STATISTICAL ANALYSIS PLAN

Study:

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

Title: DARE

Study Code: EAE-2017/MM02

Version 1.0, EN

Date: 02-02-2018

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Document History

Version	Date	Comments	Revised section(s) if applicable
1.0	02-02-2018	First Version	

Distribution List

Company	Name	E-Mail Address

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General Info

Trial Name	DARE
Study Code	EAE-2017/MM02
Document Name	STATISTICAL ANALYSIS PLAN
Production	
Date	02-02-2018
Responsible	George Cheliotis
Last Mutation	
Date	Not Applicable
Responsible	
Current Version	Vers. 1.0
Status	Final Document
Number of Pages	28
Owner Organization	
Producer Organization	HeaDS
Goal/Contents	Description of the listings, tables, graphics and statistical analyses of the study

List of Abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CKD	Chronic Kidney Disease
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DaraD	Daratumumab with Dexamethasone
DMP	Data Management Plan
DoR	Duration of Response
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EoT	End of Treatment
FAS	Full Analysis Set
IMWG	International Myeloma Working Group
IV	Intra-Venus
MM	Multiple Myeloma
M-protein	Serum monoclonal paraprotein
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PRRenal	Partial Renal Response
PT	Preferred Term
QW	weekly intervals
Q2W	every 2 weeks
Q4W	every 4 weeks
RI	Renal Impairment
RRR	Renal Response Rate
RRMM	Replaced/Refractory Multiple Myeloma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TNT	Time to Next Therapy
WOCBP	Women of childbearing potential

1. Scope of the Document

This document describes the listings, tables, graphics and statistical analyses of the DARE study ("Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment.") 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.

2. General Analysis Framework

Data will be entered electronically on the electronic Case Report Form (eCRF) by the investigator or authorized personnel in the participating sites via an electronic data capture (EDC) platform using a web-based secure server.

In case of incomplete dates, imputations will be applied as specified in the Data Management Plan (DMP). For the calculation of durations, the imputed date will be used. In listings, the incomplete date will be presented. In case further pre-processing to create derived variables is required these derived variables will be contained in the analysis datasets, rather than creating them within the reporting programs.

2.1 Databases

Extracts of the data base will be used regularly to facilitate the program writing. The data extracts will be transferred to the analysis environment and will be used as the basis for the analysis.

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

4. Short Trial Description

Study Title:	Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment
Methods:	This is a multicenter, single arm, open-label phase 2 study. Approximately 38 subjects will be enrolled to receive daratumumab + dexamethasone. Treatment cycles haveduration is 28 days. Subjects will receive treatment until disease progression or unacceptable toxicity. Drug administration and follow-up visits will occur more frequently for early cycles (weekly for the first 8 weeks, every two weeks for weeks 9-24 and then every 4 weeks). Disease evaluations will occur monthly and consist mainly of measurements of myeloma proteins. Other assessments may include bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin, and β2- microglobulin and albumin. Assessment of myeloma response and disease progression will be conducted in accordance with the modified International Myeloma Working Group (IMWG) response criteria. Assessment of renal response will be conducted in accordance with the IMWG response criteria. Survival status and data of subsequent antimyeloma treatment will be collected post-treatment.
Objectives:	The primary objective of this study is to evaluate progression free survival (PFS) in patients with relapsed/refractory MM (RRMM)with renal impairment (RI). The secondary objectives are the following: • To evaluate Overall Response Rates (ORR) • To evaluate Renal Response Rates (RRR) • To evaluate duration of response in patients with RI. • To evaluate time to next therapy. • To evaluate Overall Survival (OS). • To assess the safety and tolerability of Daratumumab with dexamethasone in patients with RRMM and RI.
Endpoints	Primary endpoint: Progression-free survival Secondary Endpoints: • Overall response rate • Renal Response Rates (RRR) • Duration of response • Time to next therapy • Overall survival • Safety; adverse events (AE)
Population:	About 38 patients will be enrolled. Main inclusion criteria are the following: 1. Males and females at least 18 years of age. 2. Voluntary written informed consent before performance of any study-related procedure 3. Myeloma requiring systemic therapy

