Protocol title

Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

The DARE study

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	13 Oct 2017
Amendment 1	15 Mar 2018
Amendment 2	13 Jul 2018
Amendment 3	09 Jul 2019
Amendment 4	08 Jun 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (08 JUNE 2020)

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

The overall reason for the amendment: To update the protocol regarding the overall duration of the study, from 30 to 37 months.

Applicable Section(s)	Description of Change(s)
Rationale: The enrolment period is changed from 18 to 24 months, and the total study duration from 30 to 37 months.	
Protocol summary Section 4.1 Section 6.1.6 Section 7.2.2	The sections were updated accordingly.
Rationale: To update the known potential risks of daratumumab administration according to the most recent risk language of the drug.	
Section 2.1	Text was updated accordingly.

Amendment 3 (09 JULY 2019)

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

The overall reason for the amendment: To update the protocol based on new guidelines regarding the risk of HBV reactivation, give clarifications regarding the subject population, and provide additional recommendations on handling daratumumab delays and toxicities.

Applicable Section(s)	Description of Change(s)
Rationale: The sections below were revised following the new guidelines on patient screening for HBV.	
Section 5.1	The following sentence was added to provide guidance regarding the contraception of the female partner of a male patient: "The additional contraception of female partners of childbearing potential should also be considered"
Section 5.2	Additional information was provided on the eligibility criteria of the subject population.
Section 7.1.3 and 7.1.4	The section of Study Procedures/Evaluations was amended with two paragraphs, as follows: **7.1.3 HBV Serology** All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose. **HBV DNA Tests:** Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 7.2). Where required by local law, the results of HBV testing may be reported to the local health authorities.
Table 7.2	The schedule of events was updated according to the guidelines discussed in the main body.
Section 7.3.1	Two paragraphs were added regarding management of Hepatitis B Virus Reactivation: Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see Section 7.1.4). For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study

	treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.
Appendix 2	A paragraph was added regarding primary antiviral prophylaxis for HBV reactivation
Appendix 8	Appendix 8 was added to provide additional information on HBV management.

Applicable Section(s)	Description of Change(s)
Rationale: The list of known potential risks associated with daratumumab was updated according to the latest data.	
Section 2.1	The section was updated accordingly.

Applicable Section(s)	Description of Change(s)
Rationale: The sections below were revised in order to clarify the eligibility criteria.	
Sections 5.1 and 5.2	Eligibility criteria were amended in order to clarify that patients who undergo intraperitoneal dialysis can be included, and patients with Amyloidosis shall be excluded.

Applicable Section(s)	Description of Change(s)
Rationale: The sections below were revised in order to provide recommendations on toxicity management and delays/missed doses of daratumumab.	
Section 6.1.5	The section regarding daratumumab dose modifications/delays was amended with: • specific information on how to handle particular toxicities; • a table with the respective dose delay/resumption schedule; • a paragraph regarding interruption of missed doses.

Applicable Section(s)	Description of Change(s)
Rationale: The schedule of events was updated in order to specify that β2 microglobulins and LDH assessment will only be performed at screening.	
Table 7.2	The schedule of events was updated accordingly.

Applicable Section(s)		Description of Change(s)
Rationale: More details and clarification on Safety events of special interest events		
Section 8.4.3	Events of Special Interest	Safety events of special interest include, but are not limited to: • Secondary Primary Malignancies • Infusion Related Reactions • Medication Error, intercepted medication error or potential medication error (with or without patient exposure to IMP, e.g., product name confusion, product label confusion, intercepted prescribing or dispensing errors) • Abuse/Misuse/Overdose • Occupational Exposure

	• Drug-Drug Interaction • Suspected Transmission of Infectious Agents • Exposure from breastfeeding • Unexpected therapeutic benefit or clinical benefit • Inadvertent or accidental exposure

Applicable Section(s)	Description of Change(s)
Rationale: The sections below were revised in order to provide information on the Revised International Staging System for Multiple Myeloma.	
Appendix 3	A table explaining the different stages and the respective requirements was added.

Applicable Section(s)	Description of Change(s)
Rationale: Minor corrections/updates	
All over the protocol	Minor corrections for typographic errors, total number of participating Sites, title and address updates were performed throughout the protocol.

Amendment 2 (13 JULY 2018)

The overall reason for the amendment: To update the protocol based on Italian health authority recommendations.

Applicable Section(s)	Description of Change(s)
Rationale: The below sections were revised following the request of the Italian health authority, regarding the addition of a formal Interim Safety review by the Sponsor for the assessment of the study treatment safety profile in the population under evaluation.	
Section 10.4.7 Planned Interim Analyses	Clarifications were provided regarding planned interim analysis: No formal interim analysis for efficacy is planned but an in interim analysis for safety will be performed.
10.4.7.1 Safety Review	The paragraph was amended as follows: The Sponsor Scientific Committee will perform an overall evaluation of the safety data when 19 patients (50%) have received at least 1 dose of daratumumab. If a safety signal is identified and the Sponsor Scientific Committee determines that the safety profile of the study treatment is unfavorable, the recruitment of the rest of the subjects will be interrupted and the study may be stopped due to safety concerns. In the event of such a study termination all current subjects that are receiving daratumumab treatment may receive subsequent alternative treatment outside of the study as per the investigator's judgement and routine practice. More details on the Interim Safety Review will be provided in the Statistical Analysis Plan for this study.

Amendment 1 (15 MAR 2018)

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

The overall reason for the amendment: To clarify the below listed sections of the protocol and align it with other protocols of daratumumab studies

Applicable Sections	Description of Changes
Rationale: To change the meaning of the abbreviation SD from Standard Deviation which is used twice in the text, to Stable disease which is recurrent, so to avoid confusion.	
List of Abbreviations	Change of the meaning of the abbreviation SD from Standard Deviation to Stable disease
Rationale: To reconcile inclusion criteria in the summary with inclusion criteria in main body (section 5.1)	
Protocol Summary: Population; Section 5.1: Inclusion criteria	.Inclusion criteria were updated as per main text
Rationale: To describe more clearly the current approval status of the study drug with respect to the population included in the study so as not to confuse that daratumumab is not approved for the RRMM population.	
Section 1.2: Introduction; section 2.1: Known potential risks	The text was amended to: "Daratumumab in combination with dexamethasone is not approved for the indication under study." in Section 1.2 and the approval status of daratumumab with respect to the patient population (MM patients with renal impairment) is described in section 2.1: "Daratumumab is approved for the treatment of MM, yet data on the treatment of patients with renal impairment are very limited"
Rationale: Update of the known potential risks for Daratumumab according to the updated risk language for the drug	
Section 2.1: Known potential risks	Pulmonary edema was added to the uncommon Adverse Events and Difficulty with blood testing and IAT was removed. The IRR sub-section text was amended to: "Of the 820 subjects who received daratumumab in the monotherapy and combination Studies, IRRs were reported in approximately half (48%) of subjects. The most common IRRs were cough (10%), dyspnoea (9%), chills (6%), throat irritation (6%), nasal congestion (5%), bronchospasm (5%), nausea (5%), and vomiting (5%). Grade 3 IRRs were reported in 6% of subjects. No Grade 4 IRRs were reported. For the majority of subjects (378 of 392; 96%) an IRR occurred with the first infusion" as per IB language.
Rationale: To clarify the characteristics of the population included in the study	
Section 4.1 Description of the Study Design	Rephrased sentence to: "This is a multicenter, Phase 2, single arm, open-label study evaluating daratumumab with dexamethasone (DaraD) in subjects with RRMM who have received at least two prior lines of treatment, with both bortezomib- and lenalidomide-based regimens and have renal impairment."
Rationale: update inclusion criteria with documented presence of multiple myeloma	

Section 5.1: Participant Inclusion Criteria	Criterion 3 was rephrased to depict that subjects must have documented multiple myeloma Measurable disease has been registered as a separate criterion (Criterion 6)
Rationale: To specify that patients with active hepatitis A are also excluded and to update the COPD/asthma and cardiac disease exclusion criteria as per other daratumumab protocols	
Section 5.2 Participant Exclusion Criteria	Active Hepatitis A is added to the exclusion criteria. COPD/asthma exclusion criterion has been updated. Cardiac disease exclusion criterion has been updated to clarify that uncontrolled cardiac arrhythmias are excluded.
Rationale: To include recurrent Grade 3 IIRs in the reasons for withdrawing daratumumab as per Appendix 2 guidelines	
Section 5.3.1 Reasons for Withdrawal or Termination	A grade 3 IRR recurring 3 times during one infusion was added to the list of reasons to withdraw daratumumab
Rationale: To remove pregnancy as a definite drug discontinuation criterion as per the latest daratumumab safety update	
Section 5.3.1 Reasons for Withdrawal or Termination	Pregnancy was removed from the list
Rationale: To clarify that dose adjustment or modification is not allowed for daratumumab	
Section 6.1.5 Dose Adjustments/Modifications/Delays	The text “No dose adjustment or modification is permitted for daratumumab” was added
Rational: To clarify when the assessments are to be performed and reconcile this table (Table 7.1) with the Schedule of Events (Table 7.2)	
Table 7.1 – Disease assessments	Text was added specifying that IFE will be performed as needed to confirm CR (instead of disease progression) and that sFLC will be performed as needed to confirm sCR and on Day 1 of each cycle only for patients that have no measurable M-protein by PEP. The text in the MRD section was replaced for clarity.
Rational: To clarify: 1) that cardiac imaging assessments (MUGA or ECHO) are acceptable if they are performed within 42 days from C1D1 and 2) that MUGA will be performed if ECHO is not available	
Section 7.1.2.6: Cardiac assessments, Section 7.2.1: Screening, Section 7.2: Schedule of Events	Section 7.1.2.6: Text was amended to: “A 2-dimensional echocardiogram (or if not available a MUGA scan) and an electrocardiogram will be performed at screening or within 42 days of Cycle 1 Day 1. Echo (or MUGA) may be repeated throughout the study as clinically indicated”; Section 7.2.1: cardiac assessments was added to the exams that can be performed within 42 days from C1D1 and MUGA was added to the list f Screening assessments as an alternative to ECHO; Schedule of Events: footnote was added clarifying that cardiac ECHO or MUGA are acceptable within 42 days from C1D1

Rationale: To clarify that skeletal survey assessments are acceptable if they are performed within 42 days of C1D1 same as with STPs	
Section 7.1.1.5 Skeletal survey, Section 7.2.1 Screening	Text was added clarifying that any imaging assessments already completed during the regular work-up of the patient within 42 days prior to start of treatment can be considered as the baseline images.
Rationale: To clarify that eGFR will be used for assessment of renal function instead of Creatinine Clearance	
Section 7.2.1 and Table 7.2	Creatinine clearance was replaced with eGFR
Rationale: To include the FEV1 test in the screening assessments for subjects with known or suspected COPD as per updated exclusion criterion	
Section 7.2.1 and Table 7.2	FEV1 test for subjects with known or suspected COPD was added
Rational: To clarify the circumstance under which use of corticosteroids other than dexamethasone is allowed.	
Section 7.3.2 Prohibited Medications, Treatments and Procedures, Section 6.1.4: Dosing and administration	Text was added specifying that concomitant corticosteroids other than dexamethasone are allowed as pre- and post-infusion medications as well. In section 6.1.4 the phrase “on the days that dexamethasone dosing is concurrent” was added to specify the instructions for dexamethasone administration
Rational: To provide instructions for the treatment of patients that require hemodialysis	
Section 7.3.3 Rescue Medications, Treatments and Procedures	Section was added instructing that daratumumab should be administered on the day with the maximum distance from the subsequent dialysis
Rational: Adaptation of the pregnancy section as per the latest risk language to reflect that continuation of treatment with daratumumab will be assessed by the investigator after consultations with Sponsor and subject.	

