allergic • Headache • Presyncope • Syncope
Psychiatric disorders	• Agitation • Anxiety • Confusion • Restlessness
Renal and urinary disorders	• Henoch-Schonlein purpura nephritis • Nephritis allergic • Genital oedema
Respiratory, thoracic and mediastinal disorders	• Allergic rhinitis • Bronchospasm • Cough • Dyspnea • Hoarseness • Hypoxia • Laryngeal inflammation • Laryngeal oedema • Laryngospasm • Laryngotracheal oedema • Nasal congestion • Oculorespiratory syndrome • Oropharyngeal blistering • Oropharyngeal oedema • Oropharyngeal spasm • Oropharyngeal swelling • Pharyngeal oedema • Pharyngeal swelling • Pulmonary oedema • Respiratory failure • Rhinitis allergic • Sneezing • Sore throat • Stridor • Tracheal oedema • Voice alteration • Wheezing
Skin and subcutaneous tissue disorders	• Acute generalised exanthematous pustulosis • Bullous dermatitis • Bullous haemorrhagic dermatosis • Cutaneous vasculitis • Dermatitis • Dermatitis acneiform

MedDRA SOC	PTs
	• Dermatitis allergic • Dermatitis atopic • Dermatitis bullous • Dermatitis exfoliative • Dermatitis exfoliative generalised • Dermatitis psoriasiform • Drug eruption • Eczema • Eczema nummular • Eczema vesicular • Eczema weeping • Epidermal necrosis • Epidermolysis • Epidermolysis bullosa • Erythema multiforme • Erythema nodosum • Erythroderma • Exfoliative rash • Fixed eruption • Generalised bullous fixed drug eruption • Henoch-Schonlein purpura • Hypersensitivity vasculitis • Interstitial granulomatous dermatitis • Mucocutaneous rash • Nodular rash • Palpable purpura • Pruritus • Purpura • Rash • Rash acneiform • Rash erythematous • Rash follicular • Rash macular • Rash maculo-papular • Rash maculovesicular • Rash morbilliform • Rash papulosquamous • Rash pruritic • Rash pustular • Rash rubelliform • Rash scarlatiniform • Rash vesicular • Stevens-Johnson syndrome • Symmetrical drug-related intertriginous and flexural exanthema • Toxic epidermal necrolysis • Urticaria • Urticaria cholinergic • Urticaria chronic • Urticaria contact • Urticaria papular • Urticaria physical • Urticaria pigmentosa • Urticaria vesiculosa • Urticarial dermatitis • Urticarial vasculitis • Vasculitic rash
Vascular disorders	• Distributive shock • Flushing • Hypertension • Hypotension • Peripheral ischaemia

Key: IRR=infusion-related reaction; MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified; PT=preferred term; SOC=system organ class.

The list of IRR symptoms is not intended to provide an exclusive list of symptoms. The investigator can list other symptoms and use NCI CTCAE Version 5.0 grading or grade with overall IRR grading if none of the listed symptoms are experienced. The link to the full NCI CTCAE Version 5.0 is included below:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/NCIt_CTCAE_5.0.xlsx

The investigator may also refer to the following grading tool:

https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx.

ANNEX 5: ADDITIONAL SAMPLE SIZE CALCULATIONS

Riley et al. (2020) suggests that multiple factors should be considered when estimating sample sizes for more robust models, including (1) number of events relative to the number of candidate predictors, (2) the outcome proportion of the study population, and (3) the expected predictive performance of the model.[23] The authors suggest tailoring sample size estimates to consider the outcome proportion in the study setting, with the specific aim of minimizing the potential for model overfitting while trying to identify the most precise parameter estimates. In Section 8.5, the Sponsor provides estimated sample sizes for different mean average prediction error ≤0.05 and outcome proportions expected in the real world for populations receiving daratumumab SC, daratumumab IV, and a mixture of daratumumab IV/SC. Table 7 and Table 8 below provide sample size estimates for real world populations receiving daratumumab SC, daratumumab IV, and a mixture of daratumumab IV/SC based on:

- Precise estimation of the overall risk (Table 7)
- Target shrinkage factor of 0.9 (Table 8)
- Nagelkerke R^2 of 0.05 (Table 8).

Table 7: Estimated Sample Size Needed for a Precise Estimate of the Overall Outcome Proportion if There Were No Predictors in a Logistic Model Within a Margin of Error of ≤0.05

Mode of Administration	Estimated Outcome Proportion	Margin of Error Around Outcome Proportion	Sample Size Needed	Participants With Outcomes
Daratumumab SC use	0.02	0.05	30	1
	0.02	0.03	84	2
	0.02	0.02	188	4
Mixed use of 16% daratumumab IV and 84% daratumumab SC	0.035	0.05	52	2
	0.035	0.03	144	5
	0.035	0.02	324	11
Daratumumab IV use	0.1	0.05	138	14
	0.1	0.03	384	38
	0.1	0.02	864	86

IV=intravenous; SC=subcutaneous.

Table 8: Estimated Sample Size Needed to Achieve Uniform Shrinkage With a Target Shrinkage Factor of 0.9, Candidate Predictors Parameters Ranging From 5 to 20, and a R^2 Nagelkerke of 0.05

Mode of Administration	Outcome Proportion	Number of Prediction Parameters	Shrinkage Factor	R^2cs	Max (R^2cs)	R^2 Nagelkerke	EPP	Sample Size Needed
Daratumumab SC use	0.02	5	0.9	0.009	0.178	0.05	20.1	5032
	0.02	10	0.9	0.009	0.178	0.05	20.1	10178
	0.02	15	0.9	0.009	0.178	0.05	20.1	15094
Mixed use of 16% daratumumab IV and 84% daratumumab SC	0.035	5	0.9	0.013	0.252	0.05	24.1	3575
	0.035	10	0.9	0.013	0.252	0.05	24.1	7150
	0.035	15	0.9	0.013	0.252	0.05	24.1	10310
Daratumumab IV use	0.1	5	0.9	0.024	0.478	0.05	37.0	1850
	0.1	10	0.9	0.024	0.478	0.05	37.0	3700
	0.1	15	0.9	0.024	0.478	0.05	37.0	5550

IV=intravenous; SC=subcutaneous; CS=Cox-Snell; EPP=events per predictor variable.
These calculations assume 0.05 is an acceptable difference in apparent & adjusted R^2, that there is a 0.05 margin of error in estimation of the intercept, and the prevalence of events per predictor parameter is 0.1.

PARTICIPATING PHYSICIAN AGREEMENT

JNJ-54767414 (daratumumab)
Protocol 54767414NAP4001

PARTICIPATING PHYSICIAN 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 conduct of the study and the obligations of confidentiality.

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): PPD

Institution: Janssen Research & Development, LLC

Signature: PPD PPD Date: _____
Date: 2022.07.15 00:32:27 +02'00'
(Day Month Year)

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

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Status: Approved, Date: 12 July 2022