19 June 2025
EMA/CHMP/144719/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: Daratumumab

Procedure No. EMEA/H/C/004077/II/0077

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACTM	active monitoring
ADR	adverse drug reaction
AE	adverse event
ASCT	autologous stem cell transplant
BOD	biochemical or diagnostic
BMPC	bone marrow plasma cell
CCO	clinical cutoff
CD	cluster of differentiation
CI	confidence interval
COVID-19	Coronavirus Disease 2019
Cmax	maximum observed serum concentration
CR	complete response
CRAB	calcium, renal, anaemia, bone
CSR	clinical study report
CT	computed tomography
Ctrough	trough concentration
Dara	daratumumab SC
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
FLC	free light chain
GCP	Good Clinical Practice
HR	hazard ratio
ICH	International Council for Harmonisation
Ig	immunoglobulin
IMWG	International Myeloma Working Group
IRC	independent review committee
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous(ly)

K-M	Kaplan-Meier
KRd	carfilzomib, lenalidomide, and dexamethasone
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRI	magnetic resonance imaging
NDMM	newly diagnosed multiple myeloma
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease/disease progression
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival on first-line treatment for MM
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
R	lenalidomide
Rd	lenalidomide and dexamethasone
r-ISS	revised International Staging System
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SC	subcutaneous(ly)
sCR	stringent complete response
SD	standard deviation
SLiM-CRAB	clonal bone marrow plasma cells ≥60%, serum (involved/uninvolved) FLC ratio ≥100, >1 focal bone lesions on MRI, calcium elevation, renal insufficiency, anaemia, or bone disease due to lytic bone lesion
SMM	smouldering multiple myeloma
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse event
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 5 November 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include daratumumab for the treatment of adult patients with smouldering multiple myeloma (SMM) at high risk of developing multiple myeloma based on results from studies 54767414SMM3001 (AQUILA) and 54767414SMM2001 (CENTAURUS). SMM3001 (AQUILA) is a Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects with High-risk Smoldering Multiple Myeloma. SMM2001 (CENTAURUS) is a Randomized Phase 2 Trial to Evaluate Three Daratumumab Dose Schedules in Smoldering Multiple Myeloma.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.2 of the RMP was also submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the PI in accordance with the latest EMA excipients guideline.

Information relating to orphan designation

Darzalex, was designated as an orphan medicinal EU/3/13/1153 on 17 July 2013. Darzalex was designated as an orphan medicinal product in the following indication:

• Treatment of plasma cell myeloma

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0264/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Darzalex as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Darzalex

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance

The MAH received Protocol Assistance from the CHMP on 25 February 2016 (EMEA/H/SA/2456/5/2015/PA/II) and 20 July 2017 (EMEA/H/SA/2456/5/FU/1/2017/PA/II). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	5 November 2024
Start of procedure:	30 November 2024
CHMP Rapporteur Assessment Report	5 February 2025
PRAC Rapporteur Assessment Report	31 January 2025
PRAC members comments	5 February 2025
CHMP Co-Rapporteur Assessment	7 February 2025
PRAC Outcome	13 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2025
Request for supplementary information (RSI)	27 February 2025
CHMP Rapporteur Assessment Report	17 April 2024
PRAC Rapporteur Assessment Report	24 April 2024
PRAC members comments	30 April 2024
Updated PRAC Rapporteur Assessment Report	Not applicable
PRAC Outcome	8 May 2025
CHMP members comments	12 May 2025
Request for Supplementary Information	22 May 2025
Submission of responses	27 May 2025
Restart of procedure	28 May 2025
CHMP Rapporteur Assessment Report	04 Jun 2025
CHMP members comments	10 Jun 2025
Updated CHMP Rapporteur Assessment Report	12 Jun 2025

Timetable	Actual dates
Opinion	19 Jun 2025

2. Scientific discussion

2.1. Introduction

The purpose of this application is to extend the approved indications for daratumumab to include:

DARZALEX is indicated for the treatment of adult patients with smouldering multiple myeloma (SMM) at high risk of developing multiple myeloma.

2.1.1. Problem statement

Disease or condition

Smouldering multiple myeloma (SMM) is diagnosed in persons who meet the following criteria

- Serum monoclonal (M) protein ≥3 g/dL and/or 10 to 59 percent bone marrow clonal plasma cells.
- Absence of lytic lesions, anaemia, hypercalcemia, and kidney impairment (end-organ damage) that can be attributed to the plasma cell proliferative disorder and the absence of biomarkers associated with near inevitable progression to end-organ damage (≥60 percent clonal plasma cells in the marrow; involved/uninvolved free light chain [FLC] ratio of ≥100 with involved FLC >100 mg/dL; or more than one focal bone lesion on magnetic resonance imaging [MRI]).

Multiple myeloma (MM) is thought to evolve from premalignant, asymptomatic plasma cell disorders that are characterized by monoclonal plasma cell proliferation in the bone marrow without end-organ damage (Kyle 2009; Kyle 2010; Landgren 2009; Weiss 2009). Smouldering multiple myeloma (SMM), an asymptomatic precursor stage of MM, accounts for approximately 15% of all myeloma patients (Rios-Tamayo 2014) and is associated with an overall risk of progression to malignancy of 10% per year within the first 5 years (Rajkumar 2015). Over time, SMM has been characterized to determine high-risk subsets in the optimal phase of MM evolution in which to evaluate early treatment strategies (Rajkumar 2015). Several models characterizing patients as high-risk SMM have been proposed (Mateos 2016; Rajkumar 2013) and continue to evolve (Mateos 2020; Cowan 2023). Compared with the overall SMM population, risk models show that high-risk SMM patients have an increased risk of progression to symptomatic MM of approximately 50% within the first 2 years, supporting the need for effective treatment options in this patient subgroup (Mateos 2016; Rajkumar 2013).

Epidemiology

Since smouldering multiple myeloma is an asymptomatic condition there are limited data regarding its epidemiology. The most comprehensive data is from a population-based study from Iceland in which >75,000 asymptomatic adults over age 40 were screened with serum protein electrophoresis and serum free light chain assay. Bone marrow biopsy was used to evaluate in subjects with detected monoclonal paraprotein. The prevalence of SMM in this population was 0.5% overall (95% CI 0.49-0.57 percent). Rates increased with age from <0.25 percent in those under 50 years to >1 percent in those over 80 years. (Thorsteinsdóttir, Nat Med., 2023)

Clinical presentation, diagnosis and stage/prognosis

Patients with smouldering multiple myeloma are often asymptomatic. The condition can be diagnosed by chance following a routine health check or blood tests performed for diagnosing or screening for another condition.

The natural history of patients with smouldering multiple myeloma (SMM) is highly variable. Patients progress to symptomatic myeloma or AL amyloidosis at approximate rates of

- 10% per year for the first five years
- 3% per year for the next five years
- 1-2% per year for the following 10 years

A median time to progression of 4.8 years to MM was observed (Kyle, NEJM, 2007).

There are different stratification systems for SMM. Presently, the Mayo 2018/International Myeloma Working Group (IMWG) risk stratification system (Lakshman, Blood Cancer J, 2018) is commonly used and recommended in the ESMO guideline on multiple myeloma (2021). They are also called the 20/2/20 criteria and include the following three risk factors for progression

- Bone marrow plasma cells >20 percent
- Monoclonal (M) protein >2 g/dL
- Involved/uninvolved free light chain (FLC) ratio >20

Low risk SMM is defined as having none of the three risk factors. Intermediate SMM risk is defined as having one of the three risk factors. High risk SMM is defined as ≥2 of the three risk factors.

The 20/2/20 criteria were validated in a retrospective analysis of 1151 patients with SMM. The estimated progression rates at two years were 6, 18, and 44 percent among those with low-risk, intermediate-risk, and high-risk disease, respectively (Mateos, Blood Cancer J, 2020).

Management

Currently, there is no approved treatment for patients with SMM. The standard of care for SMM has been observation (Rajkumar 2015) and clinical management involves monitoring patients for progression to symptomatic disease (Landgren 2013).

Current European Hematology Association, European Society for Medical Oncology, and NCCN guidelines recommend entry into clinical studies or observation for patients with high-risk SMM (Dimopoulos 2021; Multiple Myeloma NCCN Guidelines Version 4.2024).

2.1.2. About the product

Daratumumab is a human mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on normal and malignant plasma cells, among other cell types. Daratumumab binding induces cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor-mediated crosslinking of tumour-bound mAbs (Overdijk 2016). Moreover, translational biomarker studies of samples from participants treated with daratumumab in Phase 1 and Phase 2 studies have revealed previously unknown immunomodulatory effects of daratumumab (Krejcik 2016). Patients responding to daratumumab treatment show an increase in the activated CD8+ T cells expressing high levels of granzyme B (Adams 2019). Together, daratumumab's cytotoxic and immunomodulatory mechanisms of action are hypothesized to synergistically result in antimyeloma responses.

Daratumumab is approved in both an iv. and sc. formulation. The present application pertains only to the sc. formulation.

Daratumumab is currently approved for multiple indications in multiple myeloma including:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical efficacy and safety studies that are part of the clinical development program for daratumumab SC for the treatment of SMM and which are presented in this application are the pivotal Phase 3 Study 54767414SMM3001 (AQUILA; referred in this report also as SMM3001), and a supportive Phase 2 study, Study 54767414SMM2001 (CENTAURUS; referred in this report also as SMM2001).