Section: 8.4.4 Reporting of Pregnancy	The Section was amended to: A female patient will be instructed to immediately inform the investigator if she becomes pregnant during the study. The investigator shall report all pregnancies within 24 hours to the sponsor using the Pregnancy Reporting Form. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator. There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. The investigator will therefore inform the subject of the potential risks to the fetus and discuss with the Sponsor as well as the subject if it is in the subject's best interest to continue or stop treatment with daratumumab. The effect of daratumumab on sperm is unknown. Therefore, pregnancy occurring in the partner of a male patient participating in the study should also be reported by the investigator within 24 hours of awareness to the sponsor by using the Pregnancy Reporting Form
Rational: To clarify PQC reporting procedure	
Section 8.4.5 Product Quality Complaints	Text was removed so as not to confuse that PQCs will be reported as SAEs (i.e. with SAE form) Text was added in order to clarify that PQCs will be reported using the PQC form.
Rational: To reconcile the pre-infusion drug administration guideline with study-specific procedures (dexamethasone as pre-infusion medication)	
Appendix 2	20 mg dexamethasone was added in the pre-infusion medications paragraph
Rational: To include guidelines for Prophylaxis against febrile episodes and healthcare related infections	
Appendix 2	Text was added proposing the use of prophylactic levofloxacin: "Prophylactic use of antibiotics is highly recommended due to the susceptibility of multiple myeloma patients to infections. Prophylactic administration of levofloxacin (500 mg P.O. daily; dose adjusted for renal function) during the first 3 cycles of treatment is recommended as it has shown to significantly reduce febrile episodes and deaths without increasing healthcare associated infections or carriage of key nosocomial pathogens"
Rational: To update the modified IMWG criteria to the most recent version	

Appendix 4	Instructions were included for measuring STP size "≥50% increase from nadir in SPD[7] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in the short axis" and the definition of STP was added in the footnote "SPD = sum of the products of the maximal perpendicular diameters of measured lesions" In note 4, the symbol for larger (>) was changed to larger or equal (≥).
Rationale: Added Appendix 7 to provide guidelines for classification of asthma as persistent asthma is an exclusion criterion	
Appendix 7	New section was added
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CKD	Chronic Kidney Disease
CMP	Clinical Monitoring Plan
CA	Competent Authority
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Federal Drug Administration
FISH	Fluorescent In Situ Hybridization
IAT	Indirect Antiglobulin Test
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	Infusion Related Reaction
ISS	International Staging System
MM	Multiple Myeloma
M-protein	Monoclonal Paraprotein
MRD	Minimum Residual Disease
TNT	Time to Next Therapy
MR	Minimal Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PomDex	Pomalidomide + Dexamethasone
PPS	Per Protocol Set
PQC	Product Quality Complaint
PR	Partial Response
SAE	Serious Adverse Event
sCR	Stringent Complete Response
SD	Stable Disease
sFLC	Serum Free Light Chain
sIFE	Serum Immunofixation
sPEP	Serum Protein Electrophoresis
STP	Soft Tissue Plasmacytoma
uIFE	Urine Immunofixation
uPEP	Urine Protein Electrophoresis
VGPR	Very Good Partial Response
WOCBP	Women OF Childbearing Potential

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice of the international conference on Harmonization (ICH E6) and all applicable laws and regulations. The Principal Investigators will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the accredited Independent Ethics Committee (IEC) and/or Competent Authority (CA), except where necessary to eliminate an immediate hazard to the trial participants.

PROTOCOL SUMMARY

Study Title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Methods: This is a multicenter, single arm, open-label phase 2 study.
Approximately 38 subjects will be enrolled to receive daratumumab + dexamethasone. Treatment cycles have a duration of 28 days. Subjects will receive treatment until disease progression or unacceptable toxicity. Drug administration and follow-up visits will occur more frequently for early cycles (weekly for the first 8 weeks, every two weeks for weeks 9-24 and then every 4 weeks). Disease evaluations will occur monthly and consist mainly of measurements of myeloma proteins. Other assessments may include bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin, and β2- microglobulin and albumin.
Assessment of myeloma response and disease progression will be conducted in accordance with the modified International Myeloma Working Group (IMWG) response criteria.
Assessment of renal response will be conducted in accordance with the International Myeloma Working Group (IMWG) renal response criteria.
Survival status and data of subsequent anti-myeloma treatment will be collected post-treatment.

Objectives: The primary objective of this study is to evaluate progression free survival (PFS) in patients with relapsed/refractory MM (RRMM) with renal impairment (RI).
The secondary objectives are the following:

- To evaluate Overall Response Rates (ORR)
- To evaluate Renal Response Rates (RRR)
- To evaluate duration of response (DoR) in patients with RI.
- To evaluate time to next therapy (TNT).
- To evaluate Overall Survival (OS).
- To assess the safety and tolerability of daratumumab with dexamethasone in patients with RRMM and RI.

Endpoints Primary endpoint: Progression-free survival
Secondary Endpoints:

- Overall response rate
- Renal Response Rates (RRR)
- Duration of response
- Time to next therapy
- Overall survival
- Safety (adverse events)

Population:

Inclusion criteria:

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure.
3. Subject must have documented multiple myeloma as defined by the criteria below:

   Monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy proven plasmacytoma.

   AND any or more of the following myeloma defining events:

   - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
     • Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
     • Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL)
     • Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
     • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
   - Any one or more of the following biomarkers of malignancy:
     • Clonal bone marrow plasma cell percentage ≥60%
     • Involved:uninvolved serum free light chain ratio ≥100
     • >1 focal lesions on MRI studies
4. Prior treatment with at least two lines of treatment that included both bortezomib- and lenalidomide-based regimens.
5. Documented evidence of progressive disease (PD) as defined by the modified IMWG criteria (see *Appendix 4*) on or after the last regimen if the patient responded to previous regimens.
6. Subjects must have measurable disease as defined by any of the following:
   - Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL (except for IgA subtype: ≥ 0.5 g/dL) or urine M-protein level ≥ 200 mg/24 hours; or
   - Light chain multiple myeloma: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free-light-chain ratio.
7. Renal impairment defined as eGFR < 30 ml/min/1.73 m^2 (calculated with the CKD-EPI formula, see section 7.1.1.9) or in need for dialysis. Patients who undergo intraperitoneal dialysis may also be included.
8. Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2.
9. Willingness and ability to participate in study procedures.

10. Reproductive Status
    a) Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drug and one within 24 hours prior to the start of study drug. Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy.
    b) Women must not be breastfeeding.
    c) WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for 3 months after cessation of study treatment.
    d) Males who are sexually active must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy. They must also agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 90 days post-treatment completion. The additional contraception of female partners of childbearing potential should also be considered.
    e) Male patients must not donate sperm for up to 90 days post treatment completion.
    f) Female patients must not donate eggs for up to 90 days post treatment completion.
    g) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, WOCBP will still undergo pregnancy testing as described in this section.

Phase:	II
Number of Sites enrolling participants:	The study will be conducted at 6 sites located in Greece and 2 sites located in Italy.
Description of Study Treatment:	Daratumumab will be given at a dose of 16 mg/kg administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Dexamethasone will be administered according to standard clinical practice. The recommended dose of dexamethasone is 40 mg (20 mg for patients > 75 years of age) orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Participant Duration:	Subjects will receive treatment until disease progression or unacceptable toxicity. Survival status and data of subsequent anti-myeloma treatment will be collected post-treatment.
Study Duration:	The maximum duration of the study is 37 months considering an accrual period of 24 months and a follow-up of the last patient for 13 months.

Key roles

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1. Background and Rationale

1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder that is characterized by the production of monoclonal immunoglobulin in the majority of patients and invasion of adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anemia and recurrent infections.

Based on 2009-2013 cases and deaths in the United States, the number of new cases of myeloma was 6.5 per 100,000 men and women per year. The number of deaths was 3.3 per 100,000 men and women per year. In 2013, there were an estimated 95,688 people living with myeloma in the U.S. Approximately 30, 300 people in the US are expected to receive a new diagnosis of MM in 2016 (1.8% of all new cancer cases) and 12, 650 are expected to die from MM.

A hallmark feature of multiple myeloma is the production of abnormal antibodies or M-proteins. The M-protein produced by the malignant plasma cells is an IgG in about 50%-54% of myeloma patients and an IgA in about 20%. Of patients producing either IgG or IgA, 40% also have Bence Jones proteinuria, i.e. the presence of free monoclonal kappa (κ) or lambda (λ) light chains in urine. In 15 to 20% of patients, plasma cells secrete only light chain protein (light chain myeloma)[1].

MM is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anemia due to kidney disease or suppression of erythropoiesis by cancer cells but sometimes also due to iron deficiency. These signs and symptoms are commonly denoted as CRAB (Calcium elevation, Renal dysfunction, Anemia, Bone destruction).

The terms used to define patient populations studied in clinical trials have been standardized based on the American Society of Hematology–FDA panel on endpoints in myeloma [2]:

- **Refractory myeloma**: Disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response (MR) or development of progressive disease (PD) while on therapy.
  - Relapsed and refractory myeloma: Disease that is nonresponsive while on salvage therapy, or progresses within 60 days of the last therapy in patients who had achieved MR or better at some point previously before progressing in their disease course.
  - Primary refractory myeloma: Disease that is nonresponsive in patients who have never achieved a MR or better with any therapy.
- **Relapsed myeloma**: Previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory myeloma” categories.

Currently approved treatments for patients with relapsed/refractory MM include proteasome inhibitors (PI) (e.g., bortezomib, carfilzomib), immunomodulatory drugs (thalidomide, lenalidomide, or pomalidomide), histone deacetylase inhibitors and monoclonal antibodies (elotuzumab, daratumumab)[3]. However, there is no cure, and current therapies only slow disease progression, prolong survival, and reduce symptoms. Although recent advances in the development of targeted therapeutics

and stem cell transplantation have improved overall and event-free survival, the great majority of patients with myeloma will relapse and experience disease progression.

1.2 Daratumumab

Daratumumab is a human IgGκ monoclonal antibody that targets CD38, an important immunotherapy target due to its high expression on malignant plasma cells and low expression on other normal lymphoid and myeloid cells, as well as its being an important modulator of intracellular signaling.

The main anti-myeloma effect of daratumumab is attributed to its antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity[4]. An additional mode of action appears to be the induction of apoptosis via FcR-mediated crosslinking [5]. Further experiments using a Burkitt's lymphoma (Daudi) cell line mixed with human macrophages in the presence of daratumumab showed daratumumab-specific antibody-dependent cellular phagocytosis that resulted in a 50% reduction in tumor cells. Dose-dependent daratumumab-specific phagocytosis was also observed with patient-derived MM cell lines transduced with CD38[6]. See the investigator's brochure for more details.

Daratumumab in combination with dexamethasone is not approved for the indication under study. In November 2015, daratumumab (DARZALEX®) as monotherapy was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or who are double-refractory to a PI and an immunomodulatory agent. This indication was approved under accelerated approval based on the results of the pivotal open-label Phase 2 MMY2002 (SIRIUS) study in which treatment with single-agent daratumumab resulted in an Overall Response Rate (ORR) of 29.2 percent (95% CI; 20.8, 38.9). Median duration of response was 7.4 months (95% CI, 5.5-not estimable). Ninety-five percent of patients in the study were double refractory to a PI and IMiD and patients had received a median of five prior lines of therapy. No patients discontinued treatment due to infusion-related reactions (IRR) and 4.7 percent of patients discontinued treatment due to adverse events (AEs), none of which were considered drug-related. Stringent complete response (sCR) was reported in 2.8 percent of patients, very good partial response (VGPR) in 9.4 percent of patients, and partial response (PR) in 17 percent of patients. The most common adverse events, which occurred in more than 20 percent of patients, were fatigue, anemia, nausea, thrombocytopenia, back pain, neutropenia and cough[7].

These results were supported by those of the Phase 1/2 GEN501 study, which confirmed daratumumab as an effective single-agent treatment option for patients with relapsed and refractory myeloma, especially those with disease that is otherwise resistant to other treatments or those who have unacceptable side effects from other treatments. Daratumumab had an acceptable safety profile, with infusion-related reactions of grade 1 and 2 across the two dose cohorts (except for one patient with infusion-related reactions of grade 3), including mild and transient bronchospasm, headache, dyspnea, and fever. Most events occurred during the first infusion, and no patient discontinued treatment because of an infusion-related reaction. Daratumumab demonstrated a 36 percent ORR in patients treated with a 16 mg/kg dose, with responses improving (or "deepening") over time[8].

In May 2016, the European Commission granted approval of daratumumab for the monotherapy of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy.

The FDA (in November 2016) and the European Commission (in April 2017) have granted approval of daratumumab in combination with lenalidomide (an immunomodulatory agent) and dexamethasone, or

bortezomib (a proteasome inhibitor [PI]) and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy, based on data from two Phase 3 studies: MMY3003 and MMY3004.

The MMY3003 (POLLUX) trial is a Phase 3, multinational, open-label, randomized, multicenter, active-controlled study of 569 patients with multiple myeloma who have received a median of one prior line of therapy. Patients were randomized to receive either daratumumab combined with lenalidomide and dexamethasone (DARA-LEN-DEX), or lenalidomide and dexamethasone alone (LEN-DEX). Participants were treated until disease progression, unacceptable toxicity or if they had other reasons to discontinue the study. The trial was unblinded after meeting its primary endpoint of improved Progression Free Survival (PFS) in a pre-planned interim analysis. In fact, the DARA-LEN-DEX combination achieved a 63 percent reduction in the risk of disease progression or death (PFS) compared to LEN-DEX alone (Hazard Ratio [HR] = 0.37; 95 percent CI, 0.27-0.52; p<0.0001). Additionally, daratumumab significantly increased the overall response rate (ORR) [93 percent vs. 76 percent, p<0.0001] and doubled the rate of complete responses (CR) or better [43 percent vs. 19 percent, p<0.0001], as well as the rate of very good partial responses (VGPR) or better [76 percent vs. 44 percent, p<0.0001]. Overall, the safety of the daratumumab combination therapy was consistent with the known safety profile of daratumumab monotherapy and lenalidomide plus dexamethasone, respectively. Daratumumab-associated infusion-related reactions (48 percent of patients) were mostly Grade 1/2 (Grade 3/4: 5 percent/0 percent), and most (92 percent) occurred during the first infusion[9].

