STATISTICAL ANALYSIS PLAN

Study:

"Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis"

Title: EMN22

Protocol Number: EMN22/54767414AMY2005

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General Info	
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List of Abbreviations

Abbreviation	Explanation
AE	Adverse events
AESI	Adverse event of special interest
BMI	Body Mass Index
CHR	Complete Hematologic Response
CI	Confidence Interval
CR	Complete response
CRF	Case report forms
CTCAE	Common Terminology Criteria for Adverse Events
cTnT	Cardiac Troponin T
dFLC	Difference between involved FLC and uninvolved FLC
DI	Dose intensity
DoR	Duration of reponse
DSMB	Data Safety Monitoring Board
E	Mitral Valve Inflow E-wave velocity
Ea	Mitral annular Velocity of Lateral wall
ECOG PS	Eastern Cooperative Oncology Group Performance status
eCRF	Electronic case report forms
EMN	European Myeloma Network
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	End-of-Treatment
EQ-5D-5L	European Quality of Life-5 Dimensions Questionnaire
FAS	Full analysis set
FISH	Fluorescence in situ hybridization
FLC	Free light chain
HRQoL	Health-related quality of life
IABP	Intra-aortic balloon pump
IRR	Infusion-related reactions
IV	Intravenous
LOFC	Last-observation-carried-forward
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVIDd	Left Ventricular Internal Diameter in Diastole
MeDRA	Medical Dictionary for Regulatory Activities
MOD-PFS	Major Organ Deterioration Progression-Free Survival
MRD	Minimal residual disease
NCI	National Cancer Institute
NT-ProBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Overall response
ORR	Overall response rate
OrRR	Organ response rate
OS	Overall survival
PD	Progression of disease

PDI	Planned dose intensity
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
Q1	First quartile
Q3	Third quartile
RDI	Relative dose intensity
RS	Row Score
S	Score
SAP	Statistical analysis Plan
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form-36 Health Survey
SOC	System organ class
TTNT	Time to next treatment
TEAE	Treatment-emergent adverse events
VAS	Visual Analogue Scale
VGPR	Very good partial response
WHOCC-ATC	World Health Organization Collaborating Centre for Drug Statistics Methodology

1. Scope of the Document

This document describes the statistical analyses of the EMN22 study ("Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis") which are to be performed for the full reporting according to the protocol. All analyses are based on the outline given in the statistical section of the protocol (EMN22/54767414AMY2005, Version 6.0, 31 March 2023).

2. Intended Users

Intended users are Heads' staff and any external persons or agencies who need to understand the trial Statistical Analysis framework. In particular the following Heads' personnel will use the Statistical Analysis Plan (SAP):

1. The project manager to monitor operational execution and control project issues (e.g. capacity).
2. The data manager to perform all the preventive and corrective actions.
3. The clinical programmer to develop the data validation and statistical analysis program.
4. The trial statistician to perform the statistical analysis.

3. Short Trial Description

Title	Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis
Short title	EMN22
Protocol number	EMN22/54767414AMY2005
EUDRACT number	2018-004333-33
Clinical phase	Phase 2
Study design	This is a single-arm, open-label, multicenter, Phase 2 study designed to assess the safety and efficacy of daratumumab in newly diagnosed patients with stage 3B light chain (AL) amyloidosis. A safety run-in will be conducted in 6 subjects treated with daratumumab for at least 1 cycle to establish safety of daratumumab in patients with stage 3B AL amyloidosis. Dosing of these 6 subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by a Data Safety Monitoring Board (DSMB) after at least 1 cycle is completed for all 6 subjects. The evaluation of the safety run-in will not include patients who will not have completed the first cycle for reasons unrelated to study treatment. More specifically, this would refer to patients who die, withdraw from the study, or discontinue study treatment for reasons other than toxicity, i.e., disease progression, patient choice, patient lost to follow-up. If no safety signal is observed, the enrollment of the rest of the patients will begin. Subjects in the safety run in will continue all scheduled assessments as specified in the Time and Events Schedule and contribute to the overall safety evaluation. Approximately 40 subjects will receive primary therapy with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase. Each treatment cycle will last 28 days. The end of the study will be 2 years after the enrollment of the last participant.
Primary objective	To evaluate the overall survival (OS) rate at 6 months following treatment with daratumumab in frontline AL patients with stage 3B disease.

Secondary Objectives	• To evaluate the overall (ORR), very good partial (VGPR) and complete (CR) hematologic response rates at 3 and 6 months. • To evaluate the Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from the start of study treatment (Cycle 1 Day 1) until death, clinical manifestation of cardiac failure, clinical manifestation of renal failure, development of hematologic progression of disease (PD). • To evaluate PFS based on all-cause mortality and progression of disease (PD; including hematologic PD and organ (heart and kidney) PD according to consensus guidelines). • To evaluate the organ response rate (OrRR) (heart, kidney, liver). • To evaluate treatment effects on patient-reported outcomes (PROs) such as the Short Form-36 Health Survey (SF-36), European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). • To characterize time to and duration of response. • To assess the safety and tolerability of daratumumab in patients with stage 3B AL amyloidosis. • To describe the proportion of subjects who received additional treatment with bortezomib and low dose dexamethasone (at the investigator's discretion).
Exploratory Objectives	• To evaluate CD 38 expression and its correlation with response to daratumumab. • To explore minimal residual disease status in amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse. • To evaluate diastolic function following treatment with daratumumab based on analysis of transthoracic echocardiograms

Study Treatment	The original design of this study was to treat patients with daratumumab intravenous (dara IV) infusion, however as of Protocol Amendment 1, all enrolled patients are to switch from IV to subcutaneous (dara SC) administration, and all new patients to initiate treatment directly with SC, whenever daratumumab SC supplies become available at the Sites. Daratumumab is administered at a dose of 16 mg/kg as an IV infusion or 1800 mg subcutaneously weekly for the first 8 weeks (Cycles 1 and 2) of treatment and then every 2 weeks for 4 cycles (Cycles 3 to 6) and then every 4 weeks until progression of disease (according to MOD-PFS), unacceptable toxicity or subsequent therapy, for a maximum of 2 years in total. Subjects who do not achieve either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4 Day 1 (see Table 8 in main Protocol for more details), may receive, in addition to daratumumab, bortezomib (for a maximum of 6 cycles) and low dose dexamethasone (total maximum weekly dose of 20mg).
Primary Endpoint	• The OS rate at 6 months post initiation of treatment with daratumumab.
Secondary endpoints	• MOD-PFS, defined as a composite endpoint of clinically observable endpoints from Cycle 1 Day 1 to any one of the following events, whichever comes first: death, clinical manifestation of cardiac failure, clinical manifestation of renal failure, development of hematologic PD. • PFS, defined as the time from the date of Cycle 1 Day 1 to the date of first documentation of hematologic disease progression, or organ (cardiac, renal, or liver) progression/need for transplant, or need for additional therapy (excluding the addition of bortezomib under protocol) or death due to any cause, whichever occurs first according to central laboratory results and judged by international consensus guidelines. • Hematologic ORR, defined as the proportion of subjects who achieve a best hematologic response of PR or better.

	• OrRR for kidney, heart, liver, defined as the proportion of baseline organ involved subjects who achieve organ response in each corresponding organ. • PRO/HRQoL: Subscales of the EORTC QLQ-C30, SF-36, EQ-5D-5L. • Time to next treatment (TTNT), defined as the time from the date of Cycle 1 Day 1 to the start date of subsequent AL amyloidosis (non-protocol) treatment. Death due to PD prior to subsequent therapy is considered as an event. • Hematologic VGPR rate, defined as the proportion of subjects who achieve hematologic VGPR. • Hematologic CR rate, defined as the proportion of subjects who achieve hematologic CR. • Time to hematologic response, defined as the time between the date of Cycle 1 Day 1 and the first efficacy evaluation that the subject has met all criteria for hematologic PR, VGPR or CHR. • Duration of hematologic response, defined as the time between the date of initial documentation of hematologic PR, VGPR or CHR to the date of first documented evidence of hematologic progressive disease. • Time to organ response, defined as the time between the date of Cycle 1 Day 1 and the first efficacy evaluation that the subject has each corresponding organ response. • Duration of organ response, defined as the time between the date of initial documentation of each corresponding organ response to the date of first documented evidence of the corresponding organ progressive disease. • Proportion of subjects who received bortezomib and low-dose dexamethasone after Cycle 3.

Exploratory endpoints	• Evaluation of CD38 expression. • Evaluation of minimal residual disease status in subjects who achieve complete hematologic response in bone marrow. • Assessment of diastolic heart function based on analysis of transthoracic echocardiogram.
Sample size calculations	According to published data the 6-month overall survival rate of patients with stage 3B amyloidosis is about 30%. Assuming a 6-month survival rate of at least 50% in patients treated with daratumumab IV/SC a sample size of 40 subjects provides 85% power to detect a difference using a 1-sided alpha of 0.05.

4. SAP Development Parameters

4.1.1 SAP Development Team

The document was developed according to the Standard Operating Procedure (SOP): "ST-SOP-13-v.2.0-Statistical Analysis Plan". It was reviewed by the Trial Statistician. Quality assurance was the responsibility of the Associate Director of Biostatistics and Analytics.

4.1.2 SAP Life Cycle Responsibility Task Matrix

The following matrix describes the roles and responsibilities related to the use, update, improvement and reproducibility of the SAP.

Task	Frequency	Owner	Approval
Version Control	ad hoc	Trial Statistician	Project Manager
Amendments	ad hoc	Trial Statistician	Sponsor
Interaction With Other Documents	ad hoc	Trial Statistician	Project Manager
Interaction With Other Trials	ad hoc	Trial Statistician	Project Manager
Quality Assurance	ad hoc	Trial Statistician	Associate Director of Biostatistics and Analytics
SAP deviations	ad hoc	Trial Statistician	Project Manager / Associate Director of Biostatistics and Analytics / Sponsor

5. Study Objectives

5.1.1 Primary Objectives

The primary objective is to evaluate the overall survival (OS) rate at 6 months following treatment with daratumumab in frontline AL patients with stage 3B disease.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the overall (ORR), very good partial (VGPR) and complete (CR) hematologic response rates at 3 and 6 months.
- To evaluate the Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from the start of study treatment (Cycle 1 Day 1) until any one of the following events (whichever occurs first)
  - Death
  - Clinical manifestation of cardiac failure:
    - Defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).
  - Clinical manifestation of renal failure:
    - Defined as the development of end stage renal disease (need for hemodialysis or renal transplant)
  - Development of hematologic progression of disease (PD) as per consensus guidelines (two consecutive assessments are required, see section
    - From CHR, abnormal free light chain ratio (light chain ratio must double).
    - From CHR/VGPR/PR, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present)
    - Free light chain increase of 50% to >100 mg/L.
- To evaluate PFS based on all-cause mortality and progression of disease (PD; including hematologic PD and organ (heart and kidney) PD according to consensus guidelines).
- To evaluate the organ response rate (OrRR):
  - Heart
  - Kidney
  - Liver.
- To evaluate treatment effects on patient-reported outcomes (PROs) such as the Short Form-36 Health Survey (SF-36), European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).
- To characterize time to and duration of response.
- To assess the safety and tolerability of daratumumab in patients with stage 3B AL amyloidosis.
- To describe the proportion of subjects who received additional treatment with bortezomib and low dose dexamethasone (at the investigator's discretion).

5.1.3 Exploratory objectives

The exploratory objectives are:

- To evaluate CD 38 expression and its correlation with response to daratumumab.
- To explore minimal residual disease status in amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse.
- To evaluate diastolic function following treatment with daratumumab based on analysis of transthoracic echocardiograms.