The main issues discussed during scientific advice are summarised below:

- The CHMP endorsed the primary endpoint of Progression Free Survival (PFS).
- The proposed definition of "high-risk" SMM by the applicant was overall acceptable.
- The CHMP discouraged a control-arm constituting lenalidomide and dexamethasone (Rd).
- The need for support from key secondary endpoints including OS and PFS2 was highlighted as well as data indicating that potential subsequent stem cell transplantation will not be affected by the proposed treatment.

2.1.4. General comments on compliance with GCP

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Daratumumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no environmental risk assessment for daratumumab is required.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number	Phase	Study Description/Design Participant Population	Study Drugs Dose Regimen	Number of Participants in Pharmacokinetic-evaluable Analysis Set Route of Administration
SMM3001	3	Randomised, open-label Participants with high-risk SMM	Arm A: active monitoring, no study treatment Arm B: daratumumab SC 1800 mg + rHuPH20 2000 U/mL Participants in Arm B received daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) once weekly in Cycle 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and thereafter every 4 weeks for up to 39 cycles or 36 months, whichever occurred first. Each cycle was 28 days.	N=193 All participants in Arm B received daratumumab SC
SMM2001	2	Randomised, open-label Participants with intermediate or high-risk SMM	Arms A, B, and C: daratumumab 16 mg/kg IV In Arm A (long intense arm), daratumumab 16 mg/kg IV was administered weekly in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle. In Arm B (intermediate arm), daratumumab 16 mg/kg IV was administered weekly in Cycle 1 and then on Day 1 of each cycle from Cycle 2 to Cycle 20. In Arm C (short intense arm), the Treatment Phase consisted of Cycle 1 only, when daratumumab 16 mg/kg IV was administered weekly. Treatment cycles were 8 weeks in length.	N=122 All participants received daratumumab IV

IV=intravenous; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; SMM=smouldering multiple myeloma.

2.3.2. Pharmacokinetics

The phase 2 study in SMM patients was performed with three different dosing schedules of daratumumab 16 mg/kg as intravenous (IV) infusion. As the route of administration in this study is different to the one in the pivotal phase 3 study, in which daratumumab was administered subcutaneously (SC) and is not being proposed for the new indication, study SMM2001 will not be discussed further in this section.

Phase 3 Study SMM3001

Study SMM3001 is a Phase 3, randomised, open-label, 2-arm, multicentre study to evaluate the efficacy and safety of daratumumab SC administration versus active monitoring in participants with high-risk SMM.

The study consists of a Screening Phase, an Active Monitoring Phase or a Treatment Phase (daratumumab), and a Follow-up Phase. For participants randomized to active monitoring (Arm A), no disease-specific treatment was administered. For participants randomised to the daratumumab arm (Arm B), daratumumab SC (daratumumab 1800 mg + rHuPH20 2000 U/mL) was administered weekly in Cycle 1-2, every 2 weeks in Cycle 3-6, and then every 4 weeks until 39 cycles or 36 months or confirmed PD based on IRC assessment, unacceptable toxicity, or other reasons as outlined in the protocol. Each cycle was 28 days. In both arms, disease evaluation continued every 12 weeks until confirmed PD based on IRC assessment. The Follow-up Phase for each participant continued until death, lost to follow up, consent withdrawal, or study end, whichever occurred first.

In Arm B, serum samples to determine the concentration of daratumumab were obtained pre dose on Day 1 of Cycles 1, 3, 5, 7, 12, and 24; Day 4 of Cycles 1 and 3; 30 days (±3) after the last dose of daratumumab; and 8 weeks after the last dose of daratumumab. The PK-evaluable analysis set included participants who were assigned to Arm B and received at least 1 administration of daratumumab and had at least 1 PK sample concentration value after the first daratumumab administration.

Serum Daratumumab Concentrations

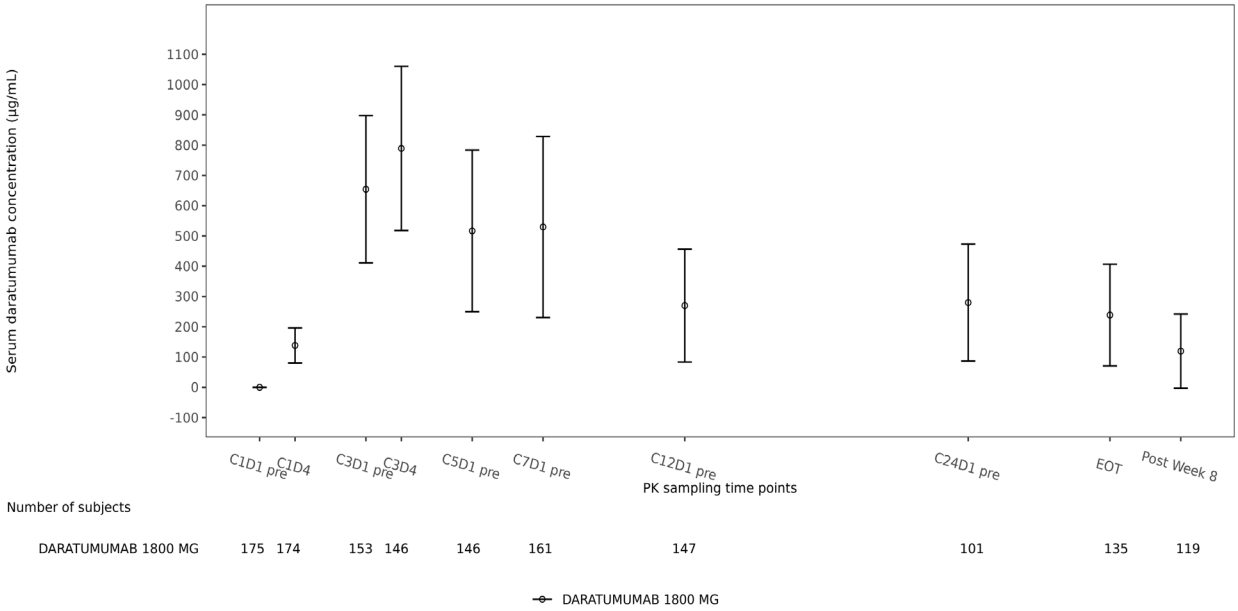
Serum Daratumumab concentrations over time are summarised in **Table 1** and **Figure 1.**

Table 1. Summary of Serum Daratumumab Concentration (µg/mL); Pharmacokinetics Evaluable Analysis Set (Study SMM3001)

	Daratumumab
Analysis set: pharmacokinetic-evaluable	193
Cycle 1 Day 1 (Pre-dose)	
N	175
Mean (SD)	BQL (NE)
Geometric Mean	BQL
Coefficient of Variation (%)	NE
Median	BQL
Range	(0; 2.1)
Cycle 1 Day 4	
N	174
Mean (SD)	138 (57.9)
Geometric Mean	122
Coefficient of Variation (%)	41.8
Median	136
Range	(0; 407)
Cycle 3 Day 1 (Pre-dose)	
N	153
Mean (SD)	654 (243)
Geometric Mean	605
Coefficient of Variation (%)	37.2
Median	635
Range	(120; 1350)
Cycle 3 Day 4	

	Daratumumab
N	146
Mean (SD)	789 (271)
Geometric Mean	737
Coefficient of Variation (%)	34.4
Median	754
Range	(152; 1590)
Cycle 5 Day 1 (Pre-dose)	
N	146
Mean (SD)	517 (267)
Geometric Mean	437
Coefficient of Variation (%)	51.6
Median	497
Range	(49; 1440)
Cycle 7 Day 1 (Pre-dose)	
N	161
Mean (SD)	530 (299)
Geometric Mean	415
Coefficient of Variation (%)	56.5
Median	523
Range	(0.278; 1560)
Cycle 12 Day 1 (Pre-dose)	
N	147
Mean (SD)	270 (187)
Geometric Mean	206
Coefficient of Variation (%)	69.1
Median	247
Range	(0; 989)
Cycle 24 Day 1 (Pre-dose)	
N	101
Mean (SD)	280 (193)
Geometric Mean	211
Coefficient of Variation (%)	69.0
Median	265
Range	(0; 1090)
End of treatment	
N	135
Mean (SD)	239 (168)
Geometric Mean	179
Coefficient of Variation (%)	70.4
Median	212
Range	(0; 995)
Post-treatment Week 8	
N	119
Mean (SD)	120 (123)
Geometric Mean	63.6
Coefficient of Variation (%)	103
Median	95.0
Range	(0; 698)
BQL=Below Quantification Limit; NE=not estimable; SD=standard deviation	
Note: Samples with a collection time out of defined windows are excluded.	
Note: Lowest quantifiable concentration in a sample=0.20 µg/mL.	

Figure 1. Plot of Mean (Standard Deviation) Serum Daratumumab Concentrations (µg/mL) Over Time; Pharmacokinetics Evaluable Analysis Set (Study SMM3001)



C=cycle; EOT=end of treatment; PK=pharmacokinetic; Pre=pre-dose.

Note: Error bars are mean +/- standard deviation; samples with a collection time out of defined windows are excluded.

Immunogenicity and pharmacokinetics

Daratumumab ADA analysis was performed using an optimized assay with drug tolerance sufficient to detect ADA in all collected samples. The ADA assay was performed with 83.6% passing rate (55 runs). All failed runs were due to failing control samples.

One participant (0.5%) had treatment-emergent anti-daratumumab antibodies. The participant was also positive for neutralizing antibodies. Regarding anti-rHuPH20 antibodies, 18 (9.3%) participants had treatment emergent antibodies.