MMY3004 (CASTOR) is a Phase 3, multinational, open-label, randomized, multicenter, active-controlled study that enrolled 490 patients with multiple myeloma who received a median of two prior lines of therapy. Thirty-three percent of patients were refractory to an immunomodulatory agent, and 32 percent were refractory to their last line of prior therapy. Patients were randomized to receive either daratumumab combined with subcutaneous bortezomib and dexamethasone (DAR-BOR-DEX) (n=251) or bortezomib and dexamethasone alone (BOR-DEX) (n=247). Participants were treated with daratumumab until disease progression or unacceptable toxicity. The DAR-BOR-DEX combination demonstrated a 61 percent reduction in the risk of disease progression or death (PFS) compared to bortezomib and dexamethasone alone (Hazard Ratio (HR) = 0.39; 95 percent CI (0.28-0.53), p<0.0001). As in the POLLUX study, daratumumab significantly increased the overall response rate (ORR) [83 percent vs. 63 percent, p<0.0001] and doubled CR or better rates [19 percent vs. 9 percent, p<0.0012], including doubling rates of VGPR rates [59 percent vs. 29 percent, p<0.0001][10].

An ongoing 4-arm, multicenter, Phase 1b study is currently evaluating the safety and efficacy of daratumumab combined with pomalidomide plus dexamethasone. The study has so far concluded that the addition of daratumumab was well tolerated and did not result in additional toxicities except for infusion reactions. Deep and durable responses were observed quickly along with a high response rate[11].

1.3 Renal Impairment in Myeloma

About 20-40% of patients with multiple myeloma (MM) will present with some degree of renal impairment (RI) and about 25% of patients will experience RI later on, during the course of their disease. Moderate and severe RI is associated with poorer overall survival (OS) and higher risk of early death. Outcomes have however improved with the introduction of novel agents. Many patients can achieve a recovery of their renal function with the prompt initiation of the appropriate anti-myeloma therapy.

The older IMWG criteria MM had set a sCr level of 2 mg/dl as the cut-off value to define symptomatic MM due to RI[12]. Patients may however already have renal disease due to their monoclonal gammopathy and creatinine is not sensitive in detecting early-stage RI. More sensitive tools could allow early RI detection and assessment of the probability of renal function restoration (Kastritis, Terpos et al. 2013). Estimated glomerular filtration rate (eGFR) is more reliable and accurate. A decrease of eGFR by ≥ 35% within 1 year, without other identifiable cause, is an indication for therapy[13]. The use of eGFR is recommended when renal function remains rather stable. Tools like RIFLE (risk, injury, failure, loss and end-stage kidney disease) and Acute Kidney Injury Network (AKIN) criteria are more sensitive for the evaluation of AKI, but data in MM patients is limited[14].

Treatment of MM aims at symptomatic improvement including renal function restoration. Normalization of sCr or eGFR increase by at least one or two CKD stages have been used as measures of renal response [12,15-17]. The 2016 IMWG consensus recommends using the Chronic Kidney Disease Epidemiology Collaboration preferably or the MDRD or CKD-EPI formulae [12,15].

The recommended first choice regime in newly diagnosed MM patients incorporates a bortezomib-dexamethasone backbone, which seems to achieve the higher and most rapid rates of renal recovery, with or without a third active agent. Thalidomide and lenalidomide are alternative options in selected patients. New drugs are additional treatment options for patients with relapsed or refractory disease, including carfilzomib, pomalidomide and monoclonal antibodies, but still data are limited in patients with RI. High dose therapy with autologous stem cell transplantation should be offered in otherwise eligible patients, despite RI, even if dialysis is required. The role of high cut-off hemodialysis membranes is still under investigation and more data are needed before these are incorporated in everyday clinical practice.

Renal recovery rates are lower in patients with RRMM compared to newly diagnosed (NDMM) patients. In patients with RRMM and RI, the use of IMiDs (lenalidomide, pomalidomide) or other agents, (carfilzomib, elotuzumab, daratumumab) may be considered if resistance to bortezomib has been established. Pomalidomide seems to have a favorable safety profile in patients with RI but data on renal recovery are yet to be presented. The choice depends on previous lines of therapy and potential sensitivity/resistance. Regarding the role of carfilzomib, although the pharmacokinetics indicate that the drug can be used without dose adjustments (Badros, Vij et al. 2013), there is insufficient data on the efficacy in terms of renal recovery and safety in patients with severe RI. Elotuzumab is a potential alternative and safe option but more data is required on safety and efficacy and any potential to reverse RI. Panobinostat should be given in combination with bortezomib and dexamethasone and only in patients naïve or sensitive to prior bortezomib, however, there are no data for patients with RI.

For patients with relapsed/refractory MM who present with new onset or pre-existing MM-related renal dysfunction, the treatment options may be quite limited especially if they have been exposed or are refractory to proteasome inhibitors and IMiDs. Daratumumab may be the major treatment option for such patients, however, there are limited data for the efficacy and safety of daratumumab in patients with severe renal dysfunction. As a monoclonal antibody, the clearance of daratumumab is not involving the kidneys and the degree of renal dysfunction is not expected to alter PKs or PDs of the drug.

No formal studies of daratumumab in patients with renal impairment have been conducted. As an IgG1κ monoclonal antibody, renal excretion metabolism of intact daratumumab is unlikely to represent major elimination route. A population PK analysis was performed based on pre-existing renal function data in patients receiving daratumumab, including 71 with normal renal function (creatinine clearance

[CRCL] ≥ 90 mL/min), 78 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 68 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 6 with severe renal impairment or end stage renal disease (CRCL< 30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function. Thus, based on this population pharmacokinetic (PK) analysis[18] no dosage adjustment is necessary for patients with renal impairment.

Combining the efficacy of daratumumab in patients with relapsed refractory MM, and the lack of effect of renal dysfunction on daratumumab PKs, it is expected that daratumumab with dexamethasone is going to be a safe and effective therapy for patients with relapsed/refractory MM and renal impairment.

1.4 Rationale

Daratumumab has proven efficacy in patients with relapsed or refractory myeloma, independently of prior exposure to bortezomib (or other PIs), IMiDs (thalidomide, lenalidomide or pomalidomide) or alkylating agents[7,19]. Single agent daratumumab has also shown to induce rapid myeloma responses, with a median time to at least PR of 0.9 months (1 cycle of therapy). Thus it is expected that daratumumab will be able to induce rapid responses in a significant proportion of heavily pretreated patients with relapsed or refractory which will have been exposed to bortezomib and lenalidomide and who will have renal dysfunction with a eGFR< 30 ml/min/1.73 m^2, which defines severe renal impairment. It has been shown that rapid myeloma response is the stronger predictor of a subsequent renal function improvement and renal response.

2. Potential risks and benefits

2.1 Known potential risks

- **Daratumumab**

As of 15 November 2019, approximately 5528 clinical trial patients with multiple myeloma and various other conditions have been treated with daratumumab intravenous or subcutaneous, alone or in combination with other therapies. Daratumumab is approved for the treatment of MM, yet data on the treatment of patients with renal impairment are very limited; moreover, not all the possible side effects and risks related to daratumumab are known and new side effects may occur. The following side effects are observed when daratumumab was given via an intravenous infusion for patients with multiple myeloma, either alone or in combination with other drugs:

- **Very common (more than 1 in 10 patients)**
  - Infusion related reaction (see below)
  - Infection of the upper respiratory tract such as nose, sinuses throat or upper airway
  - Infection of the lower airway (bronchitis)
  - Infection of the lung (pneumonia)
  - Low platelets
  - Low red blood cells
  - Low white blood cells (including neutrophils and lymphocytes)
  - Decreased appetite
  - Abnormal sensation including numbness/tingling of hands, feet or limbs (neuropathy, paresthesia)
  - Headache
  - High blood pressure

- Cough
- Shortness of breath, including wheezing
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Muscle spasms
- Swelling of hands, feet or limbs
- Fatigue, or lack of energy
- Fever
- Back pain
- Sleeplessness (insomnia)
- Joint pain

- **Common (1 to 10 in 100 patients)**
  - Urinary tract infection
  - Flu like symptoms
  - Shingles (Herpes Zoster)
  - Sepsis (a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
  - High blood glucose levels
  - Low blood calcium levels
  - Loss of body fluids, also known as dehydration
  - Irregular heartbeat
  - Chills
  - Low oxygen in the body
  - Swelling of the throat
  - Fluid in lungs (pulmonary edema)
  - Dizziness
  - Inflammation of the pancreas
  - Rash, itchy skin
  - Muscular pain in the chest
- **Uncommon (1 to 10 in 1,000 patients)**
  - Liver infection (hepatitis) in those patients who are carriers of the hepatitis B virus
  - Interference with pre-transfusion blood testing (See Blood Type and IAT, in section 7.2.1)

- **Infusion–related reactions (IRR)**

Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, low blood pressure or high blood pressure and fluid in the lungs (pulmonary edema). Most of the observed infusion-related reactions so far were mild or moderate, and ended by temporarily stopping the infusion and giving medicines to treat the side effect. Severe reactions have occurred, including narrowing and obstruction of the respiratory airway (bronchospasm), low oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid in the lungs (pulmonary edema). See *Appendix 2* for information regarding the management of IRRs and recommendations concerning the use of pre- and post-infusion medication.

- **Dexamethasone**

Dexamethasone is a synthetic pregnane corticosteroid and derivative of cortisol (hydrocortisone) and is also known as 1-dehydro-9α-fluoro-16α-methylhydrocortisone or as 9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

The following events are observed when dexamethasone was given via an intravenous infusion or orally, either alone or in combination with other drugs:

Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain, aggravation of peptic ulcers.

Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.

Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

Neurological: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.

Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis.

Ocular: Cataracts, increased intraocular pressure, exophthalmos.

Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

Hematologic: Leukocytosis.

Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

2.2 Known Potential Benefits

The prognosis of multiple myeloma patients who become refractory to lenalidomide and bortezomib is very poor, indicating the need for new therapeutic strategies for these patients. Daratumumab has already shown marked activity as a monotherapy in heavily pre-treated patients. Its Breakthrough Therapy Designation from the FDA for patients who have been exposed to lenalidomide and bortezomib, highlights the potential clinical benefit of daratumumab therapy for the treatment of patients with relapsed/refractory multiple myeloma. The presence of sever renal dysfunction is an additional adverse feature of myeloma and requires immediate management, with effective, rapidly acting therapy. In this context daratumumab offers the most active therapy that is available for patients who have already been exposed and are relapsed or refractory to proteasome inhibitors and IMIDs and who present with severe renal impairment. Daratumumab has additional advantages related to the lack of effect of the degree of renal dysfunction or dialysis to PKs and pharmacodynamics of the monoclonal antibody. Thus, daratumumab with dexamethasone is likely to provide significant clinical benefit to subjects with relapsed or refractory multiple myeloma and renal impairment.

3. Objectives and Purpose

The purpose of this study is to evaluate the effects of daratumumab with dexamethasone in subjects with relapsed or refractory multiple myeloma and renal impairment.

3.1 Primary objective

The primary objective of this study is to evaluate progression free survival (PFS) in subjects with relapsed or refractory multiple myeloma and renal impairment treated with daratumumab and dexamethasone.

3.2 Secondary objectives

The secondary objectives of the study are the following:

- To evaluate Overall Response Rates (ORR)
- To evaluate Renal Response Rates (RRR)
- To evaluate duration of response (DoR) in patients with RI.
- To evaluate time to next therapy (TNT).
- To evaluate Overall Survival (OS).
- To assess the safety and tolerability of Daratumumab with dexamethasone in patients with RRMM and RI.

4. Study Design and Study End points

4.1 Description of the Study Design

This is a multicenter, Phase 2, single arm, open-label study evaluating daratumumab with dexamethasone (DaraD) in subjects with relapsed or refractory multiple myeloma who have received at least two prior lines of treatment, with both bortezomib- and lenalidomide-based regimens and have renal impairment.

Approximately 38 subjects located in approximately 5 centers in Greece and 2 centers in Italy will receive daratumumab with dexamethasone. Treatment cycles have a duration of 28 days:

Daratumumab will be given at a dose of 16 mg/kg administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Subjects will receive pre-infusion medications before infusions to mitigate potential infusion reactions.

Dexamethasone will be administered according to standard clinical practice and at a recommended total dose of 40 mg weekly (20 mg weekly for patients >75 years of age).

Subjects will receive treatment until disease progression or unacceptable toxicity.

Drug administration and follow-up visits will occur more frequently for early cycles (e.g., weekly or bi-weekly) (see *Table 7.2*). Disease evaluations will occur monthly and consist mainly of measurements of myeloma proteins and renal function indices. Other parameters may include bone

marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin, and β2-microglobulin and albumin.