	4. Myeloma relapsing after, or refractory to, two or more different prior therapies, including immunomodulatory agents, proteasome inhibitors and chemotherapy with alkylating agents. Subject must have documented relapsed or refractory MMas defined by the criteria below: a) Monoclonal plasma cells in bone marrow ≥ 10% or presence of a biopsy proven plasmacytoma. b) Measurable disease as defined by any of the following: • Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL (except for IgA subtype: ≥ 0.5 g/dL) or urine M-protein level ≥ 200 mg/24 hours; or • Light chain multiple myeloma: Serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free-light-chain ratio. 5. An eGFR < 30 ml/min/1.73 m2 (CKD-EPI formula) or in need for dialysis 6. Eastern Cooperative Oncology Group performance-status score of 2 or less 7. Life expectancy of at least 3 months 8. Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drugs and one within 24 hours prior to the start of study drugs. Women must not be breastfeeding. WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 3 months after cessation of daratumumab treatment. Males who are sexually active with WOCBP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy.
Phase:	II
Number of Sites enrolling participants:	The study will be conducted at approximately 5 sites located in Greece and approximately 2 sites located in Italy.
Description of Study Treatment:	Daratumumab will be given at a dose of 16 mg/kg administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Dexamethasone will be administered according to standard clinical practice. The recommended dose of dexamethasone is 40 mg (20 mg for patients > 75 years of age) orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Participant	Subjects will receive treatment until disease progression or unacceptable

Duration:	toxicity. Survival status and data of subsequent antimyeloma treatment will be collected post-treatment.
Study Duration:	The maximum duration of the study is of 30 months considering an accrual period of 18 months and a follow-up of the last patient for 12 months.

5. SAP Development Parameters

5.1.1 SAP Development Team

The document was developed according to the SOP: "ST-SOP-13-v1-Statistical Analysis Plan". It was authored by the trial statistician and reviewed by the project manager. Quality assurance was the responsibility of the Chief Scientific Officer.

5.1.2 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	Project Manager	Clinical Operations Manager & Quality Assurance
Interaction With Other Trials	ad hoc	Project Manager	Clinical Operations Manager & Quality Assurance
Quality Assurance	ad hoc	Clinical Operations Manager & Quality Assurance	Chief Scientific Officer
SAP deviations	ad hoc	Trial Statistician	Project Manager / Chief Scientific Officer / Sponsor

6. Study Objectives

6.1.1 Study Population & Number of participating Sites

About 38 patients will be enrolled. The study will be conducted at approximately 5 sites located in Greece and approximately 2 sites located in Italy.

Main inclusion criteria are the following:

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure
3. Myeloma requiring systemic therapy
4. Myeloma relapsing after, or refractory to, two or more different prior therapies, including immunomodulatory agents, proteasome inhibitors and chemotherapy with alkylating agents. Subject must have documented relapsed or refractory multiple myeloma as defined by the criteria below:
   c) Monoclonal plasma cells in bone marrow ≥ 10% or presence of a biopsy proven plasmacytoma.
   d) Measurable disease as defined by any of the following:
      - Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL (except for IgA subtype: ≥ 0.5 g/dL) or urine M-protein level ≥ 200 mg/24 hours; or

- Light chain multiple myeloma: Serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free-light-chain ratio.

5. An eGFR < 30 ml/min/1.73 m2 (CKD-EPI formula) or in need for dialysis
6. Eastern Cooperative Oncology Group performance-status score of 2 or less
7. Life expectancy of at least 3 months
8. Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drugs and one within 24 hours prior to the start of study drugs. Women must not be breastfeeding. WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 3 months after cessation of daratumumab treatment. Males who are sexually active with WOCBP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy.

6.1.2 Study Drug and Dosing

Daratumumab will be given at a dose of 16 mg/kg administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Dexamethasone will be administered according to standard clinical practice. The recommended dose of dexamethasone is 40 mg (20 mg for patients > 75 years of age) orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

6.2 Study Design

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

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

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

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

Subjects will receive treatment until disease progression or unacceptable toxicity.