6. Study Methodology

6.1 Study Design

This is an open-label, multicenter, Phase 2 study in subjects with newly diagnosed stage 3B light chain (AL) amyloidosis. Approximately 40 subjects will receive primary therapy with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

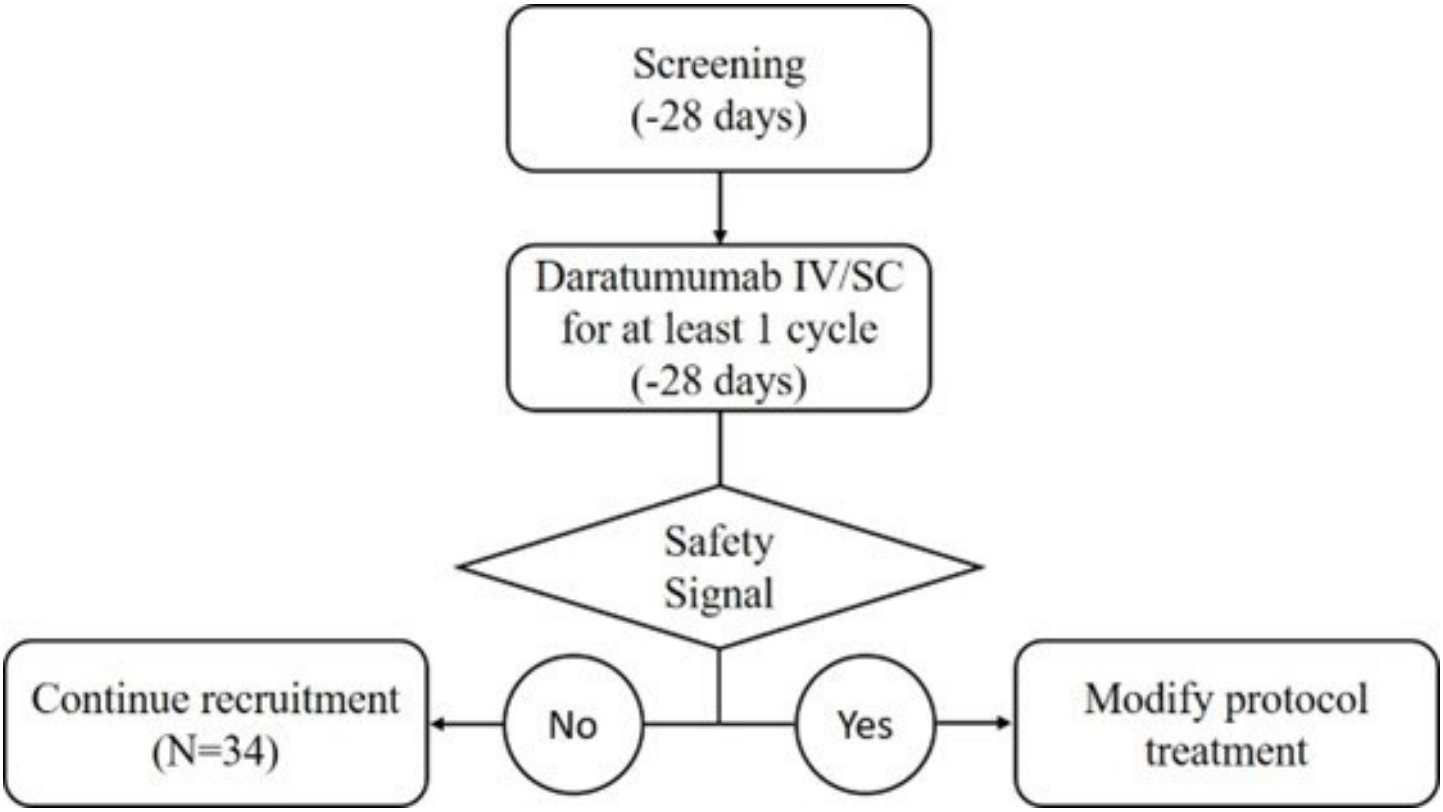
As per the study Protocol:

“A safety run-in will be conducted in 6 subjects treated with daratumumab for at least 1 cycle to establish safety of daratumumab in patients with stage 3B AL amyloidosis (Figure 1). Dosing of these 6 subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by a Data Safety Monitoring Board (DSMB) after at least 1 cycle is completed for all 6 subjects. The evaluation of the safety run-in will not include patients who will not have completed the first cycle for reasons unrelated to study treatment. More specifically, this would refer to patients who die, withdraw from the study, or discontinue study treatment for reasons other than toxicity, i.e., disease progression, patient choice, patient lost to follow-up. If no safety signal is observed, the enrollment of the rest of the patients will begin. Further details will be provided in the DSMB charter.

Subjects in the safety run in will continue all scheduled assessments as specified in the Time and Events schedule and contribute to the overall safety evaluation.”

Safety run-in was successfully completed, with no safety signal being observed. Enrolment of the rest of the patients was initiated.

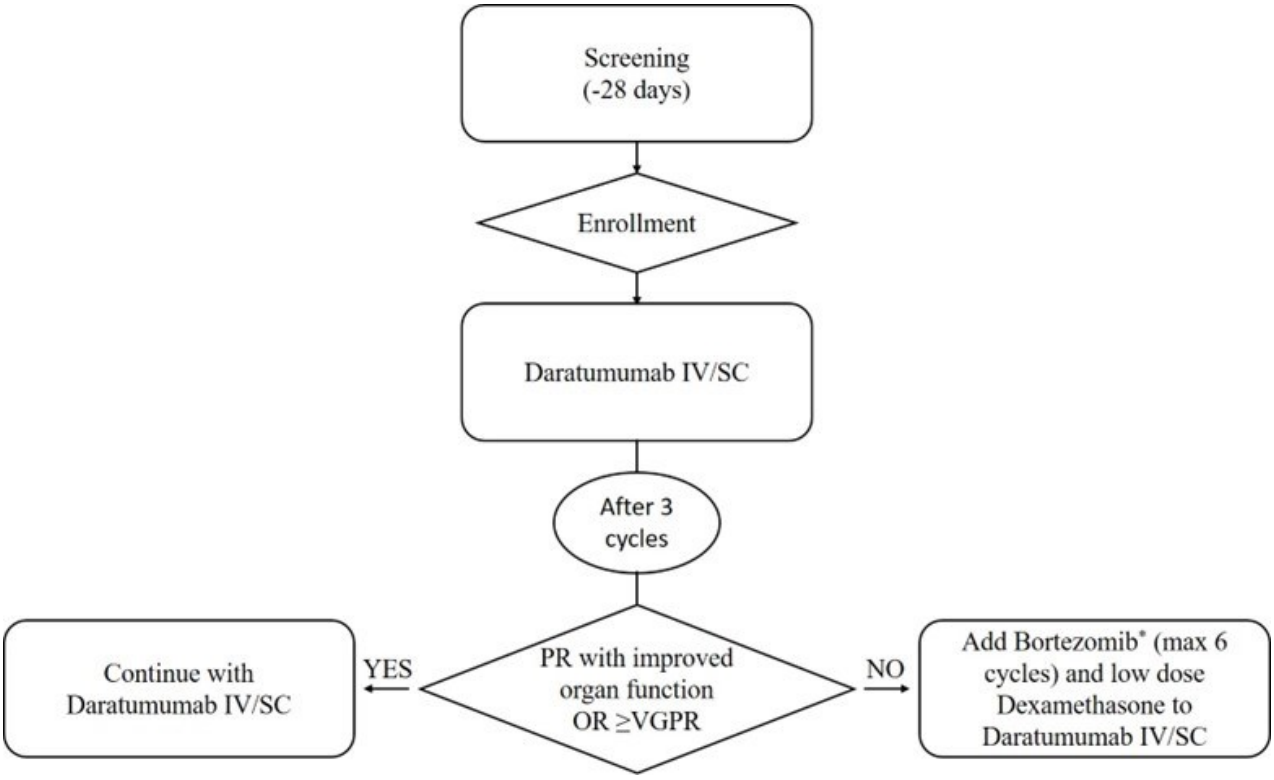
Figure 1 Schematic overview of the safety run-in



The original design of this study was to treat patients with intravenous daratumumab infusion (daratumumab IV). However, as of Protocol Amendment 1, all new subjects are dosed subcutaneously with daratumumab co-formulated with recombinant human hyaluronidase rHuPH20 (daratumumab SC). Subjects who already had begun treatment with daratumumab IV (i.e., prior to Amendment 1) must switch to daratumumab SC, on the next administration date according to the protocol schedule. Subjects receive daratumumab IV at a dose of 16 mg/kg and daratumumab SC at a fixed dose of 1800 mg according to the dosing schedule. All treatment cycles are 4 weeks (28 days) in length. Subjects receive daratumumab until disease progression (according to MOD-PFS), start of subsequent therapy, or a maximum of 2 years in total.

Patients who after 3 cycles of daratumumab monotherapy have not achieved at least a hematologic VGPR or a hematologic PR with improved major organ function (i.e cardiac or renal response per updated response criteria), may receive at the Investigator's discretion in addition to daratumumab weekly bortezomib (1.3 mg/m^2 weekly, for a maximum of 6 cycles) with low dose dexamethasone.

Figure 2 Schematic overview of the study



6.2 Duration of study participation

Duration of study participation for each participant

Subject participation include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase. Screening for eligible subjects is performed within 28 days before Cycle 1 Day 1. For subjects requiring mass spectrometry typing, the screening period is extended to 42 days. All subjects require approval from the sponsor before registration into the study. Cycle 1 should begin within 72 hours of approval for enrollment. Each following cycle should begin 28 days after Day 1 of the previous cycle, with a 5-day window permitted to accommodate holidays, weekends, or other site scheduling concerns. If Day 1 of a cycle is delayed for more than 5 days, then the entire cycle is delayed and the reason should be recorded in the CRF. Whenever study drug is administered for the first time in a cycle, that day will be considered Day 1.

Unless a subject withdraws consent for study participation or is lost to follow-up, an End-of-Treatment visit in the Post-Treatment Phase is to occur 4 weeks (±3 days) after the last dose of study treatment, or as soon as possible before the start of subsequent therapy. A second Post-Treatment visit will occur 4 weeks (±3 days) after the last dose. For subjects who discontinue study treatment, disease evaluations should continue to be performed in the Post-Treatment Observation Phase.

Subjects with confirmed disease progression according to MOD-PFS enter the Long-term Follow-up Phase.

Determination of end of the clinical trial (all participants)

This is not an event driven study. The end of the study will be at 2 years after the enrolment of the last participant.

6.3 Study Population

A complete list of all inclusion and exclusion criteria is provided in the study protocol.

6.4 Study drugs and dosing

Daratumumab is administered at a dose of 16 mg/kg as an IV infusion or 1800 mg subcutaneously weekly for the first 8 weeks (Cycles 1 and 2) of treatment and then every 2 weeks for 4 cycles (Cycles 3 to 6) and then every 4 weeks until progression of disease (according to MOD-PFS), unacceptable toxicity or subsequent therapy, for a maximum of 2 years in total.

For IV infusions, each subject's dose is calculated based on the subject's weight rounded to the nearest kilogram. The dose does not need to be recalculated for weight changes that are < 10% from baseline. The weight is used to determine the required volume of daratumumab from the vials needed for each subject. All infusions may be performed as outpatient visits. Subjects receive pre-infusion and post-infusion medications as detailed in the protocol.

Subjects that do not achieve either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4, may receive, in addition to daratumumab, bortezomib (for a maximum of 6 cycles) and low dose dexamethasone. However, the maximum total dose of 20 mg weekly dexamethasone will not be exceeded (i.e. on weeks that daratumumab is to be administered no additional dexamethasone [apart from the pre-infusion requirement] will be given).