Serum daratumumab concentrations in the participant who tested positive for treatment-emergent anti-daratumumab antibodies were in a similar range of mean serum concentrations of daratumumab in total PK-evaluable analysis set at PK sampling timepoints.

Dose proportionality and time dependencies

Only one flat dose level was used in the Phase 3 study (1800 mg). Dose proportionality has been characterised in previous submissions.

Special populations

Serum Daratumumab Concentrations by Baseline Body Weight in Study SMM3001 are summarised in

Table **2.**

Table 2. Summary of Serum Daratumumab Concentrations (µg/mL) by Baseline Body Weight; Pharmacokinetics Evaluable Analysis Set (Study SMM3001)

	Daratumumab			
	<=65 kg	>65 to 85 kg	>85 kg	Total
Analysis set: pharmacokinetic-evaluable	43	95	55	193
Cycle 1 Day 1 (Pre-dose)				
N	38	87	50	175
Mean (SD)	BQL (NE)	BQL (NE)	BQL (NE)	BQL (NE)
Geometric Mean	BQL	BQL	BQL	BQL
Coefficient of Variation (%)	NE	NE	NE	NE
Median	BQL	BQL	BQL	BQL
Range	(0; 0)	(0; 2.1)	(0; 0)	(0; 2.1)
Cycle 1 Day 4				
N	41	84	49	174
Mean (SD)	169 (53.7)	141 (60.4)	107 (39.9)	138 (57.9)
Geometric Mean	149	123	102	122
Coefficient of Variation (%)	31.8	42.7	37.1	41.8
Median	169	135	105	136
Range	(2.44; 276)	(0.299; 407)	(0; 175)	(0; 407)
Cycle 3 Day 1 (Pre-dose)				
N	32	76	45	153
Mean (SD)	821 (251)	659 (240)	527 (156)	654 (243)
Geometric Mean	782	609	499	605
Coefficient of Variation (%)	30.5	36.4	29.7	37.2
Median	786	642	524	635
Range	(320; 1350)	(170; 1200)	(120; 847)	(120; 1350)
Cycle 3 Day 4				
N	36	71	39	146
Mean (SD)	940 (261)	795 (277)	639 (180)	789 (271)
Geometric Mean	901	740	606	737
Coefficient of Variation (%)	27.8	34.8	28.1	34.4
Median	967	807	663	754
Range	(452; 1380)	(177; 1590)	(152; 946)	(152; 1590)
Cycle 5 Day 1 (Pre-dose)				
N	36	69	41	146
Mean (SD)	685 (282)	522 (250)	360 (177)	517 (267)
Geometric Mean	621	447	309	437
Coefficient of Variation (%)	41.2	48.0	49.1	51.6
Median	664	497	360	497
Range	(120; 1440)	(49; 1160)	(50.6; 748)	(49; 1440)
Cycle 7 Day 1 (Pre-dose)				
N	36	80	45	161
Mean (SD)	728 (333)	520 (287)	389 (191)	530 (299)
Geometric Mean	648	382	337	415
Coefficient of Variation (%)	45.8	55.3	49.0	56.5

	Daratumumab			
	<=65 kg	>65 to 85 kg	>85 kg	Total
Median	678	522	368	523
Range	(119; 1560)	(0.278; 1250)	(63.3; 908)	(0.278; 1560)
Cycle 12 Day 1 (Pre-dose)				
N	38	67	42	147
Mean (SD)	379 (225)	262 (161)	184 (132)	270 (187)
Geometric Mean	310	209	137	206
Coefficient of Variation (%)	59.5	61.5	71.9	69.1
Median	330	276	154	247
Range	(41.5; 989)	(0; 786)	(0; 540)	(0; 989)
Cycle 24 Day 1 (Pre-dose)				
N	29	44	28	101
Mean (SD)	437 (212)	251 (149)	162 (119)	280 (193)
Geometric Mean	392	189	130	211
Coefficient of Variation (%)	48.6	59.4	73.1	69.0
Median	397	246	132	265
Range	(122; 1090)	(2.34; 644)	(0; 510)	(0; 1090)
End of treatment				
N	31	71	33	135
Mean (SD)	341 (212)	225 (152)	174 (104)	239 (168)
Geometric Mean	294	162	141	179
Coefficient of Variation (%)	62.2	67.6	59.9	70.4
Median	306	211	157	212
Range	(0; 995)	(0; 623)	(25.3; 450)	(0; 995)
Post-treatment Week 8				
N	29	62	28	119
Mean (SD)	194 (169)	108 (99.8)	68.7 (69.6)	120 (123)
Geometric Mean	136	50.8	45.7	63.6
Coefficient of Variation (%)	86.9	92.7	101	103
Median	151	93.4	36.7	95.0
Range	(0; 698)	(0; 393)	(0; 233)	(0; 698)
BQL=Below Quantification Limit; NE=not estimable; SD=standard deviation				
Note: Samples with a collection time out of defined windows are excluded.				
Note: Pharmacokinetics evaluable: Participants who received at least 1 administration of daratumumab and have at least 1 pharmacokinetics sample concentration value after the first injection; Lowest quantifiable concentration in a sample =0.20 µg/mL.				

Serum Daratumumab Concentrations by Race (Study 3001)

Mean [SD] maximum Ctrough at Cycle 3 Day 1 pre-dose in Black/African American participants (735 [275] µg/mL, n=3) was 14.7% higher than in White participants (641 [232] µg/mL, n=121). Mean [SD] maximum Ctrough at Cycle 3 Day 1 pre-dose in Asian participants was 779 [295] µg/mL (n=18), which was 21.5% higher than in White participants.

Pharmacokinetic interaction studies

As an IgG1κ mAb, the biotransformation of daratumumab is expected to be similar to endogenous IgG (i.e., degraded into small peptides and amino acids via catabolic pathways) and subject to similar elimination pathways (Mascelli 2007; Tabrizi 2006). Renal excretion and hepatic enzyme mediated

metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. Due to the high affinity to a unique epitope on CD38, daratumumab is also not anticipated to alter the activity of drug-metabolizing enzymes. Therefore, drug interaction is not expected between daratumumab and small molecules used in combination therapies with daratumumab.

2.3.3. Pharmacodynamics

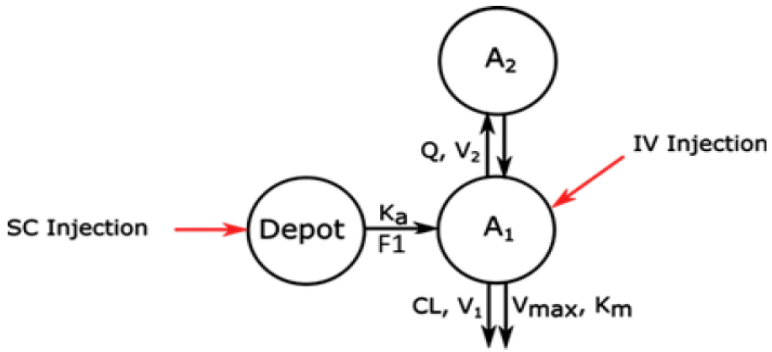
Pharmacodynamic/biomarker assessments were not conducted in Study 3001 but the mechanism of action of daratumumab has been previously characterised.

2.3.4. PopPK analysis

The Pop PK analysis was based on a total of 2,652 PK samples from 315 participants with SMM treated with daratumumab monotherapy: 1,451 SC samples from 193 participants in Study SMM3001 (Phase 3) and 1,201 IV samples from 122 participants in Study SMM2001 (Phase 2). BLQ samples constituted of 50 samples (1.89%). Nine samples with conditional weighted residuals (CWRES) >5 were kept in the Pop PK data set, and had no impact on parameter estimates in a sensitivity analysis. Of note, 6 participants had a body weight ≤50 kg and 5 participants had a body weight >120 kg.

A previous IV/SC model for daratumumab monotherapy was initially used to the fit the additional data by external validation. **Figure 2** shows the model structure.

Figure 2. Michaelis-Menten PK model for daratumumab IV/SC



Abbreviations: A_1=daratumumab amount in the central compartment; A_2=daratumumab amount in the peripheral compartment; CL=linear clearance; IV=intravenous; K_a=absorption rate constant; K_{DES}=first-order rate constant, describing the decrease of the maximum velocity of the saturable CL process over time; K_m=Michaelis-Menten constant; PK=pharmacokinetic(s); Q=intercompartmental clearance; SC=subcutaneous; V_1=volume of distribution in the central compartment; V_2=volume of distribution in the peripheral compartment; V_{max}=maximum velocity of the saturable clearance process, which decreases over time through a first-order rate (K_{DES}).

Goodness of Fit (GoF) plots indicated bias and the prediction-corrected visual predictive check (pcVPC) underprediction of observed data from both studies (data not shown). Thus, the SMM data was included in the Pop PK dataset and the model re-estimated.

Parameters of the final re-estimated model are shown in **Figure 3**.