Assessment of myeloma response and disease progression will be conducted in accordance with the modified International Myeloma Working Group (IMWG) response criteria (see *Appendix 4*).

Assessment of renal response will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria (see Appendix 5).

Survival status and data of subsequent anti-myeloma treatment will be collected post-treatment.

The maximum duration of the study is of 37 months considering an accrual period of 24 months and a follow-up of the last patient of 13 months.

4.1.1 Primary Endpoint

- Progression-free survival

4.1.2 Secondary Endpoints

- Overall response rate
- Renal Response rate
- Duration of response
- Time to next therapy
- Overall survival
- Safety (adverse events)

5. Study enrollment and withdrawal

All criteria MUST be met to be included in the study.

5.1 Participant Inclusion Criteria

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure.
3. Subject must have documented multiple myeloma as defined by the criteria below:

   Monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy proven plasmacytoma. AND any or more of the following myeloma defining events:
   - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
     - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
     - Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μ mol/L (>2 mg/dL)
     - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
     - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
   - Any one or more of the following biomarkers of malignancy:
     - Clonal bone marrow plasma cell percentage ≥60%
     - Involved:uninvolved serum free light chain ratio ≥100
     - >1 focal lesions on MRI studies

4. Prior treatment with at least two lines of treatment that included both bortezomib- and lenalidomide-based regimens.
5. Documented evidence of progressive disease (PD) as defined by the modified IMWG criteria (see *Appendix 4*) on or after the last regimen if the patient responded to previous regimens.
6. Subjects must have measurable disease as defined by any of the following:
    - Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL (except for IgA subtype: ≥ 0.5 g/dL) or urine M-protein level ≥ 200 mg/24 hours; or
    - Light chain multiple myeloma: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free-light-chain ratio.
7. Renal impairment defined as eGFR < 30 ml/min/1.73 m^2 (calculated with the CKD-EPI formula, see section 7.1.1.9) or in need for dialysis. Patients who undergo intraperitoneal dialysis may also be included.
8. Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2.
9. Willingness and ability to participate in study procedures.
10. Reproductive Status
    a) Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drug and one within 24 hours prior to the start of study drug. Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy.
    b) Women must not be breastfeeding.
    c) WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for 3 months after cessation of study treatment.
    d) Males who are sexually active must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy. They must also agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 3 months post-treatment completion.
    e) Male patients must not donate sperm for up to 90 days post treatment completion.
    f) Female patients must not donate eggs for up to 90 days post treatment completion.
    g) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, WOCBP will still undergo pregnancy testing as described in this section.

    Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Subjects must agree to the use of two methods of contraception, with one method being highly effective (tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and the other method being additionally effective (male latex or synthetic condom, diaphragm, or cervical cap).

5.2 Participant Exclusion Criteria

1. Previous therapy with daratumumab or other anti-CD38 therapy.
2. Anti-myeloma treatment within 2 weeks prior to Cycle 1, Day 1.
3. Cumulative dose of corticosteroids greater than or equal to the equivalent of 140mg prednisone for ≥ 4 days or a dose of corticosteroids greater than or equal to the equivalent of 40 mg/day of dexamethasone for ≥ 4 days within the 2-week period prior to Cycle 1, Day 1.

4. Previous allogenic stem cell transplant; or Autologous Stem Cell Transplantation (ASCT) within 12 weeks before Cycle 1, Day 1.
5. Clinical signs of meningeal involvement of multiple myeloma.
6. Subject has either of the following:
    a. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
    b. Known moderate or severe persistent asthma (see Appendix 7), within 2 years from C1D1, or currently has uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.
7. Clinically significant cardiac disease, including:
    a) Myocardial infarction within 1 year, or unstable or uncontrolled condition (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV).
    b) Uncontrolled cardiac arrhythmia (CTCAE Grade 2 or higher) (atrial fibrillation with controlled ventricular rate is allowed) or clinically significant ECG abnormalities.
    c) ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec.
8. Any of the following:
    a. Known active hepatitis A
    b. Patient is seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

    c. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
9. Known to be seropositive for human immunodeficiency virus (HIV).
10. Amyloidosis, or any prior or concurrent malignancy, except for the following:
    a) Adequately treated basal cell or squamous cell skin cancer.
    b) Any cancer (other than in-situ) from which the subject has been disease-free for 3 years prior to study entry.
11. Any of the following laboratory test results during Screening:
    a) Absolute neutrophil count $\leq 1.0 \times 10^9$/L;
    b) Hemoglobin level ≤ 7.5 g/dL (≤ 4.65 mmol/L);
    c) Platelet count $< 75 \times 10^9$/L in patients in whom < 50% of bone marrow nucleated cells are plasma cells and $< 50x10^9$/L in patients in whom more than 50% of bone marrow nucleated cells are plasma cells;
    d) Alanine aminotransferase level ≥ 2.5 times the upper limit of normal (ULN);
12. Pregnant or nursing women.

5.3 Participant Withdrawal or termination

5.3.1 Reasons for Withdrawal or Termination

Every patient has the right to discontinue study participation at any time, for any reason, and every patient may be discontinued from the study for any reason beneficial to his/her wellbeing.

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent.
- Any adverse event (AE), laboratory abnormality or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Progressive Disease.
- Grade 4 Infusion Related Reactions (IRR) to daratumumab or in case of 3 recurrences of a ≥ Grade 3 IRR during one infusion (*see Appendix 2*).
- When the study ends/is terminated.

5.3.2 Handling of Participant Withdrawals or Termination

All patients, except those who withdraw consent, will be followed up according to the study procedures. Subjects should be encouraged to continue participation in the trial until determination of disease progression. Those who discontinue study therapy before progression should allow the collection of necessary laboratory results until disease progression criteria are fulfilled. If the study drug is discontinued prior to disease progression, the reason for the discontinuation must be documented in the eCRF.

If lost to follow-up, the investigator should contact the patient or a relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal.

5.4 Premature Termination or Suspension of Study

The study can be terminated for any reason and at any time by the Sponsor. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient. All measures will be adopted to ensure the safeguarding of the patient's interests.

6. Study Treatment

6.1 Study treatments and Control Description

6.1.1 Formulation, Appearance, Packaging, and Labeling

This is an open-label study. Daratumumab is considered investigational treatment and will be supplied free of charge by the sponsor. Dexamethasone will be obtained by the Sponsor according to specific regulatory requirements. All study treatments used in this study, along with their packaging and labeling, have been approved by local Health Authorities.

Investigational Medicinal Products (IMP):

- Daratumumab (Darzalex®)

Daratumumab 20 mg/mL concentrate for solution for infusion. The solution is colorless to yellow.

Each 20 mL vial contains 400 mg of daratumumab (20 mg daratumumab per mL).

- Dexamethasone

Dexamethasone vials or tablets of various strengths and packaging configuration for oral administration.

6.1.2 Product Storage and Stability

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will be in the local language and comply with the legal requirements of each country.

Daratumumab vials should be stored at 2°-8° C in its original package to protect from light.

After dilution, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should be no more than 24 hours at refrigerated conditions (2°-8° C) protected from light, followed by 15 hours (including infusion time) at room temperature (15°-25° C) and room light (see *Appendix 1)*.

Dexamethasone does not require any special storage conditions.

6.1.3 Preparation

Daratumumab is to be prepared according to the instructions in *Appendix 1*.

6.1.4 Dosing and Administration

Daratumumab

Daratumumab will be given at a dose of 16 mg/kg administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter.

See *Appendix 2* for guidelines for the intravenous infusion of daratumumab and for pre-infusion and post-infusion medications to be given to mitigate potential infusion reactions.

Infusion-related reactions (IRRs) have been reported in approximately half of all patients treated with daratumumab. Patients should therefore be monitored throughout the infusion and the post-infusion period. The majority of IRRs occurred at the first infusion and were Grade 1-2. Four percent of all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs, as per local practice.

See the Summary of Product Characteristics for more details about daratumumab.

Dexamethasone

The recommended dose of dexamethasone is 40 mg (20 mg for patients > 75 years of age) orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle. On the days that dexamethasone dosing is concurrent with the daratumumab administration, dexamethasone will be administered at a dose of 40 mg IV or PO prior to the daratumumab infusion (IV: approximately 1 hour before, PO: 1-3 hours before) and will serve as both the pre-medication and the therapeutic dose (i.e. no other corticosteroids can administered as pre-medication on the days that dexamethasone dosing is concurrent).

See the Summary of Product Characteristics for more details about dexamethasone.

6.1.5 Dose Adjustments/Modifications/Delays

- Daratumumab

No dose adjustment or modification is permitted for daratumumab. Infusion reactions may lead to the interruption of IV daratumumab administration. Pre-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment.

For IRRs of any grade/severity, immediately interrupt daratumumab infusion and manage symptoms.The management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab as outlined below.

- Grade 1-2 (mild to moderate): Once the patient's condition is stable, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour.

- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate. The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab if the patient experiences a ≥ Grade 3 infusion-related symptom at the subsequent infusion.

- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

See *Appendix 2* for further guidelines concerning the administration of daratumumab.

See the Summary of Product Characteristics for more details about daratumumab

Daratumumab Toxicity Management

In the event of one of the following toxicities the infusion should be held to allow for recovery. The criteria for a dose delay are:

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

Daratumumab treatment should be resumed when the toxicity has resolved to Grade 2. If daratumumab administration does not commence within the prespecified window (Table 6.1) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

TABLE 6.1: DARATUMUMAB-RELATED TOXICITY MANAGEMENT DOSE DELAY/RESUMPTION SCHEDULE

Cycle	Frequency	Resumption window
Cycles 1 and 2	Weekly (QW)	>3 days next planned weekly dosing date
Cycles 3 to 6	Biweekly (Q2W)	>7 days next planned biweekly dosing date
Cycles 7 on	Every 4 weeks (Q4W)	>14 days next planned every 4 weeks dosing date

Any dose hold of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. Dose holds of more than 28 days for other reasons should be discussed with the Sponsor.

Interruption of Missed Doses

A daratumumab dose held for more than 3 days from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects missing ≥3 consecutive planned doses of daratumumab

for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

- Dexamethasone

Instructions for dose modifications of dexamethasone are shown in the table below:

Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ 3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

6.1.6 Duration of Therapy

Treatment with study drug continues until disease progression, unacceptable toxicity (adverse event related to study drug), or the subject meets other criteria for discontinuation of study drug outlined in *Section 5.3* and for a maximum period of 37 months.

6.2 Study treatment Accountability Procedures

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, will maintain accurate records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). Monitoring of drug accountability will be performed by the field monitor during the study conduct and a copy of the final drug accountability and reconciliation log will be provided by the investigator(s) at the completion of the trial.

7. Study procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Efficacy Assessments

The primary endpoint of this study is Progression Free Survival (PFS). Secondary efficacy endpoints are Overall Survival (OS), Overall Response Rate (ORR), Renal Response Rate (RRR), duration of response and time to next therapy.

Response or disease progression will be assessed by the Investigator based on the analysis of serum and urine protein electrophoresis (sPEP and uPEP), serum and urine immunofixation (sIFE, uIFE), serum free light chain protein (sFLC), imaging and bone marrow assessments as per IMWG guidelines (see *Appendix 4*). If the patient does not have documented disease progression as defined in *Appendix 4* at the time of study drug discontinuation, then tumor assessments must continue to be performed according to the same schedule shown in *Table 7.2* until disease progression even if a subsequent anti-myeloma treatment is started prior to disease progression.

Assessment of renal response will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria, based on eGFR calculated by the CKD-EPI formula.

All study assessments and laboratory tests will be performed according to standard clinical practice and as clinically indicated.

Assessments performed at external laboratories may be accepted as per institutional practice.

Disease assessments are shown in Table 7.1.

Table 7.1 – Disease assessments

M-protein by electrophoresis Serum (sPEP), Urine (uPEP)	Screening and baseline Day one of each cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
M-protein by immunofixation Serum (sIFE), Urine (uIFE)	Screening and baseline End of treatment Post-treatment follow-up every 4 weeks As needed to confirm CR (when PEP is 0 or non-quantifiable)
Serum free light chain sFLC	Screening and baseline Day one of each cycle (for patients that have no measurable serum or urine M-protein) As needed to confirm sCR End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
Clinical assessment of soft tissue plasmacytoma (STP)	Screening and baseline Day one of each cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
CT/MRI assessment of STP	If present or suspected, at screening and as clinically indicated.
Plasma cell count in bone marrow	At screening and during the study as clinically indicated to substantiate CR and PD for patients with non-measurable disease by M protein in serum and urine as well as by FLC.
Skeletal survey by X-ray and/or CT/MRI	At screening and as clinically indicated, CT/MRI in case of newly symptomatic areas with no X-ray finding.
Serum Creatinine (for patients not on dialysis)	Screening and baseline Weekly in the first two cycles then every two weeks for cycles 3-6 and then on day one of each cycle End of treatment Post-treatment follow-up every 4 weeks
Corrected calcium	Screening and baseline Day one of each cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
MRD by means of EuroFlow next generation cytometry	If required for confirmation of sCR, upon confirmed CR/sCR and thereafter every 6 months as long as CR/sCR is maintained.