Drug administration and follow-up visits will occur more frequently for early cycles (e.g., weekly or bi-weekly) (see Table 1). Disease evaluations will occur monthly and consist mainly of measurements of myeloma proteins and renal function indices. Other parameters may include bone marrow examinations, skeletal surveys, assessment of extra medullary plasmacytomas, and measurements of serum calcium corrected for albumin, and β2- microglobulin and albumin.

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

Assessment of renal response will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria (see APPENDIX 2).

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

The maximum duration of the study is of 30 months considering an accrual period of 18 months and a follow-up of the last patient of 12 months.

6.3 Study Flowchart

This interventional study records data available in the following visits.

Table 1 Schedule of Events

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

	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[8]	Post treatment FU Every 4 weeks[5]	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond						
Day of Cycle (28-days)	**-21 to 1**	**1 BL**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**			
Creatinine clearance	X	X	X	X	X	X		X		X				X		
Pregnancy test[1]	X	X														
Serum β2-microglobulin, LDH	X	X				X				X				X		
Efficacy Assessments																
Efficacy / Disease Assessment required to confirm response or disease progression should be performed as soon as possible after response or disease progression is suspected – see Protocol; *Section 7.1* for details)																
sPEP, uPEP[2]	X	X				X				X				X	X	
sIFE, uIFE[3]	X	X			.	X				X				X	X	
			To confirm CR regardless of whether measurable M-protein was present at baseline. See **Protocol;** *Section 7.1.1.1*													
sFLC assay, κ/λ ratio[4]	X	X				X				X				X	X	
			Analyzed only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met. See **Protocol;** *Section 7.1.1.2*													
Plasma cell count in bone marrow	X	Plasma cell count during the study as clinically indicated to qualify for CR; and PD for patients with non-measurable disease by M protein in serum and urine as well as by FLC. See **Protocol;** *Section 7.1.1.4*														
MRD		As per institution's practice at complete response and thereafter as clinically indicated through EuroFlow cytometry. See **Protocol;** *Section 7.1.1.6*														
Corrected calcium[6]	X	X				X				X				X	X	
Skeletal survey[7]	X	As clinically indicated; CT/MRI in case of newly symptomatic areas with no X-ray finding. See **Protocol;** *Section 7.1.1.6*														
Assessment of extramedullary soft tissue plasmacytoma	X	Clinical assessment on day one of each cycle at the End of treatment and at Post treatment follow-up every 4 weeks. CT or MRI at screening only if there are STP findings during the clinical assessment or documented evidence from previous imaging assessments and as clinically indicated. See **Protocol;** *Section 7.1.1.4*														
Response assessment by Investigator		C2D1				X				X				X	X	
Treatment																
Daratumumab		X	X	X	X	X		X		X						
Dexamethasone		X	X	X	X	X	X	X	X	X	X	X	X			
		40 mg (20 mg for patients > 75 years of age) orally, weekly														
Other anti-neoplastic therapies		Not permitted												X	X	X
Survival follow-up																X

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

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

[1] Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drug and one within 24 hours prior to the start of study drug.[2]M protein by electrophoresis in serum (sPEP) and urine (uPEP). Serum on Day 1 of each cycle until disease progression. 24-hour urine sample can be collected within ± 7 days of visit.

[3]M protein by immunofixation in serum (sIFE) and urine (uIFE). [4]Free light chain protein assessment (sFLC)

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

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

[7] As per institution's practice [8] End of treatment visit should take place 4 weeks after the last dose of the study treatment or as soon as possible before the start of subsequent therapy.

* Unless otherwise stated, all blood and urine samples must be obtained before administration of study treatment.

6.4 Study Primary and Secondary Objectives

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

Primary objective(s)

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

Secondary objective(s)

The secondary objectives of the study are the following:

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

6.4.1 Study Primary and Secondary Endpoints

Primary endpoint:

- Progression-free survival

Secondary endpoints

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

6.4.2 Sample Size and Power Calculations

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

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

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

6.5 Population of Analysis Sets

6.5.1 Full Analysis Set (FAS)

The FAS comprises all patients to whom study treatment has been assigned according to the intent to treat principle.