Figure 3. Parameter estimates of the PopPK model of daratumumab for SMM population

Parameter (Unit)	Description	NONMEM			Bootstrap (92 of 100)	
		Estimate	95% CI[c]	%RSE	Median	95%CI
θ Estimates						
CL (L/h)	Linear clearance	0.00336	(0.00292; 0.0038)	6.67	0.00338	(0.00309; 0.00376)
ALB on CLa	Effect of serum albumin concentration on linear clearance	-1.31	(-1.80; -0.818)	19.2	-1.25	(-1.78; -0.717)
WT on CLa	Effect of body weight on linear clearance	1.33	(1.08; 1.58)	9.70	1.30	(1.00; 1.58)
TPMC on CLa	Effect of type of myeloma (IgG versus non-IgG) on linear clearance	0.778	(0.549; 1.01)	15.0	0.781	(0.618; 0.928)
V1 (L)	Volume of distribution in the central compartment	4.17	(3.87; 4.47)	3.67	4.15	(3.74; 4.56)
WT on V1b	Effect of body weight on volume of distribution in the central compartment	0.709	(0.452; 0.966)	18.5	0.736	(0.547; 0.946)

Parameter (Unit)	Description	NONMEM			Bootstrap (92 of 100)	
		Estimate	95% CI[c]	%RSE	Median	95%CI
SEX on V1b	Effect of sex (female versus male) on volume of distribution in the central compartment	-0.132	(-0.2; -0.0536)	30.3	-0.124	(-0.194; -0.0318)
V2 (L)	Volume of distribution in the peripheral compartment	2.95	(2.51; 3.39)	7.53	2.76	(2.26; 3.43)
Q (L/d)	Intercompartmental clearance	0.00327	(0.00272; 0.00382)	8.65	0.0034	(0.00269; 0.0195)
Vmax (mg/h)	Maximum velocity of the saturable clearance process	0.357	(0.297; 0.417)	8.63	0.345	(0.278; 0.41)
KDES (10,000/h)	First-order rate for decrease of maximum velocity of the saturable clearance process over time	0.149	(0.0771; 0.221)	24.6	0.125	(0.0464; 0.213)
Km (µg/mL)	Michaelis-Menten constant	0.389	(0.284; 0.494)	13.8	0.539	(0.169; 4.38)
Ka (100/h)	First-order absorption rate	1.31	(1.05; 1.57)	10.0	1.33	(1.18; 1.7)
F1	Bioavailability for SC dose	0.531	(0.496; 0.566)	3.37	0.528	(0.498; 0.565)
ω2 Estimates						
IIV CL (CV%)	Inter-individual variability on CL	41.2	(40.0; 42.4)	4.97	40.9	(37.5; 45.4)
IIV V1 (CV%)	Inter-individual variability on V1	22.8	(21.7; 23.8)	6.44	23.1	(15.3; 29.9)
IIV Vmax (CV%)	Inter-individual variability on Vmax	39.5	(36.0; 43.0)	10.4	43.8	(35.1; 58.3)
IIV KDES (CV%)	Inter-individual variability on KDES	689	(649; 729)	17.5	1,520	(201; 19,000)
IIV Ka (CV%)	Inter-individual variability on Ka	65.7	(62.6; 68.8)	7.02	64.6	(40.1; 92.0)
σ2 Estimates						
ADD ERR (CV%)	Additive error term on the log-scale	27.6	(27.4; 27.8)	0.337	27.4	(22.5; 32.6)

Abbreviations: CI=confidence interval; CL=linear clearance; CV=coefficient of variation; IgG=immunoglobulin G; IIV=inter-individual variability; Ka=absorption rate constant; KDES=first-order rate constant, describing the decrease of the maximum velocity of the saturable CL process over time; MM=multiple myeloma; NONMEM=nonlinear mixed effects modeling; PPK=population pharmacokinetic(s); RSE=relative standard error; SC=subcutaneous; SD=standard deviation; SMM=smoldering multiple myeloma; TVCL=typical value of clearance; TVV1=typical value of central volume of distribution; V_1=volume of distribution in the central compartment; V_2=volume of distribution in the peripheral compartment; Vmax=maximum velocity of the saturable clearance process.

[a] $TVCL = 0.00336 \cdot \left(\frac{WT}{78}\right)^{1.33} \cdot \left(\frac{ALB}{41}\right)^{-1.31} \cdot TPMC_{CL}$ where $TPMC_{CL}$ is a shift factor of 1 for participants with non-IgG MM and 1+ 0.778 for participants with IgG MM.

[b] $TVV1 = 4.17 \cdot \left(\frac{WT}{78}\right)^{0.709} \cdot SEX_{V1}$, where $SEXV_1$ is a shift factor of 1 for male and 1-0.132 for female.

Objective function value=-2,329. Condition number=50.1.

%RSE for IIV and ADD ERR are reported on the approximate SD scale (standard error/variance estimate)/2.

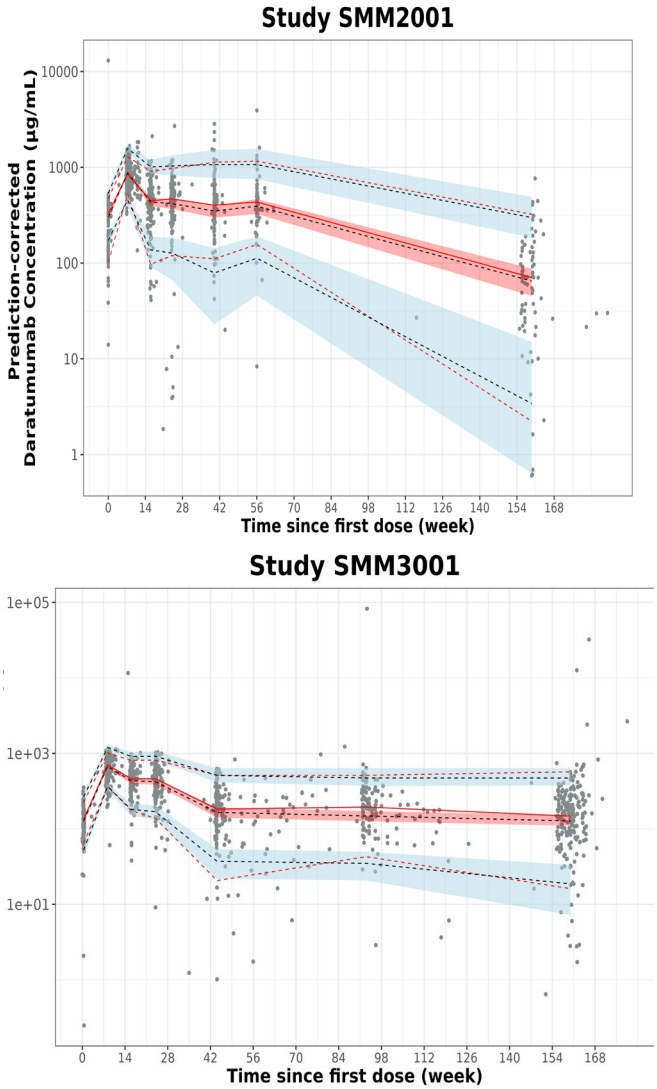
CV for IIV and ADD ERR are computed as sqrt(exp(ω2)-1) and sqrt (exp(σ2)-1), respectively.

[c] 95% CIs are calculated based on standard error from covariance matrix assuming pharmacokinetic parameters are normally distributed.

Note: Ninety-two of 100 runs of the bootstrap were incorporated in the analysis, as 6 runs with minimization terminated and 2 runs with estimates near a boundary.

The final re-estimated model was evaluated by bootstrap, GoF plots and pc-VPCs. **Figure 4** shows selected pcVPCs stratified for Study SMM2001 and SMM3001.

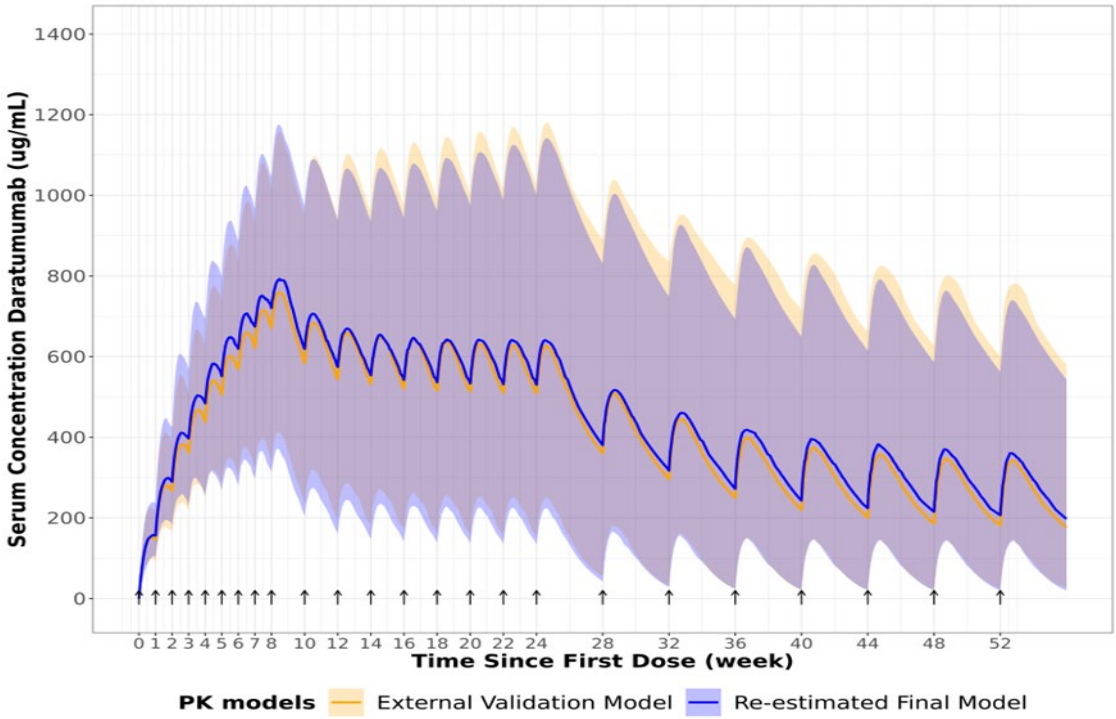
Figure 4. Prediction-corrected visual predictive check of the final re-estimated PopPK model, stratified by study



Black circles represent observation. The solid and dashed red lines represent the median and 2.5th and 97.5th percentiles of the observations. The dashed black lines represent the median and 2.5th and 97.5th percentiles of the simulations. The red and blue shaded areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles simulated by the model, respectively.