Confirmation of response

Based on IMWG criteria, response must be confirmed for all categories other than SD in order to rule out errors. A consecutive assessment can be performed at any time and confirmation should be obtained by M-protein assessments.

- Bone marrow assessments do not need to be repeated, but at least one bone marrow assessment is required to substantiate a CR.
- If imaging studies were done, they need to rule out new lytic bone lesions.
- Should confirmation assessments reveal a better category (e.g. VGPR after PR), the response category of the previous assessment will be considered as confirmed (PR).
- Should confirmation assessments reveal a worse category, (e.g. VGPR after CR), the response category of the subsequent assessment will be considered as confirmed (VGPR).
- Should repeated measurements of a variable result in more values, the worst assessment is to be considered.

Laboratory confirmation of progressive disease

A diagnosis of PD requires confirmation if determined based on M-protein measurement. Confirmation of an increase in M-protein or FLC should be obtained as soon as possible.

Sponsor confirmation of progressive disease

A diagnosis of progressive disease (that is also confirmed with a consecutive assessment if based on M-protein/serum FLC levels) must be reported, via email, to the sponsor's Medical Reviewer within 1 working day using the Progressive Disease Notification Form together with all supporting documentation for the diagnosis. The Medical Reviewer will check that the investigator's assessment of PD is in line with the IMWG criteria and will provide a confirmation on the same form and return it via email to the site. In the case that the investigator's assessment is not deemed in line with the IWMG criteria, the Medical Reviewer will provide comments in the relevant section of the notification form and may also contact the investigator to discuss the subject further.

Study treatment discontinuation and start of subsequent anti-myeloma therapy should occur only after sponsor confirmation of PD.

7.1.1.1 Serum and urine sample collection for M-protein assessment by PEP and IFE

Response to treatment is based on M-protein levels in serum and urine. Two methods may be used:

- Protein electrophoresis (PEP) provides quantitative measurements.
- Immunofixation (IFE) provides qualitative measurements (present/absent). It is a more sensitive method than PEP and is used to confirm the absence of M-protein by PEP (CR).

- Serum and urine immunofixation is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
- Subjects with measurable disease in sPEP will be assessed for response based on sPEP and not by the serum FLC assay.
- Subjects with measurable disease in both sPEP and uPEP will be assessed for response based on these two tests and not by the serum FLC assay.

Blood (serum) and 24-h urine for M-protein assessment will be collected as indicated in *Table 7-2*.

Analysis by IFE will be done for all patients at screening and baseline, and thereafter only in case of disappearance of M-protein by PEP.

All samples (blood, urine, bone marrow, etc.) are collected and analyzed according to standard clinical practice.

7.1.1.2 Free Light Chain (FLC) protein assessment

The serum FLC assay measures free kappa light chain (0.33-1.94 mg/dL or 3.3-19.4 mg/L) and free lambda light chain (0.57-2.63 mg/dL or 5.7-26.3 mg/L). The FLC ratio is defined as the kappa serum level divided by the lambda serum level. Lambda is the involved light chain if FLC ratio < 0.26. Kappa is the involved light chain if FLC ratio of > 1.65.

The FLC ratio is considered Normal if FLC ratio is within 0.26-1.65, and Abnormal if FLC ratio is <0.26 or >1.65.

FLC serves to monitor disease status when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable (i.e., serum M-protein < 0.5 g/dL (5 g/L) or urine M-protein < 200 mg (0.2 g) per 24 hours) and to identify sCR if CR criteria are met.

Blood (serum) for FLC assessment will be collected as indicated in *Table 7-2*. FLC will be analyzed only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR.

7.1.1.3 Plasma cell count in bone marrow by local assessment

A bone marrow (BM) aspirate/biopsy for plasma cell quantification will be collected as indicated in *Table 7-2* and the percentage of plasma cells will be determined by using cytological/histological examination. Either BM aspirate or biopsy can be used for this assessment, but the same method should be used throughout the trial.

A bone marrow aspirate and/or biopsy should be performed for every patient at screening. As the procedure is invasive, post-baseline assessments should be performed for confirmation of CR/sCR or, if clinically indicated, at time of suspected disease progression or end of treatment.

7.1.1.4 Assessment of Soft Tissue Plasmacytoma (STP)

Clinical assessment by investigator

The investigator should perform a clinical exam to assess the presence of STP at screening and baseline, on day one of each cycle, at end of treatment and during post-treatment follow-up.

If suspicion of a STP, not present at screening, arises during the study, a CT or MRI must be performed immediately.

- CT/MRI
  - Screening: A CT/MRI will be performed at screening within 21 days prior to start of study treatment if there is evidence of presence of an STP from the clinical examination or documented presence from previous imaging assessments. Any imaging assessments already completed during the regular work-up of the patient within 42 days prior to start of treatment can be considered as the baseline images.
  - Post-baseline: Assessments should be performed using the same imaging technique used at baseline.

- If STP is present at baseline, a CT/MRI should be performed every 12 weeks (+/- 7 days) until disease progression.
- If STP is not present at baseline, but there is a suspicion of STP and/or disease progression (based on clinical exam or symptoms) a CT/MRI should be performed promptly to confirm suspicion.

Lesion size will be measured as the sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions.

All tumor measurements must be made in millimeters. Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning or MRI.

7.1.1.5 Skeletal survey

A skeletal survey is to be performed by conventional radiography for osteolytic disease within 21 days prior to Cycle 1 Day 1 in all subjects. The survey will be performed during the study if clinically indicated. Use of conventional or low dose CT scan (i.e., of the spine) or MRI is acceptable. If imaging is performed on treatment for assessment of progression, the same imaging technique as the one used at screening must be used. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On-treatment survey should record whether there is an increase in the number or size of lytic lesions. Any imaging assessments already completed during the regular work-up of the patient within 42 days prior to start of treatment can be considered as the baseline images.

7.1.1.6 Minimal residual disease (MRD) by means of next generation flow cytometry (EuroFlow protocol).

The EuroFlow-International Myeloma Foundation (IMF) next generation flow MRD approach provides a fast, highly applicable, ultrasensitive, standardized and accurate approach for the assessment of MRD in bone marrow samples from MM patients. MRD will be analyzed upon confirmed complete response and every 6 months thereafter until progression.

7.1.1.7 Corrected calcium

Corrected calcium in serum for determination of hypercalcemia as part of response assessment will be evaluated on day one of each cycle until disease progression using the following formula:

Corrected Calcium, mg/dL = (0.8 x [Normal Albumin, g/dL - Subject's Albumin, g/dL] + Serum Ca, mg/dL

7.1.1.8 Cytogenetics by means of fluorescence in situ hybridization (FISH)

A cytogenetic analysis of bone marrow cells will be performed at screening through fluorescence in situ hybridization according to standard clinical practice for del17p, t(4;14) and t(14;16).

7.1.1.9 eGFR calculation

The calculation of eGFR will be based on the CKD-EPI formula as follow [21]:

The CKD-EPI equation is:

$$eGFR = 141 \times \min(SCr/k,1)^{a} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$$

where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

As separate equations for different populations: For creatinine (IDMS calibrated) in mg/dL:

Black female

If serum creatinine (Scr) <= 0.7

$$eGFR = 166 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.7

$$eGFR = 166 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$$

Black male

If serum creatinine (Scr) <= 0.9

$$eGFR = 163 \times (SCr/0.9)^{-0.411} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.9

$$eGFR = 163 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$$

Female, not black

If serum creatinine (Scr) <= 0.7

$$eGFR = 144 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.7

$$eGFR = 144 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$$

Male, not black

If serum creatinine (Scr) <= 0.9

$$eGFR = 141 \times (SCr/0.9)^{-0.411} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.9

$$eGFR = 141 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$$

7.1.2 Safety assessments

Safety evaluations include assessments of Adverse Events (AE), clinical laboratory tests, vital sign measurements, physical examination, assessment of ECOG performance status, cardiac imaging (screening) and ECG.

7.1.2.1 Adverse events

Monitoring for adverse events will take place continuously throughout the study, starting from informed consent until 30 days after last study treatment. See *Section 8* for details.

7.1.2.2 Clinical laboratory tests

Laboratory assessments to be performed according to standard clinical practice and medicinal products' SPCs are listed below. See *Table 7.2* for a schedule of assessments.

- Hematology: CBC, Differential (absolute counts: lymphocytes, monocytes, neutrophils, eosinophils, basophils), platelets.
- Clinical chemistry: sodium, potassium, total protein, albumin, alkaline phosphatase, γGT, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total bilirubin, BUN, creatinine, glucose, eGFR based on CKD-EPI (see section 7.1.1.9).
- Urine or Serum Pregnancy test in women who can be pregnant
- Serum β 2-microglobulin, LDH

7.1.2.3 Vital signs

Vital signs (body temperature, seated blood pressure and heart rate) will be recorded as outlined in *Table 7.2*. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing.

Vital signs will be monitored also prior to, during and after the daratumumab infusion period.

7.1.2.4 Physical examination

Physical examinations will be performed according to the visit schedule outlined in *Table 7-2*. A full physical examination will be performed at screening visit, whereas targeted exams will occur during the treatment and post-treatment periods according to the Investigator's observations and/or subject complaints on new or changed conditions.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the eCRF.

7.1.2.5 ECOG performance status

Eastern Cooperative Oncology Group (ECOG) performance status will be evaluated as indicated in *Table 7.2* using the criteria described in *Appendix 6*. The assessment should be completed prior to any study-related procedures or assessments.

7.1.2.6 Cardiac assessments

A 2-dimensional echocardiogram (or if not available a MUGA scan) and an electrocardiogram will be performed at screening or within 42 days of Cycle 1 Day 1. Echo (or MUGA) may be repeated throughout the study as clinically indicated.

7.1.3 Hepatitis B Virus (HBV) Serology

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

7.1.4 HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 7.2). Where required by local law, the results of HBV testing may be reported to the local health authorities.

7.2 Study schedule

Table 7.2 lists all of the assessments and indicates the visits when they are performed. See *Section 7.1* for details concerning each assessment. All data obtained from these assessments must be supported in the patient's source documentation. Baseline is defined as Cycle 1 Day 1 (C1D1) prior to start of study

treatment. For assessments that are not performed on C1D1, the screening results will be considered as baseline.

Post-baseline disease evaluations may be conducted ± 3 days from the scheduled (based on C1D1) visit date, if necessary. At the following visit, the subject should return to the originally planned schedule.

7.2.1 Screening

Following signature of the Informed Consent Form (ICF), screening assessments will be performed within 21 days prior to Cycle 1 Day 1, with the exception of radiological assessments and cardiac echo for which results obtained within 42 days of C1D1 are also acceptable.

A patient who has a laboratory result that does not satisfy eligibility criteria may have the test repeated when the investigator believes the re-test result is likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within the 21 day screening window. If the bone marrow sample collected at screening (aspirate) is inadequate for genetic assessments (fluorescent in situ hybridization) (FISH) and/or evaluation of percentage of plasma cells, it should be repeated within the 21 day screening window. Results from the skeletal survey or the radiologic assessments for Extramedullary Plasmacytomas, which have been performed as routine follow up within 42 days before C1D1, may be used without these tests being repeated.

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered screening failures. The reason for not starting the study treatment will be entered in the eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screening failure patients. No other data will be entered into the clinical database unless the patient experienced a Serious Adverse Event during the Screening Phase.

Patients who fail to meet any of the inclusion and exclusion criteria will be considered screening failures and may be rescreened if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are deemed eligible for rescreening must sign a new ICF.

Patient demographics and other baseline characteristics

The following data is to be recorded on the eCRF during the screening period:

- Demography (year of birth, age in years, sex, information on childbearing status of female patients, race, ethnicity).
- Medical history / current medical conditions.
- Diagnosis of Multiple Myeloma and extent of the disease (including staging at study entry, ISS and revised-ISS). Staging of MM should be done according the International Staging System (ISS) and the Revised-ISS (see *Appendix 3*).
- Bone marrow aspirate/biopsy for cytogenetics (FISH).
- All prior anti-neoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies and stem cell transplants provided as treatment for MM.
- All concomitant medications and significant non-drug therapies including transfusions of blood products administered within 14 days prior to first dose.
- The following assessments must be performed and recorded for all patients:
    - Complete physical examination including height and weight.
    - Vital signs (temperature, heart rate, diastolic and systolic blood pressure)

  - Eastern Cooperative Oncology Group (ECOG) performance status
  - Electrocardiogram
  - Cardiac imaging (ECHO or MUGA)
  - FEV1 in subjects with known or suspected COPD
  - Serum pregnancy test performed in WOCBP (two pregnancy tests, one 10-14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity ≥ 25 mIU/mL).
  - Local laboratory evaluations (hematology, clinical chemistry, eGFR).
- Disease assessments
  - In serum:
    - M-protein by PEP and IFE
    - FLC protein assessment
    - corrected calcium
    - serum Creatinine / eGFR
  - In urine (24-h urine collection required):
    - M-protein by PEP and IFE;
  - Local plasma cell count in bone marrow
  - Clinical and CT/MRI assessment of soft tissue plasmacytomas (STP)
  - Local full body skeletal survey by X-ray and/or CT/MRI
  - Blood type, Rh, and Indirect Antiglobulin Test (IAT)

Blood Type and IAT

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

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Antiglobulin or Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) [22-23]

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

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

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

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

In case of an urgent need for a blood transfusion, a blood sample should be obtained before the first infusion of daratumumab and the subject's blood type (ABO, Rh, and IAT) determined. Subjects should be provided a blood type card, which they will carry with them throughout the treatment period.