These subjects will receive 1.3 mg/m^2 bortezomib as an SC injection weekly (Days 1, 8, 15, 22) in 28-day cycles for a maximum of 6 cycles. The amount (in mg) of bortezomib to be administered will be determined by Body Surface Area (BSA), calculated according to a standard nomogram. The total calculated dose of bortezomib may be rounded to the nearest decimal point (e.g., a calculated dose of 2.47 mg can be rounded to 2.5 mg). For subjects who experience injection site reactions, bortezomib may be administered by IV injection (see bortezomib SmPC). On daratumumab treatment days, subjects should receive bortezomib after daratumumab administration. The dose of bortezomib should be recalculated should the subject experience a weight change of more than 10% from baseline.

6.5 Sample Size Calculations

According to published data the 6-month overall survival rate of patients with stage 3B amyloidosis is about 30%. Assuming a 6-month survival rate of at least 50% in patients treated with daratumumab IV/SC a sample size of 40 subjects provides 85% power to detect a difference using a 1-sided alpha of 0.05.

6.6 Interim Analyses

Not applicable.

6.7 Protocol Deviations

In general, the major protocol deviations which may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study will be listed. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be listed by category for FAS analysis set.

A listing of all major protocol deviations including participant ID, type of deviation, and reasons for deviation will be provided.

6.8 Study Flowchart

The schedule of time and events are presented in Table 1.

Table 1 Time and Events Schedule

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	Screening Phase -28 days before C1D1	Cycles 1-6 D1 of each cycle	C7+ D1	EOT Post-treatment Week 4 (±3 days)	 Post-treatment Week 8 (±3 days)	
Study treatment should be initiated within 72 hours after sponsor's approval of eligibility. Cycles are approximately 28 days in duration. The start of each cycle may occur ±5 days of the scheduled day.							
Procedures							
Informed consent	ICF must be signed before any study-related procedure is performed.						
Eligibility criteria		X					
Demography/ Medical History		X					
Issue Subject Study ID Card		X					
Height		X					
Assessment of lytic disease	To exclude multiple myeloma; skeletal survey or other imaging modality	-42 days					
FEV1 test	Subjects with known or suspected COPD or asthma, FEV1 must be measured	X					
ECOG	See appendix 1	X	X		X		
LVEF assessment	Echocardiogram preferred, other cardiac evaluation of LVEF also acceptable	X		C7D1 and when clinically indicated	X		
12-lead ECG		X			X		
Physical exam	Including neurological exam. Clinically significant abnormalities should be reported as AEs	X	Symptom and disease directed exam as clinically indicated				

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	Screening Phase -28 days before C1D1	Cycles 1-6 D1 of each cycle	C7+ D1	EOT Post-treatment Week 4 (±3 days)	 Post-treatment Week 8 (±3 days)	
Vital signs, Weight		X	Please see Table 2 in the Protocol				
Patient-Reported Outcome (PRO)	Paper PRO (EORTC QLQ-C30, EQ-5D-5L and SF-36) before any other study procedures. Window is 4 days prior to dosing.		X	Every 8 weeks	X		
Blood type, Rh and IAT	Obtain sample before first dose of daratumumab.		C1D1				
Study Drug Administration							
Daratumumab			Please see Table 2 in the Protocol	Please see Table 2 in the Protocol			
Laboratory Assessments							
Pregnancy test	For women of childbearing potential only, within 14 days prior to Cycle 1 Day 1. Pregnancy testing will not be captured in the eCRF but will be archived in the subject's source documentation.	X	Weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles				
Hematology		X	Please see Table 2 in the Protocol		X		
Serum chemistry	Including TSH and T4 at screening and subsequently if clinically indicated	X	Please see Table 2 in the Protocol		X		
Hepatitis B (HBV) serology	Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 9.6 in the Protocol	X					
HBV DNA testing[1]	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 9.6 in the Protocol	X	Every 12 weeks (window ±7 days)		X	Every 12 weeks for up to 6 months after the last dose of study treatment	
Disease Assessments							
Clinical Evaluation of MOD-PFS endpoint	The MOD-PFS endpoint is defined in Section 2.1 and includes clinical manifestation of cardiac or renal failure, or hematologic PD, or death.	X	X	Every 8 weeks until disease progression			
NYHA Functional Classification	See Attachment 4 in the Protocol	X	X	Every 8 weeks until disease progression			

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	**Screening Phase** -28 days before C1D1	**Cycles 1-6** D1 of each cycle	**C7+** D1	**EOT** Post-treatment Week 4 (±3 days)	Post-treatment Week 8 (±3 days)	
Serum disease evaluations (SPEP)	Not required on C1D1 if screening labs were within 14 days of C1D1	X	X	Every 8 weeks until disease progression			
Urine disease evaluations (UPEP)	Not required on C1D1 if screening labs were within 14 days of C1D1	X	X	Every 8 weeks until disease progression			
Serum FLC	Sample to be sent to the central laboratory	X	**X Cycle1 weekly; D1, D8, D15, D22. Cycle 2-6; D1 only.**	Every 8 weeks until disease progression			
NT-proBNP assay	Sample to be sent to central laboratory.	X	X	Every 8 weeks until disease progression			
HS Troponin T	Sample to be sent to central laboratory	X	X	Every 8 weeks until disease progression			
Subsequent Therapy	Record anticancer therapy and response to therapy		Throughout study, and at least every 16 weeks during long-term follow-up				
Stem Cell Collection	Autologous stem cell transplant is prohibited prior to the completion of cycle 6		Stem cell collection permitted. Record mobilization agents as concomitant medications and stem cell yield (number of CD34+ cells per kg and time to engraftment. See protocol				
Other malignancies			Throughout study, and at least every 16 weeks during long-term follow-up				
Survival			Throughout study, and at least every 16 weeks during long-term follow-up				
Biomarkers							
Bone Marrow Biopsy/Aspirate	Morphology, immunohistochemistry, karyotype and/or FISH required by local lab as per standard practice [del17p, t(4;14), t(11;14), amp1q21 etc]	X (-56 days)					
	CD38: 3 unstained FFPE or biopsy slides, or 2 unstained and 1 H&E slide, local laboratory	X (-56 days)					

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	**Screening Phase** -28 days before C1D1	**Cycles 1-6** D1 of each cycle	**C7+** D1	**EOT** Post-treatment Week 4 (±3 days)	Post-treatment Week 8 (±3 days)	
Bone Marrow Biopsy/Aspirate (CD38, MRD)	MRD: 3 non decalcified aspirate slides (smears or clots), OR 3mL aspirate sample in EDTA, local laboratory	X (-56 days) (only for local laboratories where MRD is detected via Next Generation Sequencing)	When clinically feasible, bone marrow aspirate will be collected at CHR				
Ongoing Subject Review							
Adverse Events	See Section 12 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug. Subsequently, only AEs considered possibly, probably, or definitely related to the study treatment need to be reported. Ongoing SAEs should be followed to resolution.					
Concomitant Medications	See Section 8 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug					

Abbreviations: AE=adverse event; AntiHBc=hepatitis B core antibody; AntiHBs=hepatitis B surface antigen; C=cycle; CHR=complete hematologic response; COPD=chronic obstructive pulmonary disease;; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= End-of-Treatment; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L=European Quality of Life Five Dimensions Questionnaire; FEV= Forced Expiratory Volume (in 1 second); FFPE=formalin fixed paraffin embedded; FISH=fluoresence in situ hybridization; FLC=free light chain; HBV=Hepatitis B Virus; HS=high sensitivity; IAT=indirect antiglobulin testing; ICF=informed consent form; LVEF=Left Ventricular Ejection Fraction; MRD=minimal residual disease; H&E= hematoxylin and eosin; NT-ProBNP=N-terminal pro-brain natriuretic peptide; PRO= patient reported outcome; SAE= serious adverse event; SF-36= Short Form-36 Health Survey; T4=thyroxine; TSH=thyroid stimulating hormone; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis;

[1] In patients who develop reactivation of HBV while on treatment, study treatment (daratumumab and velcade/dexamethasone [if applicable]) should be interrupted and appropriate treatment should be instituted as per Investigator's discretion and current clinical guidelines. Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

7. Analysis populations

For the purpose of this analysis, the following analysis populations are defined in Table 2.

Table 2 Analysis Populations

Population	Description
Screened population	All screened patients
Full Analysis Set (FAS)	All enrolled subjects who received at least one dose of daratumumab

8. Derived Variables/Definitions

8.1 Efficacy variables/definitions

- **Overall survival (OS) time**

  OS time will be calculated:

  1) For the patients that have died:

  OS time (months) = [(Date of death – Date of first administration of study treatment + 1) x 12] / 365.25.

  2) For censored patients:

  OS time (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

  Censoring date for overall survival will be the last known date of patient being alive, and it will be defined as the latest date of End-of-Study, last cycle, End-of-Treatment, maximum date of post-treatment follow-up, or maximum date of survival follow-up.

- **MOD-Progression-free survival (MOD-PFS) time**

  MOD-PFS time will be calculated:

  1) For the patients with confirmed MOD-PFS:

  MOD-PFS time (months) = [(Date of the documentation of the first MOD-PFS event (before the initiation of subsequent therapy, if applicable) – Date of first administration of study treatment + 1) x 12] / 365.25.

  2) For censored patients:

  MOD-PFS time (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

  Censoring date for MOD-PFS will be the adequate disease assessment denoting absence of MOD-PFS event, and it will be defined as the latest date of the MOD-PFS data was assessed.

Note: For patients who start a subsequent therapy, MOD-PFS censoring date will be considered the latest date of the MOD-PFS assessment before the initiation of subsequent therapy. For patients who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date.

- **Progression-free survival (PFS) time**

  PFS time will be calculated as:

  1) For the patients with event (confirmed PD (hematologic or organ) or death or subsequent therapy):

  PFS time (months) = [(Date of the first documentation of the confirmed PD or death or initiation of subsequent therapy – Date of first administration of study treatment + 1) x 12] / 365.25.

  2) For censored patients:

  PFS time (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

  Censoring date for PFS will be the adequate disease assessment denoting absence of PFS event, and it will be defined as the latest date of the PFS data was assessed.

  Note: For patients who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date.

- **Difference between involved and uninvolved free light changes (dFLC)**

  dFLC (mg/L) = involved FLC (mg/L) - uninvolved FLC (mg/L).

  Involved FLC (iFLC) is the Kappa FLC if the kappa/lambda FLC ratio is higher than 1.65, while if the kappa/lambda FLC ratio is lower than 0.26, then the Lambda FLC is the involved one.

  The dFLC will be calculated for both screening and baseline, using the corresponding values.

- **Time to next treatment (TTNT)**

  TTNT will be calculated:

  1) For patients that received a subsequent therapy, or died due to PD/ disease related reason prior to subsequent therapy:

  TTNT time (months) = [(Date of subsequent therapy/death due to PD/ disease-related death– Date of first administration of study treatment + 1) x 12] / 365.25.

  2) For censored patients:

TTNT time (months) = ((Date of censoring – Date of first administration of study treatment + 1) x 12) / 365.25.

Censoring date for TTNT will be the last known date of patient being alive, and it will be defined as the latest date of End-of-Study, last cycle, End-of-Treatment, maximum date of post-treatment follow up, or maximum date of survival follow up.
Note: Deceased patients due to other reason than PD/ disease will be censored at the date of death.

- **Time to hematologic response**

  Time to hematologic response (months) will be calculated:

  1) For patients with event (confirmed hematologic response of PR or better):

  Time to hematologic response (months) = [(Date of initial evidence of the first confirmed hematologic response (PR or better)– Date of first administration of study treatment +1) x 12] / 365.25.