Figure 5 compares simulated daratumumab concentration-time profiles following the recommended daratumumab SC 1800 mg dose regimen based on the PK parameter estimates from both the external validation model and the final re-estimated PK model

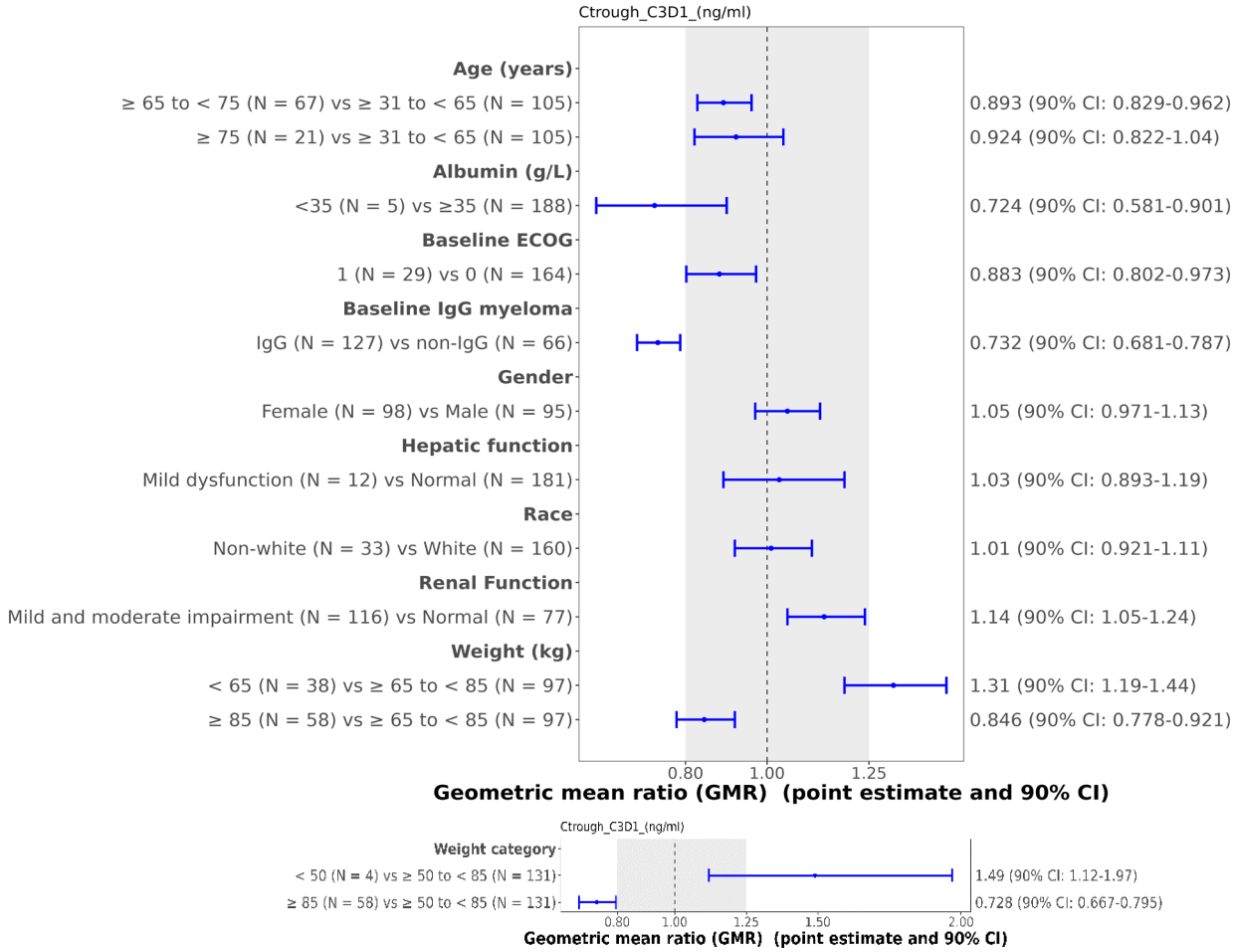
Figure 5. Model-based Simulated Concentration-time Profiles Evaluating the Effect of the External Validation and Re-estimated PK Model Parameters After Daratumumab SC 1800 mg Dose Regimen in Participants With Smouldering Multiple Myeloma



PK=pharmacokinetic(s); SC=subcutaneous
The orange and blue line and shaded regions represent the median and 90% prediction intervals of simulated daratumumab concentration-time profiles for the external validation and re-estimated final PK models, respectively.

The subgroup analysis for the post-hoc estimates of $C_{trough.C3D1}$, showed that body weight, and albumin concentration were not clinically meaningful, as the 90% CI of the GMR for covariate effects fell within the 0.8 to 1.25 interval represented by the shaded area in $C_{trough,C3D1}$ (**Figure 6)**.

Figure 6. Multivariate Forest Plot of the Covariate Evaluation for Daratumumab $C_{trough.C3D1}$ per the Recommended Dose Schedule for Daratumumab Therapy Using the Final PPK Model



CI=confidence interval; C_{trough}=trough concentration; CXDX= Cycle X Day X; ECOG=Eastern Cooperative Oncology Group; GMR=geometric mean ratio; IgG=immunoglobulin G; vs=versus Solid blue point represents GMR and short horizontal bar represents 90% CI. Dashed line represents reference value of 0. Shaded area represents spans from GMR 0.8-1.25. Values represent GMR and the associated CI, which have been adjusted by the different covariates included in the analysis.

Exposure-response modelling

A Maximum a posteriori (MAP approach) using the re-estimated model and the feature MAXEVAL=0 in nonlinear mixed effects modelling (NONMEM) was performed to obtain empirical Bayes estimates for derivation of individual daratumumab exposure metrics for participants that received at least one dose of daratumumab SC in Study SMM3001.

The relationship between drug exposure (Ctrough,max) and the primary efficacy endpoint PFS was evaluated graphically using Kaplan-Meier plots and by Cox proportional hazard models. Treatment with daratumumab SC demonstrated a significant improvement in PFS in Study SMM3001, reducing the risk of disease progression or death by 53% (HR=0.468; 95% CI: 0.344-0.636; 2-sided p<0.0001), compared with active monitoring in population with high risk SMM. Notably, participants with higher exposure of daratumumab (Q2 to Q4 of daratumumab Ctrough.max) exhibited improved PFS (**Table 3**).

Table 3. Cox proportional hazard univariate exposure-response models for PFS

Model	Subgroup	-2LL	N	Nref	HR (95% CI)	p-value
Model A	Treatment (Daratumumab vs Active monitoring)	1,870.0	193	196	0.468 (0.344-0.636)	<0.0001
Model B	$C_{trough.max}$ (Q2 vs Q1)	637.9	48	49	0.336 (0.176-0.641)	0.0009
	$C_{trough.max}$ (Q3 vs Q1)	637.9	48	49	0.311 (0.161-0.602)	0.0005
	$C_{trough.max}$ (Q4 vs Q1)	637.9	48	49	0.282 (0.143-0.558)	0.0003
Model C	$C_{trough.max}$ (Q1 vs Active monitoring)	1,850.0	49	196	1.051 (0.692-1.594)	0.817
	$C_{trough.max}$ (Q2 vs Active monitoring)	1,850.0	48	196	0.362 (0.207-0.634)	0.0004
	$C_{trough.max}$ (Q3 vs Active monitoring)	1,850.0	48	196	0.332 (0.186-0.590)	0.0002
	$C_{trough.max}$ (Q4 vs Active monitoring)	1850.0	48	196	0.304 (0.167-0.554)	<0.0001
Model D	$C_{trough.max}$ (µg/mL)	1859.0	-	-	0.999 (0.998-0.999)	<0.0001

Abbreviations: -2LL=twice the negative log-likelihood; CI=confidence interval; $C_{trough.max}$=maximum trough concentration; HR=hazard ratio; N=number of participants in subgroup; Nref=number of participants in reference; Q#=quantile; vs=versus.

The covariate analysis for PFS was performed to further understand the E-R relationship. The covariates that showed a correlation with PFS were ECOG and risk stratification per IMWG. The effect of type of myeloma (IgG versus non-IgG) was not significant in the E-R analysis for efficacy. Consequently, the small difference in PK does not translate into an effect on efficacy and thus this covariate is likely not clinically meaningful and does not need dose adjustment.

To adjust for the effects of ECOG and risk stratification, a multivariate cox regression analysis was conducted in a step-wise manner. Cox proportional hazard models including ECOG and risk stratification as well as the daratumumab exposure ($C_{trough.max}$) were performed. The inclusion of the covariates ECOG and risk stratification into the model did not alter the E-R relationship (data nor shown). Therefore, no dose adjustment was recommended based on these factors.