6.5.2 Per Protocol Analysis Set (PPS)

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

6.5.3 Safety Set

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

6.5.4 Subgroups

In this study, no sub group analysis was planned to be performed within the primary and secondary endpoints analysis. However, it is considered necessary to further examine the data that will be collected, in order to provide insights for this non-in depth investigated population. Hence, additional subgroup and exploratory analyses will be performed (see 6.6). The following subgroups will be used for the additional analyses:

- ISS stage at the time of diagnosis
- Revised ISS stage at the time of diagnosis
- eGFR (< 15 vs ≥15 at baseline)
- Patients with at least one eGFR>30 measurement over the whole observation period vs patient without such a measurement
- ECG (normal vs at least one abnormality)
- Prior treatments (2-5 treatments vs >5 treatments)
- LDH ()
- FISH risk (low risk, standard risk, intermediate risk & high risk) (1)
- Age at diagnosis (<60 vs. ≥60).
- MRD negativity (negative vs. positive).

6.5.5 Interim Analysis

N/A

6.6 Statistical Methodology

All statistical analyses will be performed using SAS® version 9.4 (64-bit) or later, a validated statistical software package, (SAS Institute, Inc., Cary, NC, USA).

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

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

The primary efficacy endpoint is PFS for patients, who received daratumumab at the dose of 16 mg/kg, as assessed by the Investigator. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented (see Section 6.6.1.3). The analysis will be performed when at least 20 PFS events have been documented.

6.6.1 Methods of Statistical Analyses

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

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

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

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

Descriptive statistical analysis will be performed for all study data and epidemiological methods will be applied. Continuous variables will be summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median and range] (Table 2). Categorical/distinct variables will be displayed as frequency tables (N, %) (Table 3), by group.

Additional sub-group analyses will be performed. The basic demographic characteristics, the primary and the secondary endpoints will be summarized by group. Between groups comparisons will be performed. The sub groups that will be used are derived based on known risk factors that are associated either with the MM or with the RR. Hence, all the endpoints will be analyzed in the following subgroups:

- ISS stage at the time of diagnosis
- Revised ISS stage at the time of diagnosis
- ECG (normal vs at least one abnormality)
- Prior treatments (2-5 treatments vs >5 treatments)
- LDH ()
- FISH risk (low risk, standard risk, intermediate risk & high risk) (1)
- Age >60 vs ≤60
- MRD negativity (negative vs. positive).

Additional exploratory analyses will be performed, in order:

- To compare the PFS, the OS, the ORR and the number of prior treatments at baseline (2-5 treatments vs >5 treatments) between patients with eGFR < 15 vs ≥15 at baseline.
- To compare the PFS, the OS, the ORR and the number of prior treatments at baseline (2-5 treatments vs >5 treatments) between patients with at least one eGFR>30 measurement over the whole observation period vs patient without such a measurement
- To compare the PFS, the OS, the ORR and the number of prior treatments at baseline (2-5 treatments vs >5 treatments) between patients with observed renal response and patients without renal response
- To evaluate if the FISH risk and renal response, measured as RRR are correlated.
- To evaluate if the FISH risk and renal response, using as cut-off point the eGFR>30, are correlated.
- To evaluate if the FISH risk and Prior treatments (2-5 treatments vs >5 treatments) are correlated

6.6.1.1 Patient-Reported Outcome (PRO) Measurements

No PROs will be used.

6.6.1.2 Statistical tests

Association between categorical variables will be assessed using either chi-square test ($\chi 2$), Fisher exact test or McNemar test, as appropriate (Table 4). Furthermore, in order to examine the differences in thevalues of continuous variables at different time periods, Wilcoxon signed rank test for related samples and U-Mann Whitney test for independent samples will be used (Table 5).