  2) For censored patients:

  Time to hematologic response (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

  Censoring date for time to hematologic response will be the latest adequate disease assessment denoting absence of confirmed hematologic response of PR or better, and it will be defined as the latest date of the hematologic response data was assessed.
  Note: Patients who do not have any post-baseline disease assessments will be censored at the administration of study treatment date.

- **Time to organ response**

  Time to organ response (months), for each corresponding organ (heart, kidney, liver) will be calculated:

  1) For patients with event (organ response):

  Time to organ response (months) = [(Date of organ response (heart, kidney, liver) – Date of first administration of study treatment +1) x 12] / 365.25.

  2) For censored patients:

  Time to organ response (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

Censoring date for time to organ response will be the latest adequate disease assessment denoting absence of organ response, and it will be defined as the latest date of the organ response data was assessed, for each corresponding organ.

Note: Patients who do not have any post-baseline disease assessments will be censored at the administration of study treatment date.

- **Time to first response**

  Time to first response (months) will be calculated for patients with confirmed hematologic response as:

  Time to first response (months) = [(Date of the first evidence of first confirmed at least Partial Response – Date of first administration of study treatment +1) x 12] / 365.25.

- **Time to best hematologic response**

  Time to best response (months) will be calculated for patients with confirmed hematologic response as:

  Time to best response (months) = [(Date of the first evidence of the best confirmed response – Date of first administration of study treatment +1) x 12] / 365.25.

- **Time to hematologic VGPR**

  Time to hematologic VGPR (months) will be calculated for patients with confirmed hematologic response as:

  Time to hematologic VGPR (months) = [(Date of the first evidence of confirmed VGPR – Date of first administration of study treatment +1) x 12] / 365.25.

- **Time to hematologic CR**

  Time to hematologic CR (months) will be calculated for patients with confirmed hematologic response as:

  Time to hematologic CR (months) = [(Date of the first evidence of confirmed CR – Date of first administration of study treatment +1) x 12] / 365.25.

- **Duration of hematologic response (DoR)**

  Duration of hematologic response (months) will be calculated for patients achieved at least hematologic partial response as:

1) For patients with event (confirmed hematologic PD or death due to PD or disease-related reason before the initiation of subsequent therapy, if applicable):

DoR time (months) = [(Date of initial documentation of the confirmed PD or death due to PD / disease-related reason – Date of evidence of initial confirmed hematologic response of PR or better +1) x 12] / 365.25.

2) For censored patients:

DoR time (months) = [(Date of censoring – Date of first evidence of initial confirmed hematologic response of PR or better +1) x 12] / 365.25.

Censoring date for DoR will be the latest adequate disease assessment denoting absence of confirmed hematologic disease progression, and it will be defined as the latest date of the hematologic disease progression data was assessed (before the initiation of subsequent therapy, if applicable).

- **Duration of organ response (DoR)**

Duration of organ response will be provided separately for heart, kidney and liver.

Duration of organ response (months) will be calculated within patients with organ response as:

1) For patients with event (organ PD or death due to PD or disease-related reason before the initiation of subsequent therapy, if applicable) as:

DoR time (months) = [(Date of initial documentation of the PD or death due to PD/disease-related reason - Date of first organ response +1) x 12] / 365.25.

2) For censored patients:

DoR time (months) = [(Date of censoring – Date of organ response +1) x 12] / 365.25.

Censoring date for DoR will be the adequate disease assessment denoting absence of organ progression and it will be defined as the latest date of the organ progression data was assessed (before the initiation of subsequent therapy, if applicable).

Landmark Overall Survival

Landmark Overall Survival time will be calculated:

1) For the patients that have died:

OS time (months) = [((Date of death – Date of first administration of study treatment + 1) x 12) / 365.25]-landmark time in months.

2) For censored patients as

OS time (months) = [((Date of censoring – Date of first administration of study treatment + 1) x 12) / 365.25]- landmark time in months.

Censoring date for overall survival will be the last known date of patient being alive, and it will be defined as the latest date of End-of-Study, last cycle, End-of-Treatment, maximum date of post-treatment follow-up, or maximum date of survival follow up.

- **MOD-Event-free survival (MOD-EFS) time**

  MOD-EFS time will be calculated:

  1) For the patients with confirmed MOD-EFS event:

  MOD-EFS time (months) = [(Date of the documentation of the first MOD-EFS event– Date of first administration of study treatment + 1) x 12] / 365.25.

  2) For censored patients:

  MOD-EFS time (months) = [(Date of censoring – Date of first administration of study treatment + 1) x 12] / 365.25.

  Censoring date for MOD-EFS will be the adequate disease assessment denoting absence of MOD-EFS event, and it will be defined as the latest date of the MOD-EFS data was assessed.

  Note: For patients who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date.

8.2 Patient-reported outcomes variables/ definitions

- **EORTC QLQ-C30:**

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items (Table 3). Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

Table 3. Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range[1]	Item numbers
Global health status / QoL				
Global health status / QoL (revised)[2]	QL2	2	6	29,30
Functional scales				
Physical functioning (revised)[2]	PF2	5	3	1 to 5
Role functioning (revised)[2]	RF2	2	3	6,7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20,25
Social functioning	SF	2	3	26,27
Symptom scales/items				
Fatigue	FA	3	3	10,12,18
Nausea and vomiting	NV	2	3	14,15
Pain	PA	2	3	9,19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28
[1]Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range =3.				
[2](revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.				

The principle for scoring these scales is the same in all cases[1]:

1. Estimate the average of the items that contribute to the scale; this is the raw score.

For all scales, the RawScore (RS), is the mean of component items I_1, I_2,…, I_n:

$$RS = (I_1 + I_2 + \cdots + I_n)/n$$

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100.

For Functional scales, the standardized score S is:

$$S = \left\{1 - \frac{RS - 1}{range}\right\} * 100$$

For Symptom scales/items and Global health status/QoL, the standardized score S is:

$$S = \left\{\frac{RS - 1}{range}\right\} * 100$$

If at least half of the items from the scale have been answered, use all the items that were completed, and apply the standard equations given below for calculating the scale scores; ignore any items with missing values when making the calculations. If more than half of the items from the scale are missing, set scale score to missing and for single-item measures, set score to missing.

Also, the EORTC QLQ-C30 Summary Score, proposed by Giesinger et al. 2016[1], is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available.

The summary score is calculated as follows:
Summary Score = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhoea)/13.

- **SF-36**

The SF-36 taps eight multi-item scales: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health (Reported Health Transition item). Item values are recoded in order to calculate scale scores.

Verbatim items are reported in Table 4 while scoring information in Table 5.

Table 4 Verbatim items

Item	Verbatim item
1	In general, would you say your health is:
3a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
3b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
3c	Lifting or carrying groceries
3d	Climbing several flights of stairs
3e	Climbing one flight of stairs
3f	Bending, kneeling, or stooping
3g	Walking more than a mile
3h	Walking several blocks
3i	Walking one block
3j	Bathing or dressing yourself
4a	Cut down the amount of time you spent on work or other activities
4b	Accomplished less than you would like
4c	Were limited in the kind of work or other activities
4d	Had difficulty performing the work or other activities (for example, it took extra effort)
5a	Cut down the amount of time you spent on work or other activities
5b	Accomplished less than you would like
5c	Didn't do work or other activities as carefully as usual
6	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
7	How much bodily pain have you had during the past 4 weeks?
8	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
9a	Did you feel full of pep?
9b	Have you been a very nervous person?
9c	Have you felt so down in the dumps that nothing could cheer you up?
9d	Have you felt calm and peaceful?
9e	Did you have a lot of energy?

9f	Have you felt downhearted and blue?
9g	Did you feel worn out?
9h	Have you been a happy person?
9i	Did you feel tired
10	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
11a	I seem to get sick a little easier than other people
11b	I am as healthy as anybody I know
11c	I expect my health to get worse
11d	My health is excellent

Table 5 Scoring information

Scale	Items	Response choices	Precoded item value	Final item value
Physical functioning	**3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j**	Yes, limited a lot	1	1
		Yes, limited a little	2	2
		No, no limited at all	3	3
Role- physical	**4a, 4b, 4c, 4d**	All of the time	1	1
		Most of the time	2	2
		Some of the time	3	3
		A little of the time	4	4
		None of the time	5	5
General health	**1**	Excellent	1	5
		Very good	2	4.4
		Good	3	3.4
		Fair	4	2
		Poor	5	1
	11a & 11c	Definitely true	1	1
		Mostly true	2	2
		Don’t know	3	3
		Mostly false	4	4
		Definitely false	5	5
	11b & 11d	Definitely true	1	5
		Mostly true	2	4
		Don’t know	3	3
		Mostly false	4	2
		Definitely false	5	1
Vitality	**9a, 9e**	All of the time	1	5
		Most of the time	2	4
		Some of the time	3	3
		A little of the time	4	2
		None of the time	5	1
	9g, 9i	All of the time	1	1
		Most of the time	2	2
		Some of the time	3	4
		A little of the time	4	5
		None of the time	5	6
Social functioning	**6**	Not at all	1	5
		Slighlty	2	4
		Moderately	3	3
		Quite a bit	4	2
		Extremely	5	1
	10	All of the time	1	1
		Most of the time	2	2
		Some of the time	3	3
		A little of the time	4	4
		None of the time	5	5
Role- emotional	**5a, 5b, 5c**	All of the time	1	1
		Most of the time	2	2

		Some of the time	3	3
		A little of the time	4	4
		None of the time	5	5
Mental Health	**9b, 9c, 9f**	All of the time	1	1
		Most of the time	2	2
		Some of the time	3	3
		A little of the time	4	4
		None of the time	5	5
	9d & 9h	All of the time	1	5
		Most of the time	2	4
		Some of the time	3	3
		A little of the time	4	2
		None of the time	5	1
Bodily pain	**7**	None	1	6
		Very mild	2	5.4
		Mild	3	4.2
		Moderate	4	3.1
		Severe	5	2.2
		Very severe	6	1
	8- if item 7 is not answered	Not at all	1	6
		A little bit	2	4.75
		Moderately	3	3.5
		Quite a bit	4	2.25
		Extremely	5	1
	8- if both items 7 & 8 are answered	Not at all	1	6 (if item 7 precoded value=1)
		Not at all	1	5 (if item 7 precoded value=2-6)
		A little bit	2	4
		Moderately	3	3
		Quite a bit	4	2
		Extremely	5	1

After item recoding, a raw score is computed for each scale, which is the sum of responses for all items in that scale, as shown in Table 5. Generally, if the responder answers at least 50% of the items in a multi-items scale, the score should be calculated ignoring any missing items, otherwise the score for that scale should be set to missing.. Each row scale score is then transformed into a 0-100 scale using the formula (1):

$$Transformed\ Scale = \left[\frac{(actual\ raw\ score - lowest\ possible\ low\ score)}{Possible\ raw\ score\ range}\right] x100 \qquad (1)$$

Table 6 provides the necessary information to apply this formula to each scale.

Table 6 Formulas for scoring and transforming scales

Scale	Sum final item values (after recoding items as in Table 5)	Lowest and highest possible raw scores	Possible raw score range
Physical functioning	3a+3b+3c+3d+3e+3f+3g+3h+3i+3j	10,30	20
Role-physical	4a+4b+4c+4d	4,20	16
Bodily pain	7+8	2,12	10
General health	1+11a+11b+11c+11d	5,25	20
Vitality	9a+9e+9g+9i	4,20	16
Social functioning	6+10	2,10	8
Role-emotional	5a+5b+5c	3,15	12
Mental health	9b+9c+9d+9f+9h	5,25	20

- **EQ-5D-5L**

The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain / discomfort and anxiety / depression) and each dimension has five response levels. EQ-5D-5L health states can be summarized using a single summary number (index value or utility score). An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The collection of index values (weights) for all possible EQ-5D health states is called a value set. Most EQ-5D value sets have been obtained from a standardized valuation exercise, in which a representative sample of the general population in a country/region is asked to place a value on EQ-5D health states. Country-specific EQ-5D value sets will be used for participants from each center, except for participants from Greece that the Italy-based value set will be adopted, as there is no available value set for Greece[2].