7.2.2 Treatment Period

Up to 38 patients will be treated in 28-day cycles until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to other reason (see *Section 5.4.1*). A 24-month accrual period is planned for the study and the last patient enrolled will be followed up for a maximum of 13 months. The entire study will therefore have a total maximum duration of 37 months. See *Table 7.2* for the assessment schedule, *Section 7.1* for details about assessments and *Section 6.1* for information about treatment. The general visit window during the treatment period is +/- 3 days.

End of Treatment Visit

An End-of- Treatment Visit will take place 4 weeks after the last dose of study treatment, or as soon as possible before the start of subsequent therapy, unless the subject withdraws consent for study participation or is lost to follow up. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment.

7.2.3 Follow-up Period

Post-treatment follow-up

Patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent should continue to be followed for response assessments every 4 weeks as in *Table 7.2*. The reason for completion/discontinuation should be recorded on the eCRF.

If a patient starts new anti-neoplastic therapy prior to disease progression, every attempt should be made to perform tumor evaluations until documented disease progression. In addition, all new anti-neoplastic therapy administered starting from the last dose of the study treatment until death, lost to follow-up, or withdrawal of consent will be recorded in the eCRF.

Survival follow-up

Subjects will be followed every 12 weeks, or more frequently, after disease progression for survival and subsequent myeloma therapy until the end of study.

Table 7.2 – Schedule of Events

	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[8]	Post treatment FU Every 4 weeks[5]	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond						
Day of Cycle (28-days)	**-21 to 1**	**1 BL**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**			
Demographic/baseline Assessments																
Informed consent	X															
Demography	X															
Inc./Exc. criteria	X															
Medical history	X															
MM diagnosis/history	X															
International Staging System (ISS)	X															
Cytogenetics (FISH) at study entry	X															
Safety Assessments																
Physical examination	X	X				X				X				X		
Vital signs	X	X	X	X	X	X		X		X				X	X	
Weight	X	X	X	X	X	X		X		X				X	X	
Performance status (ECOG)	X	X				X				X				X		
Adverse Events	Continuously from ICF until 30 days after last study treatment														Treatment related SAEs	
Concomitant medication, transfusions	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cardiac imaging: ECHO or MUGA[9]	X	As clinically indicated														
FEV1***	X															
ECG	X	As clinically indicated														
Lab Assessments*																
Blood type assessment and indirect antiglobulin results[0]	X															
Hematology	X	X	X	X	X	X		X		X				X		
Clinical chemistry	X	X	X	X	X	X		X		X				X		
eGFR	X	X	X	X	X	X		X		X				X		
Pregnancy test[1]	X	X														

Day of Cycle (28-days)	Screening ≤ -21 to 1	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[8]	Post treatment FU Every 4 weeks[5]	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond						
		1 BL	8	15	22	1	8	15	22	1	8	15	22			
Serum β2-microglobulin, LDH	X															
Hepatitis B serology[10]	X															
HBV-DNA PCR testing[11]	X	Every 12 weeks (window ±7 days)												X	Every 12 weeks for up to 6 months after the last dose of study treatment	
Efficacy Assessments																
Efficacy / Disease Assessment required to confirm response or disease progression should be performed as soon as possible after response or disease progression is suspected – see *Section 7.1* for details)																
sPEP, uPEP[2]	X	X				X				X				X	X	
sIFE, uIFE[3]	X	X			.	X				X				X	X	
			To confirm CR regardless of whether measurable M-protein was present at baseline. See *Section 7.1.1.1*													
sFLC assay, κ/λ ratio[4]	X	X				X				X				X	X	
			Analyzed only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met. See *Section 7.1.1.2*													
Plasma cell count in bone marrow	X	Plasma cell count during the study as clinically indicated to qualify for CR and PD for patients with non-measurable disease by M protein in serum and urine as well as by FLC. See *Section 7.1.1.3*														
MRD		As per institution's practice at complete response or better and thereafter every 6 months as long as CR/sCR is maintained through EuroFlow cytometry. See *Section 7.1.1.6*														
Corrected calcium[6]	X	X				X				X				X	X	
Skeletal survey[7,9]	X	As clinically indicated; CT/MRI in case of newly symptomatic areas with no X-ray finding. See *Section 7.1.1.6*														
Assessment of extramedullary soft tissue plasmacytoma	X	Clinical assessment on day one of each cycle at the End of treatment and at Post treatment follow-up every 4 weeks. CT or MRI at screening only if there are STP findings during the clinical assessment or documented evidence from previous imaging assessments and as clinically indicated. See *Section 7.1.1.4*														
Response assessment by Investigator		C2D1				X				X				X	X	
Treatment																
Daratumumab		X	X	X	X	X		X		X						
Dexamethasone		X	X	X	X	X	X	X	X	X	X	X	X			
		40 mg (20 mg for patients > 75 years of age) orally, weekly														

	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[8]	Post treatment FU Every 4 weeks[5]	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond						
Day of Cycle (28-days)	**-21 to 1**	**1 BL**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**			
Other anti-neoplastic therapies		Not permitted												X	X	X
Survival follow-up																X

^ The majority of screening assessments are to be performed within 21 days from the date of ICF signature until C1D1. See *Section 7.2.1* for details.

[0] i In addition to ABO and Rh blood typing, indirect antiglobulin test (also known as indirect Coombs test) will be performed; it is recommended that the subject carries a card with the blood antigen profile at all times during the study.

[1] Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drug and one within 24 hours prior to the start of study drug.

[2]M protein by electrophoresis in serum (sPEP) and urine (uPEP). Serum on Day 1 of each cycle until disease progression. 24-hour urine sample can be collected within ± 7 days of visit.

[3]M protein by immunofixation in serum (sIFE) and urine (uIFE).

[4]Free light chain protein assessment (sFLC)

[5] Patients who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent should continue to be followed for response assessments every 4 weeks.

[6] Corrected calcium will be also performed as clinically indicated to confirm disease progression.

[7] As per institution's practice

[8] End of treatment visit should take place 4 weeks after the last dose of the study treatment or as soon as possible before the start of subsequent therapy.

[9] If performed within 42 days from C1D1 are acceptable

[10] Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Sections 7.1.3.

[11] For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 7.1.4.** Unless otherwise stated, all blood and urine samples must be obtained before administration of study treatment.

*** Subjects with known or suspected COPD must have an FEV test during Screening

7.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the eCRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.3.1 Precautionary Medications, Treatments, and Procedures

See *Appendix 2* for recommended pre-infusion medication.

Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see Section 7.1.4).

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

7.3.2 Prohibited Medications, Treatments and Procedures

Any systemic, anti-myeloma therapy other than daratumumab and dexamethasone are prohibited while on study therapy. Concomitant steroids, other than weekly dexamethasone (see *Section 6*) are prohibited unless used to treat an adverse event and as pre- and post-infusion medication (see Section 6 and Appendix 2).

No interaction studies have been performed with daratumumab. Guidelines for the selection and use of other concomitant medications should be derived from dexamethasone prescribing information.

7.3.3 Rescue Medications, Treatments and Procedures

See *Appendix 2* for guidelines for managing infusion-related reactions.

7.3.3.1 Hemodialysis

For patients in need of hemodialysis, daratumumab should be administered on the day with the maximum distance from the subsequent hemodialysis.

7.3.4 Participant Access to Study Treatment at Study Closure

Patients will be provided with study treatment until disease progression, death, lost to follow-up, or withdrawal of consent. The sponsor may terminate access to study drug if the study is terminated due to safety concerns.

8. Safety Monitoring and Reporting

8.1 Adverse events

8.1.1 Adverse event definition

According to the International Conference on Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that worsen during a study against the baseline conditions are to be reported as AEs.

The occurrence of adverse events should be sought by non-directive questioning of the patient during screening, after signing informed consent, and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient or through physical examination, laboratory test, or other assessments.

Laboratory abnormalities that constitute an Adverse Event should be recorded on the Adverse Event page of the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g. anemia instead of low hemoglobin).

8.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not considered being SAEs are hospitalizations for: a standard procedure for therapy administration, routine treatment or monitoring of the study indication, hospitalization or prolongation of hospitalization for technical/practical or social reasons in absence of an AE, a procedure which is planned. A prolongation of such a hospitalization for a complication remains a reportable SAE.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

Intensity: all AEs will be graded according to the Common Terminology Criteria for AEs (CTCAE version 4.03) as follows (a semi-colon indicates 'or' within the description of the grade):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.2.2 Relationship to Study Treatment(s)

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

• **Possibly Related –** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• **Unlikely to be related –** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provide plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• **Not Related –** The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.2.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the applicable product information (e.g. Investigator's Brochure or Summary of Product Characteristics (SPC) of the study agents.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant signs the ICF will be considered as baseline condition and not reported as an AE. However, if the study participant's condition deteriorates in severity and frequency at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (both AEs and SAEs) after the last day of study treatment. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

All identified non-serious AEs (related and unrelated) must be recorded and described on the non-serious AE page of the eCRF.

8.4.2 Serious Adverse Event Reporting

Every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness.

Any SAE experienced after this 30-day period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression

of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Information about all SAEs will be recorded on the Serious Adverse Event Report Form.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.4.3 Events of Special Interest

Safety events of special interest include, but are not limited to:

- Secondary Primary Malignancies
- Infusion Related Reactions
- Medication Error, intercepted medication error or potential medication error (with or without patient exposure to IMP, e.g., product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Abuse/Misuse/Overdose
- Occupational Exposure
- Drug-Drug Interaction
- Suspected Transmission of Infectious Agents
- Exposure from breastfeeding
- Unexpected therapeutic benefit or clinical benefit
- Inadvertent or accidental exposure

All events of special interest should be especially monitored and reported to the sponsor as SAEs and within 24 hours of site awareness, even if considered non-serious and regardless whether or not an (S)AE occurred. All of the events of special interest should be recorded on the eCRF.

8.4.4 Pregnancy

A female patient will be instructed immediately to inform the investigator if she becomes pregnant during the study. The investigator shall report all pregnancies within 24 hours to the sponsor using the Pregnancy Reporting Form. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. The investigator will therefore inform the subject of the potential risks to the fetus and discuss with the Sponsor as well as the subject if it is in the subject’s best interest to continue or stop treatment with daratumumab.

The effect of daratumumab on sperm is unknown. Therefore, pregnancy occurring in the partner of a male patient participating in the study should also be reported by the investigator within 24 hours of awareness to the sponsor by using the Pregnancy Reporting Form..

8.4.5 Product Quality Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an effect on the safety and efficacy of the product; therefore the timely, accurate, and complete reporting and analysis of PQC information are crucial for the protection of subjects, Investigators, and the Sponsor.

All PQCs must be reported to the Sponsor using the PQC form within 24 hours upon awareness, regardless if the relevant defect is combined with a (S)AE or not. Where possible, a sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

8.4.6 Annual Safety Report

An Annual Safety Report will be submitted to the Competent Authorities and Ethics Committees once a year, according to the relevant local regulations.

8.5 Safety Oversight

Safety data will be reviewed by the study Scientific Committee approximately every 6 months (after first randomized patient started study treatment).

9. Clinical Monitoring

Clinical site monitoring will conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol, with GCP, and with applicable regulatory requirements.

Monitoring for this study will be performed by a Contract Research Organization (CRO).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10. Statistical considerations

10.1 Statistical and Analytical Plans

The primary analysis will be performed when the targeted number of events required for the primary analysis has been reached.

10.2 Statistical Hypotheses

The primary efficacy endpoint is PFS as assessed by the Investigator.

The expected median PFS with daratumumab treatment in the SIRIUS study was 5.6 months in the patients who received daratumumab at the dose of 16 mg/kg.

In order to test at α=0.05 the null hypothesis that the PFS is less than 3 months versus the alternative hypothesis that PFS is at least 5 months with a power of 90%, 34patients must be included in the study. This calculation assumes exponential survival curves, an accrual time of 18 months and a length of follow up period of 30 months. Assuming a drop-out rate of about 10%, 38 patients are needed.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented (see Section 10.4.2).

The analysis will be performed when at least 20 PFS events have been documented.