Medical history and safety will be coded by MedDRA (the most updated version available) while System Organ Class (SOC) and Preferred Term (PT) will be tabulated in frequency tables (N, %).

Concomitant medication(s) will be coded through the ATC Drug Classification dictionary by WHO Collaborating Centre for Drug Statistics Methodology in terms of therapeutic subgroup, chemical subgroup and chemical substance and will be presented in frequency tables.

6.6.1.3 Primary Endpoint Analysis

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

Progression Free Survival (PFS)

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

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

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

6.6.1.4 Secondary Endpoint Analysis

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

Overall Response Rate (ORR)

ORR is defined as the proportion enrolled subjects who achieve a best response of partial response (PR) or better using the Modified criteria of the IMWG (

Rajan, A. M., and S. V. Rajkumar. "Interpretation of cytogenetic results in multiple myeloma for clinical practice." Blood cancer journal 5.10 (2015): e365.

APPENDIX 1) as their best overall response.

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

Renal Response Rate (RRR)

Rrr is defined as the proportion enrolled subjects who achieve a best response of renal partial renal response (PRRenal) or better using the criteria of the International Myeloma Working Group (IMWG) (APPENDIX 2).

Duration of Response (DoR)

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

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

Time to Next Therapy (TNT)

TNT will be defined as the time, in months, from Cycle 1 Day 1 to the date to next anti-neoplastic therapy or death from any cause, whichever comes first. For subjects who neither start a new anti-neoplastic therapy nor die, survival time will be censored at the date of their last available follow-up assessment.

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

Overall Survival (OS)

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

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

6.6.1.5 Safety Analysis

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

Adverse events

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

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

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

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

Laboratory parameters

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

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

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

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

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value, for laboratory tests where CTCAE grades are not defined.

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

Other safety data

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

ECG

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

Vital signs

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

ECOG PS

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

6.6.1.6 Treatments (study treatment, concomitant therapies)

The Safety set will be used for the following analyses.

Investigational treatment

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

Concomitant treatments

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

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

6.6.1.7 Planned Data Displays

Data displays below present an indicative list of templates for the tables and figures that will be produced.

The following data displays are based on dummy data.

Table 2: Descriptive Analysis of Continuous Variables

		Groups	
		Group A	**Group B**
VAR1	Mean		
	SD		
	Q1		

	median		
	Q4		
	Min		
	Max		
	N		
VAR2	Mean		
	SD		
	Q1		
	median		
	Q4		
	Min		
	Max		
	N		
…			

Table 3: Descriptive Analysis of Categorical Variables

		Groups			
		Group A		Group B	
		N	%	N	%
VAR1	Level1				
	Level2				
	Level3				
VAR2	Level1				
	Level2				
…					

Table 4. Test statistics for categorical variables

		Cohort						
		Cohort A			Cohort B			P-value
		N	%	95% CI	N	%	95% CI	
VAR1	Level1							
	Level2							
	Level3							
VAR2	Level1							
	Level2							
…								

Table 5. Test statistics for continuous variables – T-test/Mann-Whitney

		Group	
		Group A	Group B
VAR1	Mean		
	sd		
	Q1		
	median		
	Q4		
	Min		
	Max		
	N		

	P-value		
VAR2	Mean		
	sd		
	Q1		
	median		
	Q4		
	Min		
	Max		
	N		
	P-value		
...			

6.7 References

1. Rajan, A. M., and S. V. Rajkumar. "Interpretation of cytogenetic results in multiple myeloma for clinical practice." Blood cancer journal 5.10 (2015): e365.

APPENDIX 1

Table 6. Modified International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

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

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

APPENDIX 2

Table 7. IMWG Renal Response Criteria

Criteria for the Definition of Renal Response to Antimyeloma Therapy		
Renal Response	Baseline eGFR, mL/min/1.73 m2*	Best eGFR Response mL/min/1.73 m2
Complete response	<50	≥60
Partial response	< 15	30-59
Minor response	<15 15-29	15-29 30-59

Abbreviations: CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate.

*eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 8. Simplified renal response criteria

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