The EQ-5D-5L utility index using the Italian and French value sets will be calculated as follows:

$$EQ-5D-5L\ index = 1 - \sum_{i=1}^{5} w_{ij}$$

where i is the corresponding dimension and w_{ij} is the assigned value (weight) of the corresponding response level j.

The EQ-5D-5L utility index using the Dutch value sets will be calculated as follows:

$$EQ-5D-5L\ index = 1 - 0.047 - \sum_{i=1}^{5} w_{ij}$$

where i is the corresponding dimension and w_{ij} is the assigned value (weight) of the corresponding response level j. If all response levels are equal to 1, then the $EQ-5D-5L$ utility $index$ will be set equal to 1.

The weights for each dimension corresponding to each response level are provided in Table 7 by country.

Table 7 EQ-5D-5L value sets by country

Dimension	Response level	France	Netherlands	Italy
Mobility	1	0	0	0
	2	0.038	0.035	0.051
	3	0.048	0.057	0.064
	4	0.179	0.166	0.244
	5	0.325	0.203	0.329
Self-care	1	0	0	0
	2	0.037	0.038	0.046
	3	0.051	0.061	0.056
	4	0.172	0.168	0.216
	5	0.258	0.168	0.257
Usual activities	1	0	0	0
	2	0.033	0.039	0.050
	3	0.040	0.087	0.064
	4	0.157	0.192	0.225
	5	0.240	0.192	0.255
Pain/ discomfort	1	0	0	0
	2	0.022	0.066	0.044
	3	0.047	0.092	0.109
	4	0.264	0.360	0.318
	5	0.444	0.415	0.322
Anxiety/ depression	1	0	0	0
	2	0.020	0.070	0.044
	3	0.047	0.145	0.109
	4	0.200	0.356	0.318
	5	0.258	0.421	0.322

8.3 Treatment variables/definitions

- **Date of first administration of study treatment**

  The date of first administration of study treatment (Cycle 1 Day 1) is the start date when a non-zero dose of daratumumab was administered.

- **Date of last administration of study treatment**

  The date of last administration of study treatment is the latest date when a non-zero dose daratumumab was administered.

- **Number of treatment cycles**

  The number of treatment cycles for each patient is the sum of treatment cycles that the patient received study treatment.

- **Duration of exposure to study treatment**

  Duration of exposure to study treatment for patients who took at least one dose of daratumumab, borezomib or dexamethasone will be calculated, for each drug, as:

✓ Duration of exposure (months) = [(Date of last administration of study treatment - Date of first administration of study treatment + 1) x12]/ 365.25.

✓ Duration of exposure (cycles) = Number of treatment cycles on study treatment (i.e., number of cycles the patient received at least one treatment component).

The duration of exposure to study treatment includes the periods of temporary interruptions of the study treatment for any reason.

- **Cumulative dose**

  Cumulative dose will be defined as the total dose given during the study treatment exposure and will be calculated for each of the study treatment components separately (daratumumab, bortezomib, dexamethasone), whenever is applicable, as the sum of all non-missing/non-zero dose values of that study treatment component, regardless of visit/cycle

  The total cumulative dose will be calculated in mg for daratumumab, in mg for dexamethasone and in mg/m^2 for bortezomib.

- **Dose intensity (DI)**

Dose intensity (DI) of daratumumab and bortezomib (when applicable) will be defined as:

DI (dose unit/month) = Cumulative dose (dose unit) / Duration of exposure to study drug (months)

- **Planned dose (PDI)**

  Planned dose (PDI) is the assigned planned dose to be given to the subjects as per protocol, and it will be used for the calculation of Relative dose intensity (RDI).

  As Daratumumab initially was planned to be administered at a dose of 16 mg/kg and as per protocol amendment 1 as an IV infusion or 1800 mg subcutaneously, planned dose intensity will be considered only for patients that started medication with SC, or for entire periods that patients were treated with SC after switching from IV:

  1) For Cycles 1-2 of treatment: Planned DI = 7200 mg/month
  2) For Cycles 3-6 of treatment: Planned DI = 3600 mg/month
  3) Post Cycle 7: Planned DI = 1800 mg/month

- **Relative dose intensity (RDI)**

  The Relative dose intensity (RDI) of daratumumab is the ratio of the dose intensity and planned dose intensity (PDI), and it will be based on patients/ periods that Daratumumab was administrated SC.

  RDI will be expressed as a percentage, and it will be defined as:

  RDI = 100 * Dose Intensity (mg/month) / PDI (mg/month), separately for each period

8.4 Other derived variables/definitions

- **End of follow-up and duration of follow-up**

  The end date of follow-up will be the maximum study date. The maximum study date will be determined by the maximum collection/assessment date within the clinical database.

  Duration of follow-up will be calculated as:

  Duration of follow-up (months) = [(Date of death or end date of follow-up – Date of first administration of study treatment + 1) x12] / 365.25

- **Body Mass Index (BMI)**
  - ✓ BMI (kg/m^2) = Weight (Kg) / Height^2 (m)

- **BMI groups**
  - ✓ Underweight (BMI < 18.5 Kg/m^2)
  - ✓ Normal weight (18.5 Kg/m^2 ≤ BMI < 25 Kg/m^2)
  - ✓ Overweight (25 Kg/m^2 ≤ BMI < 30 Kg/m^2)
  - ✓ Obese (BMI ≥ 30 Kg/m^2)

- **Presence of at least one high-risk cytogenetic abnormality**

  The presence of at least one high-risk cytogenetic abnormality will be defined as at least one abnormal result in any of the FISH tests (17p13, 1q21, t(4;14), t(11;14), t (14;16)). If any of 17p13, 1q21, t(4;14), t(11;14), t (14;16) tests is not done/ not evaluable and normal results are recorded for the evaluable tests, the presence of at least one cytogenetic abnormality will be characterized also as not evaluable.

- **Revised Mayo 2012 stage**

  Patients are assigned a score of 1 for each of
  - dFLC ≥ 18 mg/dL (180 mg/L)
  - cTnT ≥ 0.025 ng/mL (25 pg/mL)
  - NT-ProBNP ≥ 1,800 pg/mL.

  Summing the above scores, the revised Mayo 2012 stage is:
  - I if the sum of scores is equal to 0 (the patient does not have any of the above conditions)
  - II if the sum of scores is equal to 1 (the patient has any of the above conditions)
  - III if the sum of scores is equal to 2 (the patient has any two of the above conditions)
  - IV if the sum of scores is equal to 3 (the patient has all the above conditions)

9. Coding

The Anatomical Therapeutic Chemical (ATC) drug classification dictionary of the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC-ATC) will be used for coding medications (latest version at the time of analysis onset). Concomitant medication and subsequent treatments will be coded by the WHOCC ATC in terms of main anatomical pharmacological group (1st level), and chemical substance (5^{th} level), as applicable.

All recorded AEs and medical history will be coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) (the most updated version at the timing of coding).

All AEs will be assessed by the Investigator for severity according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (14 June 2010). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each AE.

10. Statistical Methodology

10.1 General statistical methodology

Statistical analysis and generation of tables and patient data listings will be performed using SAS® statistical analysis software (the most updated version at the time of analysis onset). Figures will be created by validated graph programs, such as SAS® and/or Microsoft Excel. Categorical variables will be presented in frequency tables (number of patients and corresponding percentage), while summary statistics [number of patients with available data (n), mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) percentiles, minimum (min) and maximum (max)] will be used for continuous variables. Statistical tests to be performed, other than the primary endpoint, will be considered of exploratory nature, and the level of significance will be set to $\alpha = 0.05$. Differences between groups for time to event endpoints will be investigated based on log-rank or Wilcoxon test, depending on the proportionality of hazards assumption, while for the rest of endpoints based on Wilcoxon rank sum. Individual differences between timepoints will be assessed using the Wilcoxon sign-rank test. The direction of the association of the time to event analysis by subgroup will be supported by Hazard Ratio and corresponding 95% CI.

Definition of baseline

Baseline data will be considered the data collected closest in time to the date of first administration of study treatment (but prior to first dosing of any of the study drugs).

Missing or partial dates

The imputation of partial dates will be done only if the date involved in the computation of variables needed for the study analysis. If the date is completely missing, no imputation will be performed. In case of partially missing dates the following rules will be applied:

- If only the day is missing: the day will be set to the first day of the month for start dates and to the last day of the month for end dates.
- If both the day and month are missing: the date will be set to the 1st of January for start dates and to the 31st of December for end dates.
- If day, month and year missing: no imputation will be performed.

In case where a partial date after the general imputation rule comes in reasonable opposition with another date in the eCRF (e.g., end of a concomitant medication prior to the start date of study treatment; end date after the selected cut-off date), then the date will be imputed so as to be in reasonable time sequence, as applicable.

Handling of missing data

No imputation will be conducted for missing data, with the exception of the dates as described above. Censoring rules will be applied for time-to-events endpoints.

10.2 Subgroup analysis

Study endpoints may further be examined in pre-specified subpopulations as defined in **Table 7.** These analyses may be performed provided that the number of patients in each group will allow for meaningful inferences and are applicable for the analysis.

Table 8. Subgroup analyses: Stratification factors

Item	Variables	Endpoints to be examined
Stratification factor	Best hematologic Response at 1 month (NR vs PR/VGPR/CR)	OS
	Best hematologic Response at 3 months (NR vs PR/VGPR/CR)	
	Best hematologic Response at 6 months (NR vs PR/VGPR/CR)	
	Best hematologic Response at 1 month (NR/PR vs VGPR/CR)	
	Best hematologic Response at 3 months (NR/PR vs VGPR/CR)	
	Best hematologic Response at 6 months (NR/PR vs VGPR/CR)	
	Cardiac response at 3 months (yes, no)	
	Cardiac response at 6 months (yes, no)	
	Best hematologic response at 1 month (CR vs VGPR vs PR vs NR/death)	
	Best hematologic response at 3 months (CR vs VGPR vs PR vs NR/death)	
	Best hematologic response at 6 months (CR vs VGPR vs PR vs NR/death)	
	Organ involvement apart from heart (yes, no)	
	MRD status (positive/negative) at 3 months	
	MRD status (positive/negative) at 6 months	
	NTproBNB (≥ vs < median) at screening	OS, ORR
	NTproBNB (≥ vs < median) at baseline	
	dFLC (≤ vs > 400 mg/L) at baseline	
	dFLC (≤ vs > 400 mg/L) at screening	
	dFLC (< vs ≥ 180 mg/L) at screening	
	dFLC (< vs ≥180 mg/L) at baseline	
	dFLC (< vs ≥ 100 mg/L) at screening	

dFLC (< vs ≥100 mg/L) at baseline	
iFLC (< vs ≥ 200 mg/L) at screening	
iFLC (< vs ≥ 200 mg/L) at baseline	
HS Troponin (≥ vs < median) at screening	
HS Troponin (≥ vs < median) at baseline	
HS Troponin (> vs ≤ 77 pg/ml) at screening	
HS Troponin (> vs ≤ 77 pg/ml) at baseline	
Hematologic Response at 3 months (NR vs PR/VGPR/CR)	Change in NT-proBNP & HS Troponin T (absolute
Hematologic Response at 6 months (NR vs PR/VGPR/CR)	Change in NT-proBNP & HS Troponin T (absolute
Initiation of bortezomib treatment (yes, no)	OS, PFS, ORR

10.3 Analysis Time Windows

Assessments within the time windows provided in Table 9 will be used for hematologic and organ responses.