10.3 Analysis Datasets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned according to the intent to treat principle.

Per Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who received at least one dose of the study drug and had no major protocol deviation. Protocol deviations leading to exclusion from the PPS will be defined in the Statistical Analysis Plan.

Safety Set

The Safety Set consists of all patients who received at least one dose of study treatment. Patients who have been randomized and did not take at least one dose of study treatment will not be included in the safety set. Patients will be analyzed according to the study treatment they actually received.

10.4 Description of Statistical Methods

10.4.1 General Approach

All data collected in this study will be listed and summarized as appropriate as described below. Data from all sites will be pooled and summarized.

Continuous data will be summarized by mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

One-sided alpha level 0.025 will be considered. No alpha level adjustment will be carried out for primary and secondary outcome variables.

10.4.2 Analysis of the Primary Efficacy endpoint(s)

The efficacy analysis will be performed based on the FAS as primary analysis and on the PPS as supportive analysis.

Progression Free Survival (PFS)

Progression free survival is defined as the time, in months, from treatment initiation (Cycle 1 , day 1) to the date of the first documented disease progression or death due to any cause, whichever comes first. Clinical deterioration will not be considered progression. For subjects who neither progress nor die, the survival time will be censored at the date of their last disease assessment. For subjects who start a new anti-tumor treatment, survival time will be censored at the date of the start of the new treatment.

The PFS function will be estimated using the Kaplan-Meier product-limit method. Median and two-sided confidence intervals (CI) for median PFS will be computed by and Kaplan-Meier plots of PFS will be presented.

Absolute frequencies and proportions of patients with disease progression or all-cause death will also be provided.

10.4.3 Analysis of the Secondary Endpoint(s)

All secondary efficacy analyses will be performed based on the FAS.

Overall Response Rate (ORR)

Overall response rate is defined as the proportion enrolled subjects who achieve a best response of partial response (PR) or better using the Modified criteria of the International Myeloma Working Group (IMWG) (*see Appendix 4*) as their best overall response.

The response rate, along with its exact two-sided 95% CI, will be computed.

Renal Response Rate (RRR)

Renal Response Rate is defined as the proportion enrolled subjects who achieve a best response of renal partial response (PRRenal) or better using the criteria of the International Myeloma Working Group (IMWG) (*see Appendix 5*).

Duration of Response (DoR)

Duration of response will be restricted to the subjects that achieve a best objective response of PR or better. It is measured from the time, in months, that the criteria for objective response are first met until the date of a progression event (according to the primary definition of PFS). A subject with objective response who does not have a progression event will be censored at the same time they were censored under the primary definition of PFS.

The DoR function will be estimated using the Kaplan-Meier product-limit method. Median and two-sided confidence intervals for median duration of response will be computed and Kaplan-Meier plots of DoR will be presented.

Time to Next Therapy (TNT)

Time to next therapy will be defined as the time, in months, from Cycle 1 Day 1 to the date to next anti-neoplastic therapy or death from any cause, whichever comes first. For subjects who neither start a new

anti-neoplastic therapy nor die, survival time will be censored at the date of their last available follow-up assessment.

Time to next therapy will be calculated using a log-rank test procedure. The TNT function will be estimated using the Kaplan-Meier product-limit method. Median and two-sided confidence intervals for median TNT will be computed. Kaplan-Meier plots of TNT will be presented.

Overall Survival (OS)

Overall survival is defined as the time, in months, from the first dose of therapy to the date of death from any cause. If a patient is not known to have died, survival time will be censored at the date of last contact ("last known date alive").

Overall survival will be estimated using the Kaplan-Meier product-limit method. Median and corresponding two-sided 95% confidence intervals will be computed. Kaplan-Meier plots of OS will be presented.

10.4.4 Safety Analyses

Safety analyses will be conducted on the Safety Set and will be reported.

Adverse events

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4.03).

The incidence of AEs will be tabulated by MedDRA System Organ Class and Preferred Term. The incidence of AEs will also be summarized by system organ class, preferred term and severity (based on CTCAE grades).

The same analysis will be repeated for SAEs regardless of drug relationship, for drug related SAEs, AEs with CTCAE grade 3 or 4 and for drug related AEs. AEs for which relationship to study drug is not specified will be considered treatment-related.

Deaths reportable as SAEs will be listed by patient and tabulated by type of AE.

Laboratory parameters

Categorization of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or according to normal ranges for those parameters without available CTCAE grading. The calculation of CTCAE grades will be purely based on the observed laboratory values, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (low and high) classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value, for laboratory tests where CTCAE grades are not defined.

Listings of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will also be generated.

Other safety data

ECGs, vital signs and ECOG PS will be listed and summarized.

ECG

- Shift table baseline to worst on-treatment result
- Listing of ECG evaluations for all patients with at least one abnormality
- Change from baseline QTcF

Vital signs

- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

ECOG PS

- Shift tables comparing the baseline PS with the worst post-baseline result

10.4.5 Baseline Descriptive Statistics

All data about patient demographics and baseline characteristics will be summarized on the FAS, overall, by means of summary descriptive statistics.

A complete description of patient disposition will be provided, specifying the number of enrolled patients, number of patients at each visit, completed and discontinued patients, and the reason for the discontinuation.

The analysis populations will be described and the reasons for excluding the patient from any analysis set will be provided with the number of protocol violators per each criterion.

Medical history data will be presented by MedDRA System Organ Class and Preferred Term.

10.4.6 Treatments (study treatment, concomitant therapies)

The Safety set will be used for the following analyses.

Investigational treatment

Duration of study treatment, cumulative dose, average daily dose, actual dose intensity and relative dose intensity of each of the components of study treatment will be summarized and for every 28-day cycle. The number of patients with dose changes/interruptions will be, along with the reasons for the dose change/interruptions.

Concomitant treatments

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by WHO Anatomical Therapeutic Chemical (ATC) Class, Preferred Term. These summaries will include medications starting on or after the start of study treatment (defined as cycle 1 day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medication or significant non-drug therapy starting and ending prior to the start of study treatment will be listed.

For the analyses of transfusions, only transfusions received after start of study treatment and up to 30 days after last dose will be considered. The number of patients with transfusions and number of transfusions per patient will be analyzed.

10.4.7 Planned Interim Analyses

No formal interim analysis for efficacy is planned. An interim analysis for safety will be performed as described below.

10.4.7.1 Safety Review

The Sponsor Scientific Committee will perform an overall evaluation of the safety data when 19 patients (50%) have received at least 1 dose of daratumumab. If a safety signal is identified and the Sponsor Scientific Committee determines that the safety profile of the study treatment is unfavorable, the recruitment of the rest of the subjects will be interrupted and the study may be stopped due to safety concerns. In the event of such a study termination all current subjects that are receiving daratumumab treatment may receive subsequent alternative treatment outside of the study as per the investigator's judgement and routine practice. More details on the Interim Safety Review will be provided in the Statistical Analysis Plan for this study.

10.4.7.2 Efficacy Review

No formal efficacy review is planned.

10.4.8 Additional Sub-group Analyses

Additional sub-group analyses will be detailed in the Statistical Analysis Plan.

10.4.9 Multiple Comparison/Multiplicity

Unless stated otherwise, one-sided alpha level 0.025 will be considered. No alpha level adjustment will be carried out for primary and secondary endpoints.

10.4.10 Exploratory Analyses

Additional exploratory analyses will be detailed in the Statistical Analysis Plan.

10.5 Sample Size

The calculations were based on previous data for daratumumab in patients with relapse or refractory myeloma. The median PFS with daratumumab treatment in the SIRIUS study was 5.6 months in patients who received daratumumab at the dose of 16 mg/kg.

In order to test at α=0.05 the null hypothesis that the PFS is less than 3 months versus the alternative hypothesis that PFS is at least 5 months with a power of 90%, 34 patients must be included in the study. This calculation assumes exponential survival curves, an accrual time of 18 months and a length of follow up period of 30 months. Assuming a drop-out rate of about 10%, 38 patients are needed.

Sample size was computed by "SWOG One arm survival sample size and power" *(www.swogstat.org/stat/public/one_survival.htm)*

10.6 Measures to Minimize Bias

10.6.1 Enrolment/Masking procedures

Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The coordinating investigator or designated staff will assign the subject number. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the patient fails to enroll for any reason, the reason will be entered into the Screening Disposition page

10.6.2 Blinding - Unblinding

Since this is an open-label study, the treatment will be open to patients, investigator staff, and personnel performing the assessments.

11. Source Documents and Access to source data / documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of Regulatory Agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medical-technical departments involved in the clinical trial.

The eCRF will not be the only record of the patient's participation in the study in order to ensure that anyone who accessed the patient's medical record would have adequate knowledge that the patient is participating in the trial.

Inclusion/Exclusion Criteria Source Documentation Requirements

The minimum source documentation requirements for the Inclusion/Exclusion criteria that specify a need for documented medical history (see Section 5.1 and Section 5.2) are the following:

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

12. Quality Assurance and Quality Control

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13. Ethics/Protection Human of Subjects

13.1 Ethical standards

This clinical study shall be implemented and reported in accordance with the ICH Guidelines for Good Clinical Practice, all applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Institutional Review Board (IRB)/independent Ethics Committee (IEC) and competent authority

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the relevant IRB/EC and Competent Authority (CA) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC and or CA before the changes are implemented to the study. All changes to the consent form will be IRB/EC and/or CA approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1Consent/Assent and other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to enrolment in the trial and before any study related procedure takes place.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB/EC-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/EC or pharmaceutical company supplying study product(s) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/EC and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will not include the participant's contact details or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected.

13.5 Insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial. The Investigator(s) will remain responsible towards the sponsor of any fault or misconduct regarding the performance of the Study.

14. Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

- Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they are trained.

Web-based software will be used and no installation procedure is needed. Each site will be authorized by the Administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring User ID and Password and may read, modify and update only the information he/she previously reported. Each page reports site code and patient code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The Investigator will certify that the data entered into the eCRF is complete and accurate.

After database lock, the investigator will receive a CD-ROM of patient data for archiving at the investigational site.

- Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered into the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. If clarifications are needed, the Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows as well as the on-line and off-line checks are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA).

Data about the study drug are tracked using the eCRF. The system is supplied by CRO, who also manages the database.

The occurrence of any protocol deviations will be checked and the database will be locked and made available for data analysis after these actions have been completed and the database has been declared complete and accurate.

14.2 Study Records Retention

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or

guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than twenty five (25) years from the completion of the study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with the national laws.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents.

14.4 Publication and Data Sharing Policy

This study will ensure that the public has access to the published results of the research.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

14.5 End of study report

The sponsor will notify the accredited Ethics Committee and the Competent Authority for the end of study within a period of 90 days. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the Competent Authority within 15 days, including the reasons for the premature termination.

The sponsor will submit the clinical study report with the final results of the study to the accredited Ethics Committee and the Competent Authority within one year after the end of study.

15. Study Administration

15.1 Study Leadership

The Scientific Committee will govern the conduct of the study and will be composed of the Sponsor Representative, the Co-ordinating Investigator and the Scientific Co-Ordinating Investigator. The Scientific Committee will meet in person at least annually.

16. Conflict of Interest (COI) Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. Financial disclosures shall be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

17. References

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APPENDIX

Appendix 1 – Preparation of Daratumumab

This medicinal product is for single-use only.
Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colorless to yellow. Do not use if opaque particles, discoloration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride. Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), 13 polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discoloration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C - 25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C - 8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

Appendix 2 – Guidelines for Administrating Daratumumab

Following dilution, daratumumab infusion should be intravenously administered at the appropriate initial infusion rate, as presented in the table below. Incremental escalation of the infusion rate should be considered only if the previous infusion of daratumumab was well tolerated.

Infusion rates for daratumumab

	Dilution volume	Initial infusion rate (first hour)	Increments of infusion rate[a]	Maximum infusion rate
First infusion	1,000mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion [b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.
[b] A dilution volume of 500 mL should be used only if there were no ≥ Grade 1 IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no ≥ Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.

Management of infusion-related reactions

Pre-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment with DARZALEX.

For IRRs of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms.

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below.

- Grade 1-2 (mild to moderate): Once the patient's condition is stable, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to a maximum rate of 200 mL/hour (Table above).
- Grade 3 (severe): If the intensity of the IRR decreases to Grade 2 or lower, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate (Table above). The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX if the patient experiences a ≥ Grade 3 infusion-related symptom at the subsequent infusion.
- Grade 4 (life threatening): Permanently discontinue DARZALEX treatment.

Recommended concomitant medications

Pre-infusion medication

Pre-infusion medications should be administered to reduce the risk of IRRs to all patients approximately 1-3 hour prior to every infusion of DARZALEX as follows:

- intravenous corticosteroid (dexamethasone 20 mg, methylprednisolone 100 mg , or equivalent dose of an intermediate-acting or long-acting corticosteroid)) plus
- oral antipyretics (paracetamol 650 to 1,000 mg), plus
- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medication

For the prevention of delayed IRRs, oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards) should be administered on each of the two days following all infusions (beginning the day after the infusion).