The relationship between drug exposure and safety endpoints were only evaluated graphically by means of exploratory bar plots and are not further discussed in this report.

2.3.5. Discussion on clinical pharmacology

In the phase 3 study SMM3001, in patients with high-risk smouldering multiple myeloma, daratumumab exposure was similar to that in multiple myeloma monotherapy studied with the maximum Ctrough (cycle 3, day 1 pre-dose) mean ± SD of 654 ± 243 µg/mL following the recommended 1800 mg administration of daratumumab solution for subcutaneous injection (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter). The Ctrough decreased to 530 ± 299 µg/mL at Cycle 7 Day 1 pre-dose with less frequent dosage of every 2-weeks, then further decreased to 270± 187 µg/mL at Cycle 12 Day 1 pre-dose with every 4-week dosage and was stable through Cycle 24 Day 1 pre-dose (280 ± 193 µg/mL). Serum daratumumab concentrations were quantifiable at the EOT (239 [168] µg/mL) and 8 weeks post treatment (120 ± 123 µg/mL).

The coefficient of variation for serum daratumumab concentrations ranged from 34.4% to 69.1% in Cycles 1 through 24, and 70.4% and 103% at the EOT and 8 weeks post treatment, respectively.

Mean ± SD maximum Cmax was observed on Cycle 3 Day 4 (789 [± 271] µg/mL) following weekly doses of daratumumab SC for 8 weeks, which was a 5.72-fold increase compared with the Cmax at Cycle 1 Day 4 (138 [57.9] µg/mL), indicating accumulation of daratumumab in systemic circulation following weekly dosage.

Sampling for surveillance of ADA was extensive covering the full treatment period in SMM3001. Consistent with observations in previous clinical studies, immunogenicity of daratumumab appeared to be low with no obvious impact on pharmacokinetics or exposure.

Daratumumab was administered as a flat dose to all body weight groups. As expected, higher serum concentrations of daratumumab were observed in participants with lower body weight, and lower serum daratumumab concentrations were observed in participants with higher body weight at all PK sampling timepoints. Mean [SD] maximum Ctrough of daratumumab at Cycle 3 Day 1 pre-dose was 24.6% higher in the lowest body weight subgroup ≤65 kg, 821 [251] µg/mL) compared with the medium body weight subgroup (>65 to 85 kg, 659 [240] µg/mL). For the highest body weight subgroup (>85 kg), mean maximum Ctrough at Cycle 3 Day 1 pre-dose was 527 [156] µg/mL, which was 20.0% lower compared with the medium body weight subgroup. Mean [SD] maximum Ctrough at Cycle 3 Day 1 pre-dose were comparable between the medium body weight subgroup and the total PK-evaluable analysis set (654 [243] µg/mL). The coefficient of variation for serum daratumumab concentrations ranged from 27.8% to 73.1% in Cycles 1 through 24 across all baseline body weight subgroups ≤65 kg, >65 to 85 kg, and >85 kg).

The effect of body weight on daratumumab pK is already described in sections 4.4 and 5.2 in SmPC based on previous studies. As the percent difference in exposure between the body weight groups were within the variability (CV%) for the individual body weight groups up to >120 kg, this is not considered clinically meaningful and therefore of no concern. A warning is included in section 4.4 and 5.2 of the SmPC stating that the exposure is lower in the patient group with body weight > 120 kg and therefore there is potential for reduced efficacy. However, as the number of patients in this group is low, no dose adjustment can be recommended.

Given the relatively small number of Black/African American participants compared with White participants, only limited conclusions regarding the effect of race/ethnicity on PK of daratumumab SC can be made from the observed data for this subgroup. Exposure at maximum Ctrough in Black/African American participants (n=3) was 14.7% higher than in White participants (n=121). Exposure in Asian participants (n=18) was 21.5% higher than in White participants. The difference is within interindividual variability in exposure and is therefore not considered clinically meaningful.

The ER analysis from both efficacy and safety was based on patients from the AQUILA study. Results indicated a relation of low exposure (Ctrough,max Q1) to reduced PFS compared to Q2-Q3 which was further confirmed by univariate Cox PH models. ECOG and risk stratification per IMWG were further evaluated in multivariate Cox PH models stratified for exposure quartiles as both showed correlation to PFS. When these were however, further evaluated in models stratified by Ctrough,max exposure quartiles vs active monitoring, the HR remained the same indicating no impact of these factors on PFS.

Overall, the re-estimated model seems acceptable for description of daratumumab PK following monotherapy in SMM patients and to derive exposure metrics for E-R analyses.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of daratumumab is considered well-known and demonstrated to be reasonably similar between patient groups with SMM and MM receiving the same dosing schedules.

2.4. Clinical efficacy

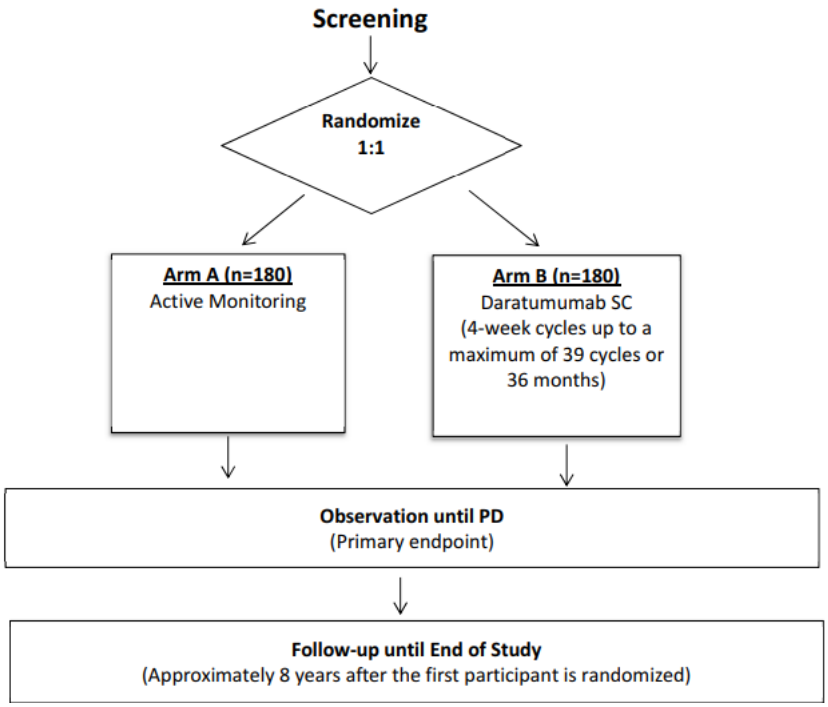
2.4.1. Main study

SMM3001 (Aquila): A phase 3 randomized, multicenter study of subcutaneous daratumumab versus active monitoring in subjects with high-risk smouldering multiple myeloma

Methods

A diagrammatic representation of the study design is presented in **Figure 7**.

Figure 7. Schematic Overview of Study 54767414SMM3001



Study participants

Inclusion Criteria (selection)

1. At least 18 years of age or at least the legal age of consent in the jurisdiction in which the study is taking place, whichever is the older age.
2. Diagnosis of SMM (per IMWG criteria) for ≤5 years with measurable disease at the time of randomization, defined as serum M protein ≥10 g/L or urine M protein ≥200 mg/24 hours or involved serum FLC ≥100 mg/L and abnormal serum FLC ratio.
3. Clonal BMPCs ≥10%; and

   At least 1 of the following risk factors;

a. Serum M protein ≥30 g/L,

b. IgA SMM,

c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG should be considered in determination for immunoparesis; IgD and IgE are not considered in this assessment),

d. Serum involved: uninvolved FLC ratio ≥8 and <100, or

e. Clonal BMPCs >50% to <60% with measurable disease.

4. ECOG performance status score of 0 or 1.

5. Pretreatment clinical laboratory values meet the following criteria during the Screening Phase:

a. Absolute neutrophil count ≥1.0 x 109/L (ie, ≥1000/ μ L)

b. Platelet count ≥50 x 10^9/L (not permissible to transfuse a subject within 2 weeks prior to the Screening platelet count to reach this level)

c. Aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN)

d. Alanine aminotransferase (ALT) ≤2.5 x ULN

e. Total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinaemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 x ULN is required)

6. A woman of childbearing potential must have a negative serum or urine pregnancy test at screening within 14 days prior to randomization.