Table 9 Analysis time windows

Response	Response time	Time window
Best hematologic response	1 month	Best response up to 31 days
	3 months	Best response up to 91 days
	6 months	Best response up to 183 days
	9 months	Best response up to 273 days
	12 months	Best response up to 365 days
	18 months	Best response up to 546 days
	24 months	Best response up to 730 days
Best cardiac response	3 months	Best response up to 91 days
	6 months	Best response up to 183 days
	9 months	Best response up to 273 days

	12 months	Best response up to 365 days
	18 months	Best response up to 546 days
	24 months	Best response up to 730 days
Organ response	3 months	Organ response between 2.5-3.1 months
	6 months	Organ response between 5.5-6.1 months
	9 months	Organ response between 8.5-9.1 months
	12 months	Organ response between 11.5-12.1 months
	18 months	Organ response between 17.5-18.1 months
	24 months	Organ response between 23.5-24.1 months

10.4 Statistical specifications

10.4.1 Subject disposition

The number of subjects who were screened; screen failures; eligible for enrolment; enrolled but not treated; administrated at least one dose of study treatment (i.e., FAS) will be presented as a table, along with a CONSORT diagram.

Tables and graphs will be based on screened population.

10.4.2 Demographics and anthropometric characteristics at baseline

The following patient and anthropometric characteristics will be presented in frequency tables (n, %) at baseline for the FAS:

- Age categories (<75 and ≥75 years)
- Gender
- Race

- Childbearing potential, for females

In addition, age will be summarized (n, mean, SD, median, Q1, Q3, min and max).

10.4.3 General medical history

General medical history/comorbidities will be descriptively analysed. Patient's distribution by MedDRA SOC and PT will be presented at screening, overall and by NCI CTCAE grade based on the FAS. Prior medical procedures and medical procedures during the trial will be provided by MedDRA SOC and PT.

10.4.4 Baseline patient and clinical characteristics

Patient and clinical characteristics recorded at screening and included in the inclusion/exclusion criteria of this clinical trial will be provided. The following variables will be summarized in the FAS:

- NYHA classification of heart failure (I, II, IIIA, IIIB, IV)
- ECOG PS (0, 1, 2, 3, 4)
- NT-proBNP (pg/ml)
- HS Troponin T (pg/ml)
- dFLC (mg/L)

The following variables recorded at baseline will be presented using the number of patients with available data and the respective proportion (n, %):

- BMI group
- NYHA classification of heart failure (I, II, IIIA, IIIB, IV)
- ECOG PS (0, 1, 2, 3, 4)
- Revised Mayo 2012 stage (I, II, III, IV)
- Presence of M-protein in serum (immunofixation) (positive, negative) and immunotype
- Presence of M-protein in urine (immunofixation) (positive, negative) and immunotype
- Organ involvement apart from heart (yes, no) and organ involved apart from heart (the proportion of patients by involved organ will also be calculated over the total number of patients with organ involvement apart form heart)
- Presence of at least one high-risk cytogenetic abnormality (yes, no) & description (17p13, 1q21, t(4;14), t(11;14), t (14;16), overall chromosome number (hypoploidy, diploidy, hyperploidy, not evaluated by FISH)

- Plasma cells categories (<10%, 10%-30%, >30%) in bone marrow aspirate or in bone marrow biopsy (if both assessments are available, the maximum value will be used)
- Prior cancer-related surgery (yes, no)
- Prior radiotherapy (yes, no)
- Biopsy result (Congo red staining) (negative, positive, not yet available)

The following variables will be presented using summary statistics (n, mean, SD, median, Q1, Q3, min and max):

- Vital signs and anthropometric characteristics: height (cm), weight (kg), BMI, pulse (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (^{o}C)
- Hematology: white blood cell count (10^3/µL), absolute lymphocytes, absolute neutrophils, red blood cell count (10^6/µL), hemoglobin (g/dL) and platelet count (10^3/µLU).
- Number of organs involved apart from heart
- Serum chemistry: alanine aminotransferase [ALT] (U/L), total bilirubin (µmol/L), direct bilirubin (if history of Gilbert's syndrome) (mg/dL), albumin (g/dL), calcium (mmol/L), alkaline phosphatase [ALP] (U/L), aspartate aminotransferase [AST] (U/L), creatinine (µmol/L), estimated glomerular filtration rate [eGFR] (mL/min/1.73m^2), glucose (µmol/L), phosphate (µmol/L), potassium (mmol/L), sodium (mmol/L), thyroid stimulating hormone (mU/L), serum thyroxine (T4) (nmol/L), prothrombin time (PT) (sec), partial thromboplastin time (PTT) (sec), factor X levels (%), total protein in the urine (g/L).
- Plasma cells (%) in bone marrow aspirate or in bone marrow biopsy (if both assessments are available, the maximum value will be used)
- Serum M-protein (g/L), kappa FLC (mg/L), lambda FLC (mg/L), FLC ratio, dFLC (mg/L), involved FLC type (kappa, lambda)
- Urine M-protein (g/24h)
- Cardiac biomarkers: NT-proBNP (pg/ml), HS Troponin T (pg/ml)
- LVEF value (%) and result (normal, abnormal, unknown)
- Diastolic dysfunction assessment: Left ventricular internal diameter in diastole (mm), left ventricular intra- ventricular septal thickness (mm), left ventricular posterior wall thickness (mm), mitral valve inflow E-wave velocity (E) (cm/sec), mitral annular velocity of lateral wall (Ea) (cm/sec), E/Ea ratio

The above analysis will be presented in FAS.

10.4.5 Concomitant & subsequent treatment

Concomitant treatment

Concomitant medications taken concurrently with the study treatment will be summarized by the WHOCC ATC in terms of main anatomical pharmacological group and chemical substance in the FAS. The number and proportion of patients who received each medication at baseline and those who received each medication at least once throughout the study will be presented.

Subsequent treatment

The number and proportion of patients who received subsequent therapy for AL amyloidosis or stem cell transplant will be presented in the FAS. Individual listings for the systemic treatment will be provided, presenting the regimen, start date and reason for subsequent treatment.

10.4.6 Drug exposure

The number and proportion of patients:

- by total number of cycles received daratumumab
- by total number of cycles received bortezomib
- with at least one IV daratumumab administration
- with at least SC IV daratumumab administration
- with at least one dose delay (for each drug)
- with at least one reason for dose delay (for each drug)
- with at least one dose skip (for each drug)
- with at least one reason for dose skip (for each drug)
- with at least one dose reduction (for bortezomib and dexamethasone)
- with at least one reason for dose reduction (for bortezomib and dexamethasone)
- with at least one cycle delay throughout the study
- with at least one reason for cycle delay, for those with at least one cycle delay will be presented.

Also, summary statistics will be presented for:

- the total number of cycles received daratumumab, overall and by type of administration (IV, SC)the total number of cycles received bortezomib

- the total number of cycles delayed
- the duration of exposure (months) to daratumumab and bortezomib
- cumulative dose for daratumumab, bortezomib and dexamethasone
- cumulative dose for daratumumab by type of administration (IV, SC)
- actual DI for daratumumab and bortezomib (when applicable)
- RDI for daratumumab.

The analysis of study drug exposure will be conducted in the FAS. Daratumumab exposure variables will be also presented for those who only received daratumumab and for those who received additional treatment with bortezomib and dexamethasone.

10.4.7 Endpoint analysis

10.4.7.1 Primary Endpoint Analysis

OS rate at 6 months post initiation of treatment with daratumumab.

For the analysis of the primary endpoint, survival analysis techniques will be employed based on the FAS. Death from any reason will be considered as event, while patients that are alive or their vital status are unknown will be censored at the date, they were last known to be alive. For the calculation of the OS time and the censoring date rules please refer to Section 8.1.

The number of patients that are alive or dead will be presented along with the median survival time and the corresponding 95% CI. Overall Survival rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 week, 2 weeks, 3 weeks, 1 month, and for every three months following Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

Primary Hypothesis.

The primary hypothesis of this study is that the 6-month OS rate will exceed 30%, which according to published data stands for the 6-month OS rate for patients with newly diagnosed stage 3B AL amyloidosis patients after therapy with Daratumumab.

In statistical terms:

H_0: Overall survival rate at 6 months $\leq$ 30%

H_1: Overall survival rate at 6 months > 30%

In order to investigate this one-sided primary hypothesis on a level of significance of $\alpha = 0.05$, a 90% two-sided CI for the 6-month overall survival rate will be provided. If the lower bound of the 6-month overall survival confidence interval is superior to the historical OS rate (30%), then the null hypothesis will be rejected, and it will be declared that the 6-month OS rate of the current study is superior to the historical 6-month OS rate (30%).

10.4.7.2 Secondary Endpoint Analysis

The secondary endpoints are the following:

- **MOD-PFS**

  MOD-PFS will be defined as a composite endpoint of clinically observable endpoints from Cycle 1 Day 1 to any one of the following events, whichever comes first, before the initiation of subsequent therapy, if applicable:

  - Death.
  - Clinical manifestation of cardiac failure, defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).
  - Clinical manifestation of renal failure, defined as the development of end stage renal disease (need for hemodialysis or renal transplant).
  - Development of hematologic progression of disease (PD) as per consensus guidelines (two consecutive assessments are required.

  For the MOD-PFS, survival analysis techniques will be employed on the FAS. Death from any reason, clinical manifestation of cardiac failure, clinical manifestation of renal failure or development of confirmed hematologic progression of disease (PD), whichever comes first, will be considered as event.

  Patients who neither progress nor die or whose vital status is unknown will be censored at the date of their last adequate disease assessment. For patients who start a new treatment, MOD-PFS will be censored at the date of the last adequate assessment before the start of the new treatment. Subjects who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date. For the calculation of the MOD-PFS time and the censoring date rules please refer to Section 8.1.

  The number of patients with and without MOD-PFS event will be presented along with the median MOD-PFS time and the corresponding 95% CI. MOD-PFS rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1.

The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **PFS**

PFS will be defined as the time from the date of Cycle 1 Day 1 to the date of first documentation of the following events, whichever comes first, before the initiation of subsequent therapy according to central laboratory results and judged by international consensus guidelines:

- hematologic disease progression
- organ (cardiac, renal, or liver) progression/need for transplant
- need for additional therapy (excluding the addition of bortezomib under protocol)
- death due to any cause

For the PFS, survival analysis techniques will be employed on the FAS. Hematologic disease progression, organ (cardiac, renal, or liver) progression/need for transplant, need for additional therapy (excluding the addition of bortezomib under protocol), or death due to any cause, whichever comes first, will be considered as event. Patients who neither progress/need transplant nor die or whose vital status is unknown will be censored at the date of their last adequate disease assessment. Subjects who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date. For the calculation of the PFS time and the censoring date rules, please refer to Section 8.1.

The number of patients with and without PFS events will be presented along with the median PFS time and the corresponding 95% CI. PFS rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Hematologic ORR**

Hematologic ORR will be defined as the proportion of subjects who achieve a hematologic response of Partial Response (PR) or better over the total number of patients in FAS.