Additionally, for patients with a history of obstructive pulmonary disorder, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be

considered. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation
Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Infection Prophylaxis: Prophylactic use of antibiotics is highly recommended due to the susceptibility of multiple myeloma patients to infections. Prophylactic administration of levofloxacin (500 mg P.O. daily; dose adjusted for renal function) during the first 3 cycles of treatment is recommended as it has shown to significantly reduce febrile episodes and deaths without increasing healthcare associated infections or carriage of key nosocomial pathogens.

HBV prophylaxis: Primary antiviral prophylaxis for HBV reactivation is permitted as per local standard of care. Please refer to Section 7.1.4 for more details about the management of HBV reactivation

Source: Drayson, Mark T et al "Tackling Early Morbidity and Mortality in Myeloma (TEAMM): Assessing the Benefit of Antibiotic Prophylaxis and Its Effect on Healthcare Associated Infections in 977 Patients." Blood 130.Suppl 1 (2017):903

Appendix 3a – The International Staging System (ISS) for Multiple Myeloma

Stage	Criteria	Median Survival (Months)
Stage 1	Serum β 2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
Stage 2	Not stage I or III (There are two categories for stage II) serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL OR β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level	44
Stage 3	Serum β2-microglobulin ≥ 5.5 mg/L	29

Greipp PR, San Miguel JF, Brian GM et al. International Staging System for Multiple Myeloma. J Clin Oncology 2005 23:3412-3420.

Appendix 3b – The Revised International Staging System (ISS) for Multiple Myeloma

Stage	Criteria	Median Survival (Months)
Stage 1	ISS stage I and standard-risk CA by iFISH and normal LDH	Not reached
Stage 2	Not R-ISS stage I or III	83
Stage 3	ISS stage III and either high-risk CA by iFISH or high LDH	43

Abbreviations: ISS: International Staging System, CA: chromosomal abnormalities, LDH: lactate dehydrogenase; R-ISS, revised International Staging System.

Chromosomal abnormalities detected by iFISH:
High risk: del(17p), and/or translocation t(4;14), and/or translocation t(14;16)
Standard risk: No high-risk CA

LDH:
Normal: Serum LDH < the upper limit of normal
High: Serum LDH > the upper limit of normal

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncology 2015 33(26): 2863–2869

Appendix 4 – Modified International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

Response	***IMWG criteria***
Stringent complete response (sCR)	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[1] by immunohistochemistry or immunofluorescence.[2]
Complete response (CR)	Negative immunofixation on serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow.[1]
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
Partial response (PR)	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h. If serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
No change/Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or progressive disease.
Progressive disease (PD)[3]	Any of the following: • Increase of ≥ 25% from lowest response value in any one or more of the following: o Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[4] o Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) o Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL o Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[5] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (≥50% increase from nadir in SPD[7] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in the short axis). • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.87 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[4] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.87 mmol/L] • Decrease in hemoglobin of $\geq$ 2 g/dL [1.24 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more]
Relapse from CR[3] (To be used only if the end point studied is DFS)[6]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of $\geq$ 5% plasma cells in the bone marrow[5] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[1] Confirmation with repeat bone marrow biopsy not needed.

[2] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[3] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

[4] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[5] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[6] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

[7] SPD = sum of the products of the maximal perpendicular diameters of measured lesions

Appendix 5 – IMWG Renal Response Criteria and simplified renal response criteria

Criteria for the Definition of Renal Response to Antimyeloma Therapy		
Renal Response	Baseline eGFR, mL/min/1.73 m^2*	Best eGFR Response mL/min/1.73 m^2
Complete response	<50	≥60
Partial response	< 15	30-59
Minor response	<15 15-29	15-29 30-59
Abbreviations: CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate. *eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.		

Simplified criteria Renal Response criteria
• Patients who presented with stage 5 RI (eGFR < 15 ml/min/1.73 m^2)should double their eGFR and improve to at least stage 4
• Patients with stage 4 (eGFR 15-29 ml/min/1.73 m^2), increase their eGFR by at least 50% and improve to at least stage 3 (GFR ≥ 60 mL/min/1.73 m^2)
• Patients with stage 3 (eGFR 30-59 ml/min/1.73 m^2), increase their eGFR by at least 50% and improve to at least stage 2 (GFR ≥ 60 mL/min/1.73 m^2)

Appendix 6 – ECOG Performance Status Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
Credit to: the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 7 - Reference Charts for the Classification of Asthma

Adapted from 2007 NHLBI Guidelines for the Diagnosis and Treatment of Asthma Expert Panel Report 3)

Components of SEVERITY		Classification of Asthma Severity (Youths ≥ 12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV1/FVC: 8-19 yr 85% 20-39 yr. 80% 40-59 yr. 75% 60-80 yr 70%	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2x/month	3–4x/month	> 1x/week but not nightly	Often 7x/week
	Short-acting beta2-agonist use for symptom control	≤ 2 days/week	> 2 days/week but not > 1x/day	Daily	Several times a day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV1 between exacerbations • FEV1 > 80% predicted • FEV1/FVC normal	• FEV1 ≥80% predicted • FEV1/FVC normal	• 60%<FEV1<80% predicted • FEV1/FVC reduced >5%	• FEV1<60% predicted • FEV1/FVC reduced >5%
Risk	Exacerbation requiring oral systemic corticosteroids	0-1x/year	≥2x/year		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV1			

Appendix 8 – JSH Guidelines for the Management of Hepatitis B Virus Infection

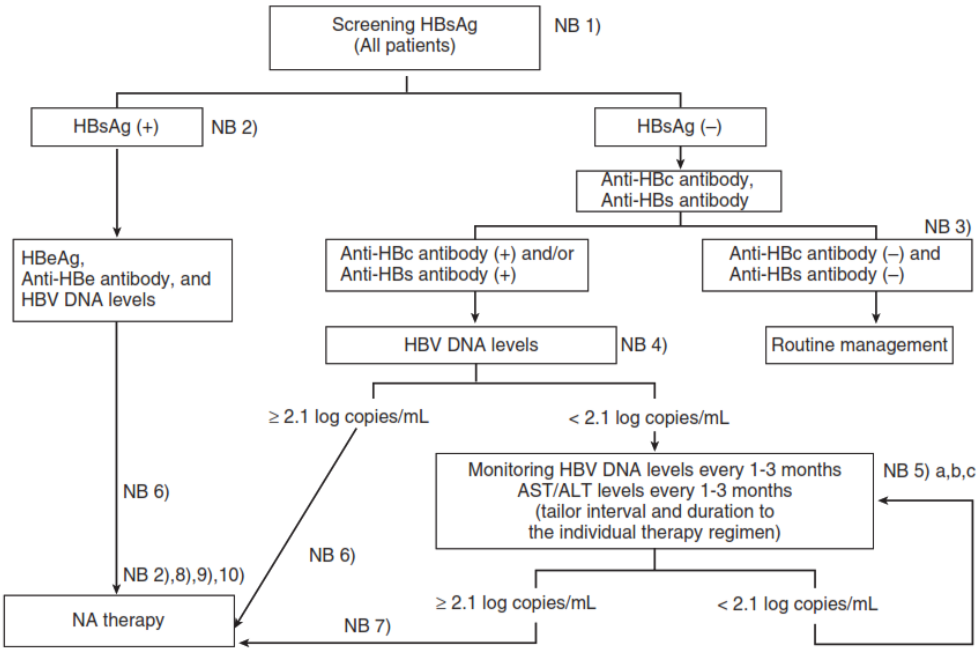

Figure: Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

Addendum: Caution is required when administering powerful chemotherapeutic agents for hematological malignancies, as during or following completion of treatment some HBsAg positive or negative patients will develop hepatitis B due to reactivation of HBV, and some of these will go on to suffer fulminant hepatitis. Consideration should also be given to the possibility of HBV reactivation in association with standard chemotherapy for hematological malignancies or solid cancers, and immunosuppressive therapy for autoimmune diseases, such as rheumatic and collagen diseases. The incidences of HBV reactivation, hepatitis and fulminant hepatitis associated with standard chemotherapy and immunosuppressive therapy are not known, and there is a lack of evidence on which to base guidelines. Furthermore, prevention of fulminant hepatitis is not guaranteed with NA therapy.

NB 1) HBV carriers and patients with resolved hepatitis B should be screened prior to immunosuppressive therapy or chemotherapy. First HBsAg testing should be performed to determine whether they are an HBV carrier. HBsAg negative patients should be tested for anti-HBc antibody and anti-HBs antibody, to confirm past infection. Highly sensitive testing methods should be used for measurements of HBsAg, anti-HBc antibody and anti-HBs antibody.

NB 2) A hepatologist should be consulted concerning HBsAg positive patients. A hepatologist should preferably be consulted for all patients administered NAs.

NB 3) In some patients undergoing retreatment who did not undergo testing for anti-HBc or HBs antibody at the time of their initial chemotherapy, and in patients who have already commenced

immunosuppressive therapy, antibody titers may be low, in which case measurement of HBV DNA levels is preferable.

NB 4) Patients with resolved HBV infection should be screened using real-time PCR measurement of HBV DNA levels.

NB 5)

a. Caution is required when treating patients with resolved HBV infection with rituximab + corticosteroid or fludarabine chemotherapy, or when they undergo hematopoietic stem cell transplantation, as these patients are at high risk of HBV reactivation. HBV DNA levels should be monitored on a monthly basis during treatment, and for at least 12 months afterward. Long-term monitoring is required for hematopoietic stem cell transplant recipients.

b. Although the incidence is low, there is a risk of HBV reactivation with standard chemotherapy regimens. HBV DNA levels should be measured every 1–3 months, with the interval and duration tailored to the individual therapy regimen. It is best to err on the side of caution with patients undergoing treatment for hematological malignancies.

c. There is also a risk of HBV reactivation associated with immunosuppressive therapy using corticosteroids, immunosuppressant agents, or molecular targeted therapy with immunosuppressant or immunomodulator activity. HBV DNA levels should be monitored on a monthly basis in patients on immunosuppressive therapy for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen.

NB 6) Administration should be commenced as soon as possible, before commencement of immunosuppressive therapy or chemotherapy.

NB 7) Administration should be commenced as soon as the HBV DNA levels exceed 2.1 log copies/mL, during or after immunosuppressive therapy or chemotherapy. If this occurs during treatment, it is preferable to consult with a hepatologist, and not immediately cease the immunosuppressant or antineoplastic agent with immunosuppressive activity.

NB 8) Entecavir is the recommended NA.

NB 9) Cessation of NA therapy can be considered if the following criteria are met.

In patients who were HBsAg positive at the time of screening, when the criteria for cessation of NA therapy in cases with chronic hepatitis B are met.

In patients who were anti-HBc antibody and/or anti-HBs antibody positive at the time of screening:

1 NA therapy has been continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy.

2 ALT (GPT) levels have been normalized during this period (excluding causes of elevated ALT levels other than HBV).

3 negative conversion of HBV DNA has occurred during this period.

NB 10) Patients should be carefully monitored, including measurement of HBV DNA levels, for at least 12 months following completion of NA therapy. Monitoring methods depend on package inserts of each NA. NA therapy should be immediately resumed if HBV-DNA levels exceed 2.1 log copies/mL during monitoring period

Source: Hepatology Research 2014;44(Suppl. 1): 1–58

Appendix 9 – Signatures

I. SPONSOR'S SIGNATURE

Study title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Protocol No: EAE-2017/MM02

Version: 5.0

Date: 08 June 2020

Sponsor representative:		
Signature:	……..……..	……
	Prof. Meletios Athanasios Dimopoulos Hellenic Society of Hematology 27 Kifisias Ave, 11523, Athens	Date (DD Mmm YYYY)

II. CO-ORDINATING INVESTIGATORS SIGNATURE

Study title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Protocol No: EAE-2017/MM02

Version: 5.0

Date: 08 June 2020

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.
Signature: ……..…….. …… Associate Prof. Efstathios Kastritis Date (DD Mmm YYYY) Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece

III. SCIENTIFIC CO-ORDINATING INVESTIGATORS SIGNATURE

Study title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Protocol No: EAE-2017/MM02

Version: 5.0

Date: 08 June 2020

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.
Signature: ……..…….. …… Prof. Meletios Athanasios Dimopoulos Date (DD Mmm YYYY) Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece

IV. NATIONAL CO-ORDINATING INVESTIGATOR SIGNATURE

Study title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Protocol No: EAE-2017/MM02

Version: 5.0

Date: 08 June 2020

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.
Signature: ……..…….. …… Associate Prof. Efstathios Kastritis Date (DD Mmm YYYY) Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece

V. PRINCIPAL INVESTIGATOR SIGNATURE

Study title: Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Protocol No: EAE-2017/MM02

Version: 5.0

Date: 08 June 2020

I have read all pages of this clinical study protocol and agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that Sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....