Exclusion Criteria (selection)

1. Multiple myeloma, requiring treatment, defined by any of the following:

a. Bone lesions (one or more osteolytic lesions on low-dose whole body computed tomography [LDCT], positron-emission tomography with computed tomography [PET-CT] or CT). Subjects who have benign/post-traumatic bone lesions visible on screening images as well as previous imaging, may be considered for inclusion. Details (diagnosis, location, duration) on benign/post-traumatic pre-existing bone lesions that can be seen on the screening images (e.g., old fractures) and were also present on previous imaging are to be reported in the CRF.

b. Hypercalcemia (serum calcium >0.25 mmol/L [>1 mg/dL] higher than ULN or >2.75 mmol/L [>11 mg/dL]). Subjects who have clinically stable hypercalcemia attributable to a disease other than multiple myeloma (e.g., hyperparathyroidism) may be considered for inclusion after a case by case review by the medical monitor.

c. Renal insufficiency, preferably determined by creatinine clearance <40 mL/min measured or estimated using the MDRD, or serum creatinine >177 µmol/L. Subjects who have clinically stable renal insufficiency attributable to a disease other than multiple myeloma (e.g., glomerulonephritis) may be considered for inclusion after a case by case review by the medical monitor.

d. Anaemia, defined as haemoglobin <10 g/dL or >2 g/dL below lower limit of normal or both; transfusion support or concurrent treatment with erythropoietin

stimulating agents is not permitted. Subjects who have clinically stable anaemia attributable to a disease other than multiple myeloma (e.g., thalassemia, vitamin B12 deficiency, iron deficiency) may be considered for inclusion after a case by case review by the medical monitor.

e. Clonal BMPC percentage ≥60%

f. Serum FLC ratio (involved:uninvolved) ≥100 (The involved FLC must be ≥100 mg/L)

g. More than 1 focal lesion ≥5 mm in diameter by MRI

2. Primary systemic AL (immunoglobulin light chain) amyloidosis.

3. Exposure to any of the following

    a. Prior exposure to daratumumab or prior exposure to other anti-CD38 therapies

    b. Prior exposure to approved or investigational treatments for SMM or MM (including but not limited to conventional chemotherapies, IMiDs, or PIs). Stable standard dosing of bisphosphonate and denosumab as indicated for osteoporosis is acceptable.

    c. Exposure to investigational drug (including investigational vaccines) or invasive investigational medical device for any indication within 4 weeks or 5 half-lives, whichever is longer, before Cycle 1, Day 1

    d. Ongoing treatment with corticosteroids with a dose >10 mg prednisone or equivalent per day at the time of randomization; or >280 mg cumulative prednisone dose or equivalent for any 4-week period in the year prior to randomization

    e. Ongoing treatment with other monoclonal antibodies (e.g., infliximab, rituximab), immunomodulators (e.g., abatacept, methotrexate, azathioprine, cyclosporine) or other treatments that are likely to interfere with the study procedures or results

4. Received treatment (chemotherapy, surgery, etc) for a malignancy (other than SMM) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion), which is considered cured with minimal risk of recurrence within 3 years.

5. Either of the following:

    a. Known or suspected chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal

    b. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

The LDCT/PET-CT/CT performed for screening should be taken into consideration to determine if additional pulmonary workup is required.

6. Any of the following:

    a. Known to be seropositive for human immunodeficiency virus (HIV)

b. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Local testing and results of hepatitis B serology (Includes HBsAg, anti-HBs, and anti-HBc) is required for all patients prior to randomization when this amendment 3 is implemented. Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR

c. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)

7. Medical or psychiatric condition or disease (e.g., active systemic disease [including presence of auto-antibodies], uncontrolled diabetes) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

8. Clinically significant cardiac disease, including:

    a. myocardial infarction within 6 months with left ventricular dysfunction or uncontrolled ischemic cardiac disease before Cycle 1 Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)

    b. Uncontrolled cardiac arrhythmia (Grade 2 or higher by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) or clinically significant ECG abnormalities

    c. Screening 12-lead ECG showing a baseline QT interval as corrected QT interval corrected for heart rate >470 msec.

The LDCT/PET-CT/CT performed for screening should be taken into consideration to determine if additional cardiac workup is required.

9. Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies, hyaluronidase, or other human proteins, or their excipients (refer to Daratumumab Investigator Brochure11), or known sensitivity to mammalian-derived products (including dairy allergy).

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

11. Pregnant, breast-feeding, or planning to become pregnant while receiving study treatment or within 3 months after the last dose of daratumumab

12. Plans to father a child while receiving study treatment or within 3 months after the last dose of daratumumab

13. Major surgery (requiring general anaesthesia or presence of other factors that determines surgery to be considered major) within 2 weeks before randomization or who have not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of daratumumab.

For the pivotal Phase 3 AQUILA study, high-risk SMM was determined based on a compilation of risk factors identified in several different models recognized at the time of study development in 2015. The determination was based on the consensus model provided by Rajkumar et al (Rajkumar 2015), which included risk factors from the Mayo 2008 criteria (Dispenzieri 2008), the PETHEMA criteria (Perez-Persona 2007), and other published risk factors. In addition, the AQUILA study criteria for high-risk SMM included criteria that could be assessed by a central laboratory or that were globally utilized in routine clinical practice. **Table 4** lists the risk factors used for inclusion of participants in the AQUILA study and notes the models from which the factors were derived.

Table 4. High-risk Inclusion Criteria in the AQUILA Study

Risk Factors	PETHEMA (2007)[1]	Mayo (2008)[2]	Other high risk factors[3]	Consensus paper (2015)[4]	AQUILA (2017)
BMPCs ≥10%		X		X	X
AND at least 1 of the following:					
Serum M-Protein ≥3 g/dL		X		X	X
Serum FLC ratio ≥8 and <100		X		X	X
IgA SMM			X	X	X
Immunoparesis with reduction of 2 uninvolved Ig isotypes				X	X
Reduction of ≥1 uninvolved Ig	X				
Clonal BMPC >50% to <60%			X	X	X

1) Perez-Persona E., et al. Blood. 2007;110(7):2586-2592.
2) Dispenzieri A., et al. Blood. 2008;111(2):785-789.
3) Kyle RA et al, N Engl J Med. 2007;356(25):2582-2590.
4) Rajkumar SV et al, Blood. 2015;125(20):3069-3075.

Treatments

For participants randomised to ACTM (active monitoring), no disease-specific treatment was administered.

Daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) was administered by SC injection. For subjects randomised to the daratumumab arm, daratumumab was administered weekly in Cycle 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and thereafter every 4 weeks until 39 cycles or up to 36 months or until confirmed PD, unacceptable toxicity, if the daratumumab dose is held for more than 28 days due to treatment-related adverse events or experiences a second primary malignancy that cannot be treated by surgery alone.

Predose Medication

In an effort to prevent IRRs, subjects in the daratumumab arm received all of the following medications 1 to 3 hours prior to each daratumumab administration):

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg orally (PO) or IV

- An antihistamine: diphenhydramine 25-50 mg PO or IV, or equivalent. Avoid the use of IV promethazine. After Cycle 6, if a subject has not developed an IRR and is intolerant to antihistamines, then modifications are acceptable as per investigator discretion. (See Attachment 4 for a list of antihistamines that may be used)
- A corticosteroid: methylprednisolone 100 mg PO or IV or equivalent for the first 2 doses and 60 mg for all subsequent doses. This reduction in steroid dose can only be done in the absence of IRR adverse events in both of the first 2 doses. Substitutions for methylprednisolone are allowed, but conversion rules have to be taken into account.

Predose administration of a leukotriene inhibitor (montelukast 10 mg PO, or equivalent) was recommended on Cycle 1 Day 1.

Postdose Medication

In an effort to prevent delayed IRRs, subjects in the daratumumab arm received a long- or intermediate-acting corticosteroid (20 mg methylprednisolone PO or equivalent, in accordance with local standards) on the 2 days following each daratumumab administration (beginning the day after daratumumab administration).

Objectives

The primary objective of this study was to determine whether treatment with daratumumab SC prolongs PFS compared with active monitoring in subjects with high risk SMM.

The secondary objectives were:
- To demonstrate additional clinical benefit (ORR, duration of response, OS, etc.) for subjects with high-risk SMM treated with daratumumab compared with active monitoring

-To assess the safety profile of daratumumab in subjects with high-risk SMM

-To assess the clinical characteristics of symptomatic MM following progression of disease after therapy with daratumumab

-To evaluate the pharmacokinetics and immunogenicity of daratumumab administered SC in subjects with high-risk SMM

-To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20)

-To evaluate the effect of treatment with daratumumab on patient-reported outcomes

Outcomes/endpoints

Primary Efficacy Endpoint

PFS, defined as the time from the date of randomisation to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurred first

Secondary endpoints

- Time to biochemical or diagnostic (SLiM-CRAB) progression defined as the earlier of time to the earlier of biochemical progression or diagnostic (BOD) progression

- Objective Response Rate (ORR), defined as, the proportion of participants with a PR or better as defined by the IMWG response criteria
- Complete Response (CR) rate, defined as, the proportion of participants with a CR (or better) as defined by the IMWG response criteria
- Time to first-line treatment for MM, defined as, the time from the date of randomisation to the date of the first-line treatment for MM
- PFS2, defined as, the time from the date of randomisation to the date of documented PD on the first-line treatment for MM or death, whichever comes first
- Overall Survival (OS), defined as, the time from the date of randomisation to the date of death
- Incidence of MM with adverse prognostic features, which include International Staging System Stage III (based on β2-microglobulin and albumin) and adverse cytogenetic characteristics
- Duration of response, defined as the time from the date of onset of first response until date of disease progression or death, whichever occurs first
- Time to response, defined as the time from randomisation until onset of first response

Sample size

The sample size calculation assumed that the median PFS for Arm A (active monitoring) was 30 months. The longer projected median PFS compared to the published 24 months was chosen to account for the fact that ultra-high risk SMM subjects, who were included in earlier studies, are now considered to have symptomatic MM according to the updated IMWG criteria, and to account for the additional risk factors included to identify high-risk SMM for this study. It was further assumed that daratumumab treatment would reduce the risk of the disease progression or death by 37.5%, i.e., assuming a HR (daratumumab vs active monitoring) of 0.625, which translates to a median PFS of 48 months for daratumumab. Taking into account the interim analysis, 165 PFS events were needed to achieve a power of at least 85% to detect this hazard ratio with a log-rank test (one sided alpha=0.025). With a 24-month accrual period and an additional 24 months of follow-up, the sample size needed for the study was approximately 360 (180 in active monitoring, 180 in daratumumab) subjects.