The hematologic response categories are shown in the below Table 10 based on the International Amyloidosis Consensus Criteria:

Table 10 International Amyloidosis Consensus Criteria

Response Category	Criteria
Complete Response	Normalization of free light chain ratio, negative serum and urine immunofixation
Very Good Partial Response	In subjects with baseline dFLC ≥ 50 mg/L, reduction in the dFLC to <40 mg/L
Partial Response	b. In subjects with baseline dFLC ≥ 50 mg/L, a reduction in dFLC by ≥ 50% (not fulfilling the VGPR criteria) c. A greater than 50% reduction in M protein concentration in subjects whose baseline dFLC is <50 mg/L and have a measurable M protein (≥5 g/L) d. ONLY in subjects with baseline dFLC ≥ 20 and < 50 mg/dL: dFLC < 10 mg/dL (but Immunofixation positive)
No response	Less than a PR
Progression	From CHR, abnormal free light chain ratio (light chain must be double) From CHR/VGPR/PR, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present) Free light chain increase of 50% to >100 mg/L

Abbreviations: CHR, Complete hematologic response; dFLC difference between involved FLC and uninvolved FLC; FLC free light chain; PR, partial response; VGPR, very good partial response

For all hematologic response categories, two consecutive assessments are required at any time based on discrete samples. The best hematologic response will be considered the highest of the confirmed responses that have been achieved as shown above. Time to first response will be defined as the date of the first Daratumumab administration to the date of the first evidence of a confirmed at least Partial Response, while time to best hematologic response will be defined as the time from the date of the first Daratumumab administration to first evidence of the best confirmed response was achieved for each patient. Summary statistics for time to first response and time to best response will be provided for the patients achieved at least Partial Response.

A table with the number and percentage of the best response of patients will be provided on the FAS, for the overall period, and at 3,6, 9, 12, 18 and 24 months. Additionally, the ORR rate will be provided along with the 95% Confidence interval for the overall period, and at 3,6, 9, 12, 18 and 24 months. 95% CIs will be calculated based on the normal approximation.

A swimmer's plot will be provided, showing the evolution of hematologic response of each patient throughout study.

- **Organ Response Rate (OrRR) for kidney, heart, liver**

  The organ response rate will be defined for each organ (kidney, heart, liver) separately, as the proportion of patients who achieve organ response, over the number of patients with the corresponding organ involvement at baseline. Additionally, any organ response will be defined as the proportion of patients with any organ response (kidney, heart, liver), over the number of patients with at least one organ involvement at baseline.

The number and percentage of baseline organ involved patients with organ response (for each organ and at any organ) along with the corresponding 95% CI will be presented, at 3 , 6, 9, 12, 18 and 24 months, based on the FAS. 95% CIs will be calculated based on the normal approximation.

- **Time to next treatment (TTNT)**

For the TTNT analysis, survival analysis techniques will be employed on the FAS. Initiation of subsequent AL amyloidosis (non-protocol) treatment or death due to PD prior to subsequent therapy or disease-related death will be considered as event, while patients that are alive and haven't initiated a subsequent therapy or whose vital status is unknown will be censored at the last date known to be alive. Deceased patients due to other reason than PD will be censored at the date of death. For the calculation of the TTNT time and the censoring date rules please refer to Section 8.1.

The number of patients that received subsequent AL amyloidosis (non-protocol) treatment or death due to PD prior to subsequent therapy or those with disease-related death and those who haven't initiated a subsequent therapy or died due to other cause than PD (excluding disease-related deaths) will be presented along with the median TTNT time and the corresponding 95% CI. TTNT rates based on Kaplan-Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Hematologic VGPR rate**

  The hematologic VGPR rate will be defined as the proportion of subjects who achieve at least a hematologic VGPR over the FAS. The number and percentage of patients with at least Hematologic VGPR along with the corresponding 95% CI will be presented, overall, at 3 months and at 6 months, based on the FAS. The time to VGPR will be defined as the date of the first Daratumumab administration to the date of the first evidence of confirmed VGPR or better. Summary statistics for time to VGPR will be provided for patients who achieved at least hematologic VGPR or better. The 95% CIs will be calculated based on the normal approximation.

- **Hematologic CR rate**

  The Hematologic CR rate will be defined as the proportion of subjects who achieve hematologic CR over the FAS. The number and percentage of patients with Hematologic CR along with the corresponding 95% CI will be presented, overall, at 3 months and at 6 months, based on the FAS. The time to CR will be defined as the date of the first Daratumumab administration to the date of the first evidence of confirmed CR. Summary statistics for time to CR will be provided for those with hematologic CR. The 95% CIs will be calculated based on the normal approximation.

- **Time to hematologic response**

  For time to hematologic response, survival analysis techniques will be employed in the FAS. Confirmed hematologic response (PR or better) will be considered as event. Patients who have not achieved a hematologic PR or better or whose hematologic response status is unknown will be censored on the date of their last adequate disease assessment documenting the absence of confirmed hematologic response of PR or better. For the calculation of the time to hematologic response and the censoring date rules please refer to Section 8.1.

  The number of patients with and without hematologic PR or better will be presented along with the median time to hematologic response and the corresponding 95% CI. Hematologic response rates of PR or better based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Duration of hematologic response**

  For Duration of Response, survival analysis techniques will be employed, for the patients that achieved at least a hematologic Partial Response in the FAS. Confirmed hematologic PD (two consecutive assessments are required) or death due to PD or disease-related reason, before the initiation of subsequent therapy, if applicable, will be considered as event. Patients who are alive and have achieved a hematologic PR or better without confirmed PD or whose hematologic progression status is unknown will be censored on the date of their last adequate disease assessment documenting the absence of hematologic disease progression, before the initiation of subsequent therapy, if applicable. For the calculation of the DoR time and the censoring date rules please refer to Section 8.1.

  The number of patients with hematologic PR or better and a confirmed PD or death due to PD or disease-related reason and those with a hematologic PR or better but without confirmed PD or death due to PD or disease-related reason will be presented along with the median duration of hematologic response and the corresponding 95% CI. DoR rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Time to organ response**

  For time to organ response, survival analysis techniques will be employed in the FAS, for each corresponding organ (heart, kidney, liver). Organ response will be considered as event. Patients who have not achieved an organ response or whose organ response status is unknown will be censored on the date of their last adequate disease assessment documenting the absence of organ response. For the calculation of the time to organ response and the censoring date rules please refer to Section 8.1.

  The number of patients with and without organ response will be presented along with the median time to organ response and the corresponding 95% CI. Organ response rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Duration of organ response**

  For the duration of organ response, survival analysis techniques will be employed for the patients that achieved organ response in the FAS. Duration of organ response will be provided separately for heart response, kidney response and liver response. Patients who have achieved an organ (heart, kidney, liver) response and have a PD or died due to PD or disease-related reason, before the initiation of subsequent therapy, if applicable, will be considered as events. Patients who are alive and have achieved an organ (heart, kidney, liver) response without PD or whose organ progression status is unknown will be censored on the date of their last adequate disease assessment documenting the absence of organ (heart, kidney, liver) progression, before the initiation of subsequent therapy, if applicable. For the calculation of the duration of organ response time and the censoring date rules please refer to Section 8.1.

  The number of patients with organ response and a PD for each organ or died due to PD or disease-related reason and those with organ response but without PD or death for each corresponding organ will be presented along with the median duration of organ response for each organ and the corresponding 95% CI. DoR rates for each organ based on Kaplan-Meier estimator will also be presented with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

- **Proportion of subjects who received bortezomib and low-dose dexamethasone after Cycle 3.**

  The number and percentage of patients who received bortezomib and low-dose dexamethasone after Cycle 3 will be presented in the FAS.

- **Patient-reported outcomes (PROs)**

➢ **EQ-5D-5L:**

Number and percentage of patients over FAS will be presented by level of perceived problems for the five dimensions comprising the descriptive part of the EQ-5D-5L at baseline. Also, for patients on treatment at cycle 4, corresponding numbers and percentages will be presented for baseline and cycle 4. Respectively, each domain answers will be presented for baseline and EOT. For patients who did not perform the EOT visit, LOCF approach will be employed, i.e. last available values will be considered as EOT.

Additionally, a cross tabulation of number and percentage of patients by level of perceived problems for the five dimensions at baseline and cycle 4 as well as baseline and EOT will be provided. Summary statistics of EQ-VAS and utility index will be presented for the FAS at baseline, for patients on treatment at cycle 4, at baseline and at cycle 4; and for patients with EOT visit, at baseline and EOT. For patients who did not perform the EOT visit, LOCF approach will be employed, i.e. last available values will be considered as EOT. Summary statistics of the within-patient change in EQ-VAS and utility index from baseline at cycle 4 and EOT will be also reported, along with a Wilcoxon sign-rank test p-value to evaluate these differences. In order to investigate any statistical differences between specific time points, mixed models for repeated measures may be employed on FAS using the EQ-VAS and the utility index as dependent variable. Mean EQ-VAS scores and mean utility indexes by cycle will be presented in a line diagram overall and by overall best response (≥VGPR vs <VGPR). The analysis will be performed in the FAS.

- **QLQ-C30 version 3:**

For the calculation of QLQ-C30 scores please refer to Section 8.2.

Summary statistics of the QLQ-C30 summary score and the scores of the five functional scales, three symptom scales, the six single items and the global health status/ QoL scale will be presented for the FAS at baseline, for patients on treatment at cycle 4 at baseline and at cycle 4 and for patients with EOT visit at baseline and EOT. For patients who did not perform the EOT visit, LOCF approach will be employed, i.e. last available values will be considered as EOT. Summary statistics of the within-patient change in score from baseline at cycle 4 and EOT will be also reported, along with a Wilcoxon sign-rank test p-value to evaluate these differences.

In order to reflect the meaningful baseline changes, a within-patient ≥ 10-point shift in either direction from baseline is considered a remarkable change in EORTC-QLQ-C30 score[3]; number and percentage of patients with >10-point improvement (improved), ≥10-point deterioration (worsened) and between 10-point improvement and 10-point deterioration (stable) will be presented at cycle 4 and EOT for all scores. For patients who did not perform the EOT visit, LOCF approach will be employed, i.e. last available values will be considered as EOT.

Number and percentage of patients with impaired functioning and clinically significant symptoms by scale will be provided for baseline, cycle 4 and EOT. For patients who did not perform the EOT visit,

LOCF approach will be employed, i.e. last available values will be considered as EOT. Cut-off values for impairment and clinically significant symptoms will be obtained from Giesinger et al. 2020[4].

The results will also be presented in two groups (SC and IV daratumumab administration), if the sample size in each group is at least 10 patients since the respective questionnaire includes two questions related to the treatment.

Mean scores by cycle will be presented in a line diagram overall by overall best response (≥VGPR vs <VGPR). Specifically, separate figures will be provided for:

- QLQ-C30 summary score and Global health status / QoL score
- Functional scales' scores (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning)
- Symptoms scales' scores (fatigue, nausea and vomiting, and pain)
- Single item symptoms' scores (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)

The analysis will be performed in the FAS.

- **SF-36:**

For the calculation of SF-36 scores please refer to Section 8.2. Summary statistics of the 8 scale scores of SF-36 will be presented for the FAS at baseline, for patients on treatment at cycle 4 at baseline and at cycle 4 and for patients with EOT visit at baseline and EOT. Also, the number and percentage of patients by each response of the Reported Health Transition item for the FAS at baseline, for patients on treatment at cycle 4, at baseline and at cycle 4; and for those with EOT visit, at baseline and EOT, will be presented. For patients who did not perform the EOT visit, LOCF approach will be employed, i.e. last available values will be considered as EOT.

Summary statistics of the within-patient change in score from baseline at cycle 4 and EOT will be also reported, along with a Wilcoxon sign-rank test p-value to evaluate these differences.

Mean scores by cycle will be presented in a line diagram, overall and by overall best response (≥VGPR vs <VGPR). Specifically, separate figures will be provided for:

- Physical health state scores (physical functioning, role limitations due to physical health, bodily pain)
- Mental health state scores (role limitations due to emotional problems, mental health, social functioning, vitality)
- General health score

The analysis will be performed in the FAS.

10.4.7.3 Exploratory Endpoint Analysis

- **Evaluation of CD38 expression**

  The number and percentage of patients with positive result in evaluation of CD38 expression will be presented, overall and by best overall response (<VGPR vs >=VGPR, <CR vs CR).

  The analysis will be performed in the FAS.

- **Evaluation of minimal residual disease (MRD) status in subjects who achieve complete hematologic response in bone marrow.**

  The number and percentage of patients who achieve MRD negativity overall and in patients who achieve complete hematologic response will be presented. Also, OS will be provided by MRD status (positive, negative) at 3 and 6 months. Details for the OS time to event analyses can be found in Sections 10.4.7.1 and 10.4.7.2, respectively. The analysis will be performed in the FAS.

- **Assessment of diastolic heart function based on analysis of transthoracic echocardiograms**

  Assessment of diastolic heart function based on analysis of transthoracic echocardiograms, as part of the safety analysis, includes the following parameters, if available locally:

  - Left Ventricular Internal Diameter in Diastole (LVIDd): (mm)
  - Left Ventricular Intra-ventricular Septal Thickness: (mm)
  - Left Ventricular Posterior wall thickness: (mm)
  - Mitral Valve Inflow E-wave velocity (E): (cm/second)
  - Mitral annular Velocity of Lateral wall (Ea): (cm/second)
  - E/Ea ratio
  - LVEF: (%)

  Summary statistics will be provided for these parameters at baseline, 3, 6, 12 and 24 months post baseline. Also, differences (absolute and percent) between baseline and 3 months post baseline as well as baseline and 6 months post baseline will be presented and evaluated by applying a Wilcoxon sign-rank test.

  The analysis will be performed in the FAS.

10.4.8 Extra analysis

1. Overall Survival Landmark analysis at 1 and 3 months

Overall Survival Landmark analysis at 1 and 3 months will be performed on the FAS. Only patients that did not discontinued for any reason at 1 and 3 months respectively will be included in this analysis. At 1 and 3 months, hematologic response will be evaluated, and patients will be grouped to those with at least PR and those with no response or progression at 1 month and 3 months respectively. The timepoints of hematologic evaluation based on which the categorization will be performed will be defined as Landmark times. From this time point, the overall survival will be evaluated for the two groups.

Death from any reason will be considered as event, while patients that are alive or their vital status are unknown will be censored at the date, they were last known to be alive. This date will be the maximum date of End-of-Study, last cycle, End-of-Treatment, maximum date of post-treatment follow up, or maximum date of survival follow up. For the calculation of the overall Landmark Survival time please refer to Section 8.1.

The number of patients that are alive and deceased will be presented along with the median survival Landmark time and its 95% CI, for those with at least PR and those with no response or progression at Landmark times. Overall Survival rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method, while differences between groups will be investigated based on log-rank or Wilcoxon test, depending on the proportionality of hazards assumption. Graphs of Kaplan-Meier survival functions will also be presented by response group.

2. Overall Survival Landmark analysis at 3 months by bortezomib initiation

Overall Survival Landmark analysis at 3 months by bortezomib initiation will be performed on the FAS. Only patients that did not discontinued for any reason at 3 months will be included in this analysis. At 3 months, patients will be grouped to those who initiated bortezomib and low-dose of dexamethasone and those that continued treatment with daratumumab monotherapy. The timepoint of bortezomib and low-dose dexamethasone initiation will be defined as Landmark times. From this time point, the overall survival will be evaluated for the two groups. This analysis does not intend to assess the Vd addition in terms of efficacy, as the underlying populations are different as per protocol.

Death from any reason will be considered as event, while patients that are alive or their vital status are unknown will be censored at the date, they were last known to be alive. This date will be the maximum date of End-of-Study, last cycle, End-of-Treatment, maximum date of post-treatment follow up, or maximum date of survival follow up. For the calculation of the overall Landmark Survival time please refer to Section 8.1.

The number of patients that are alive and deceased will be presented along with the median survival Landmark time and its 95% CI, for those with at least PR and those with no response or progression at Landmark times. Overall Survival rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method, while differences between groups will be investigated based on log-rank or Wilcoxon test, depending on the proportionality of hazards assumption. Graphs of Kaplan-Meier survival functions will also be presented by response group.

3. Cardiac biomarkers

Absolute and percent changes of HS troponin and NT-proBNP at 3 and 6 months post baseline will be summarized in the FAS. The differences (absolute and percent) of the cardiac biomarkers will be examined using the Wilcoxon signed-rank test.

4. Best cardiac response rate

Best cardiac response will be calculated using the minimum NT-proBNP post-baseline value. Best cardiac response rate will be defined as the proportion of subjects who achieve a best cardiac response over the FAS.

Cardiac response categories are presented in the below Table 11.

Table 11 Cardiac response categories

Response category	Criteria
Complete Response (CR)	NT-proBNP <450 pg/ml.
Very Good Partial Response (VGPR)	≥60% NT-proBNP reduction from baseline
Partial Response (PR)	NT-proBNP 30–59% reduction from baseline

A table with the number and percentage of the best cardiac response of patients will be provided on the FAS, for the overall period and for 3, 6, 9, 12, 18 and 24 months.

5. MOD-EFS

MOD-EFS will be defined as a composite endpoint of clinically observable endpoints from Cycle 1 Day 1 to any one of the following events, whichever comes first, :

- Death.
- Clinical manifestation of cardiac failure, defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).
- Clinical manifestation of renal failure, defined as the development of end stage renal disease (need for hemodialysis or renal transplant).
- Development of hematologic progression of disease (PD) as per consensus guidelines (two consecutive assessments are required.
- Initiation of subsequent therapy

For the MOD-EFS, survival analysis techniques will be employed on the FAS. Death from any reason, clinical manifestation of cardiac failure, clinical manifestation of renal failure or development of confirmed hematologic progression of disease (PD) and initiation of subsequent therapy, whichever comes first, will be considered as event.

Patients who neither progress nor initiate subsequent therapy nor die or whose vital status is unknown will be censored at the date of their last adequate disease assessment. Subjects who do not have any post-baseline disease assessments and who had not died will be censored at the administration of study treatment date. For the calculation of the MOD-EFS time and the censoring date rules please refer to Section 8.1.

The number of patients with and without MOD-EFS event will be presented along with the median MOD-EFS time and the corresponding 95% CI. MOD-EFS rates based on Kaplan – Meier estimator will also be presented along with the 95% CIs at 1 month, and for every three months following the Cycle 1 Day 1. The 95% CIs to be presented will be calculated based on the log-log method. Graphs of Kaplan-Meier survival functions will also be presented.

10.4.9 Safety Analysis

Safety analysis will be based on the FAS. All treatment emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and Preferred Term (PT). If multiple AEs are reported for the same patient under the same PT or SOC, they will be counted once, based on the maximum severity grade.
TEAE is defined as an event that emerges during treatment, while having been absent pre-treatment, or worsens relative to the pre-treatment state. Regarding the AEs relation to study drugs, an AE will be considered treatment related, if it is considered possibly, probably, or definitely related to study drug.

A Safety Overview table will be provided including the number and the percentage of patients that have experienced:

- at least one TEAE
- at least one serious TEAE
- at least one non-serious TEAE
- at least one serious TEAE related to any of the study drugs
- at least one non-serious TEAE related to any of the study drugs
- at least one TEAE grade ≥3
- at least one TEAE grade 3/4
- at least one serious TEAE grade ≥3
- at least one non-serious TEAE grade ≥3
- fatal TEAE
- at least one Adverse Event of Special Interest (AESI) related to any of the study drugs
- at least one TEAE leading to permanent discontinuation of any of the study drugs
- at least one Infusion Related Reaction (IRR)

Treatment Emergent AEs will be summarized by SOC and PT in separate tables for:

- all recorded TEAEs (serious and non-serious), overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) related to study treatment, overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) grade 3/4, overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) grade≥3, overall and by maximum toxicity grade

- all recorded TEAEs (serious and non-serious) grade 3/4 related to study treatment, overall and by maximum toxicity grade
- all recorded serious TEAEs, overall and by maximum toxicity grade
- all recorded serious TEAEs related to study treatment, overall and by maximum toxicity grade
- all recorded serious TEAEs grade 3/4, overall and by maximum toxicity grade
- all recorded serious TEAEs grade≥3, overall and by maximum toxicity grade
- all recorded serious TEAEs grade 3/4 related to study treatment, overall and by maximum toxicity grade
- all recorded non-serious TEAEs, overall and by maximum toxicity grade
- all recorded non-serious TEAEs related to study treatment, overall and by maximum toxicity grade
- all recorded non-serious TEAEs grade 3/4, overall and by maximum toxicity grade
- all recorded non-serious TEAEs grade≥3, overall and by maximum toxicity grade
- all recorded non-serious TEAEs grade 3/4 related to study treatment, overall and by maximum toxicity grade
- all fatal TEAEs
- all fatal TEAEs related to study treatment
- all recorded TEAEs (serious and non-serious) leading to permanent study drug discontinuation, overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) leading to permanent daratumumab discontinuation, overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) leading to permanent bortezomib discontinuation, overall and by maximum toxicity grade
- all recorded TEAEs (serious and non-serious) leading to permanent dexamethasone discontinuation, overall and by maximum toxicity grade
- all recorded AESIs, overall and by maximum toxicity grade
- all recorded AESIs related to daratumumab, overall and by maximum toxicity grade
- all recorded non-serious TEAEs related to daratumumab, overall and by maximum toxicity grade
- all recorded non-serious TEAEs related to bortezomib, overall and by maximum toxicity grade
- all recorded non-serious TEAEs related to dexamethasone, overall and by maximum toxicity grade

Other safety analyses will include:

- cross tabulation of number and percentage of patients by ECOG category at baseline and EOT (or last available)
- cross tabulation of number and percentage of patients by physical examination status at baseline and EOT (or last available)
- summary statistics for patients' weight at baseline and EOT (or last available), and for corresponding differences
- number and percentage of patients with at least one hospitalization for a primary cardiac or non-cardiac indication, length of hospitalization, use of hemodialysis, cardiac assist devices (IABP and/or LVAD), and/or solid organ transplantation of the kidney or heart.

10.4.10 Listings

A listing including the: patient id, AE description, SOC, PT, AE start date, AE end date, outcome, maximum toxicity grade, action taken, concomitant therapy given for the event and the relationship to each study drug, will be provided for:

- all non-serious TEAEs
- all serious TEAEs
- AESIs
- fatal TEAEs
- TEAEs that led to the discontinuation of daratumumab
- non-TEAEs.

10.4.11 Extra Listings

A listing of deaths will be presented including the following information: subject id, age, gender, date of first administration of study treatment, date of last administration of study treatment, date of death, primary cause of death, specification of other reason of death, SOC/PT of AE that led to death.

10.4.12 Changes from protocol

- All analysis for EMN22/54767414AMY2005 clinical study will be conducted on the Full Analysis Set population, identical to the Safety and ITT mentioned in the study protocol. Full Analysis Set consists of all enrolled subjects who received at least one dose of daratumumab. Patients that signed ICF but were not treated will be excluded from the endpoint analyses.
- For Duration of Response endpoints, deaths due to progressive disease and disease-related deaths are also considered events, as evidence of progressive disease, to ensure comparability of results with current literature
- For Time to next treatment endpoint, deaths due disease-related reasons are also considered events, along with deaths due to progressive disease, to ensure comparability of results with current literature.

11. References

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