At the end of study, approximately 134 PFS2 events would be expected in both arms (81 at the time of the primary analysis of PFS). With 134 PFS2 events, the probability of showing a positive trend, i.e., estimated HR<1, was more than 95% assuming the true HR=0.75 (median PFS2: 72 vs 96 months)

At the end of study, approximately 107 OS events would be expected in both arms (64 at the time of the primary analysis of PFS). With 107 OS events, the probability of showing a positive trend, i.e., estimated HR<1, is more than 85% assuming the true HR=0.80 (median OS: 100 vs 125 months).

Randomisation

Central randomisation was implemented to assign subjects in a 1:1 ratio to two treatment groups, using permuted blocks and stratified by the number of progression to MM risk factors (<3 vs. ≥3).

Blinding (masking)

This is an open-label study.

PFS evaluations were conducted in a blinded manner by an IRC using central laboratory results, clonal plasma cell assessments, and independent radiological reviews to ensure unbiased application of IMWG criteria.

Statistical methods

Primary Efficacy Endpoint

Determination of dates of PFS event and dates for censoring are summarised in **Table 5**.

Table 5. PFS event and censoring method

Situation	Date of Progression or Censoring	Outcome
No postbaseline disease assessment	Randomization	Censored
Disease progression prior to start of anti-cancer therapy for multiple myeloma	Earliest date that indicates disease progression	PFS event
Death prior to start of anti-cancer therapy for multiple myeloma	Date of death	PFS event
Other, such as: ○ Withdrawal of consent to study participation, ○ Lost to follow-up ○ Start of subsequent anti-cancer therapy prior to disease progression or death	Date of last disease assessment on or prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anti-cancer therapy	Censored

Intercurrent events for this variable are: 1) start of subsequent anti-myeloma treatment prior to disease progression or death, 2) treatment discontinuation, 3) study discontinuation

The strategies to account for these intercurrent events are:

• subjects will be censored at the last disease assessment prior to start of subsequent therapy (while on treatment strategy)

• Treatment discontinuation will be ignored (treatment policy strategy)

• Subjects will be censored at the last disease assessment prior to study discontinuation (hypothetical strategy)

Analysis of PFS will be performed on the ITT analysis set. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment group. The median PFS with 95% CI will be provided. The Kaplan-Meier curve for PFS will also be plotted by treatment group.

The PFS distributions between the 2 treatment groups will be compared using the stratified log-rank test. The p-value from a stratified log-rank test will be reported. The treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The stratification factor used in the analyses will be the number of risk factors associated with progression to multiple myeloma (<3 vs ≥3). In addition, landmark PFS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

Sensitivity analyses for PFS will include PFS by investigator, in which disease progression is determined based on investigator assessment per the IMWG criteria, and PFS (algorithm), in which disease

progression is determined based on a validated computer algorithm adapted based on the 2014 IMWG diagnostic criteria for multiple myeloma (Rajkumar 2014).

Supplemental analyses for PFS (IRC) will include,

1) subjects who die due to COVID-19 will be censored, i.e. deaths due to COVID prior to start of subsequent anti-cancer therapy for MM will not be counted as PFS events;

2) subjects who start subsequent anti-cancer therapy for MM prior to disease progression or death will not be censored;

3) If the PFS event date and the latest date of scheduled disease evaluation immediately preceding the event differs more than 2.5 times the disease evaluation intervals (i.e. 30 weeks), which indicates that subject missed at least 2 consecutively scheduled disease evaluation (include hemoglobin, Creatinine, Creatinine clearance, serum FLC assessment, and corrected calcium only), then the event will not be considered as a PFS event in this sensitivity analysis. Instead, the subject will be censored at the date of last disease evaluation prior to the PFS event.

Secondary endpoints

For the BOD progression subjects who have no postbaseline disease assessment, withdraw consent to study participation, start subsequent anticancer therapy prior to BOD progression or death, or who are lost to follow-up, will be censored. In addition, subjects who were already diagnosed with multiple myeloma per baseline central imaging review will be censored at randomisation.

The median time to BOD-PFS and 95% CI in each group will be estimated using the Kaplan-Meier method. The BOD-PFS distributions between the 2 groups will be compared using the stratified log-rank
test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified
Cox regression model with treatment as the sole explanatory variable.

The median PFS2 and 95% CI in each group will be estimated using the Kaplan-Meier method. The PFS2 distributions between the 2 groups will be compared using the stratified log-rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Determination of dates of PFS2 event and dates for censoring is summarised in **Table 6**.

Table 6. PF2 event and censoring method

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	Randomization	Censored
Alive and no disease progression on study treatment	Date of last disease assessment on or prior to start of 1st line of next therapy	Censored
Disease progression on study treatment and progress on the 1st line of next therapy or any death	Minimum of earliest date that indicates progression on the 1st line of next therapy and date of death	PFS2 event
Other	Minimum of start date of 2nd line of next therapy minus 1 and last date of follow-up	Censored

The median OS and 95% CI in each group will be estimated using the Kaplan-Meier method. The OS distributions will be compared between the 2 groups using the stratified log-rank test. The treatment

effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

For OS, subjects who are lost to follow-up will be censored at the last known alive date. Subjects who died after consent withdrawal will be considered as having an OS event. Subjects who are still alive at the clinical cut-off date for the analysis or the survival status is unknown will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Time to first-line treatment for MM: The median time to first-line treatment for active MM and 95% CI in each group will be estimated using the Kaplan-Meier method. The time to first-line treatment for MM distributions between the 2 groups will be compared using the stratified log-rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

For Duration of response (DOR) subjects who have not progressed or subjects who die due to causes other than disease progression will be censored at the last disease assessment date. A descriptive summary for duration of response will be provided. No statistical comparison will be made.

Interim analysis

There was one interim analysis planned for futility when approximately 60% of the PFS events (99) had occurred. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The non-binding futility boundary at this interim analysis will be determined using the Kim-Demets power spending function with parameter p=4.0. The beta spent at this analysis will be 0.0194.

Multiplicity

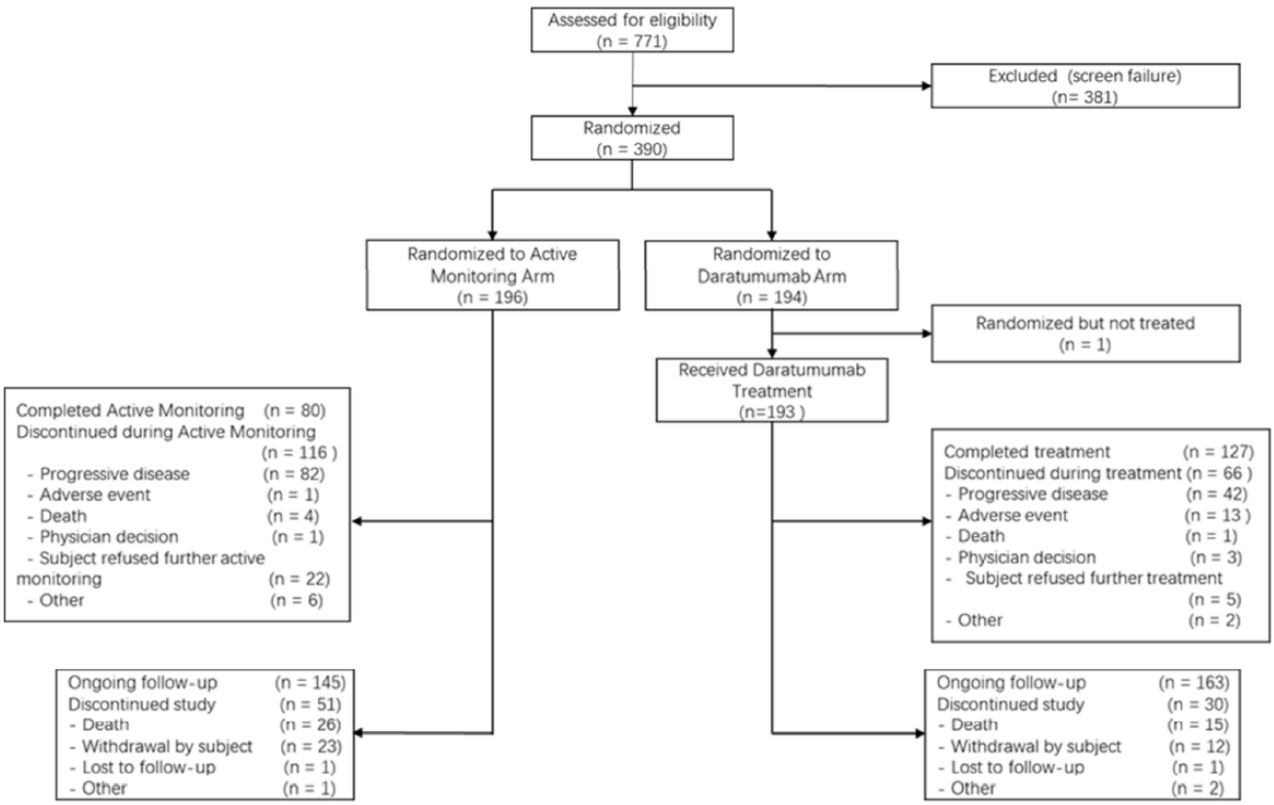
The primary hypothesis is to be tested at the 0.05 significance level. If the primary endpoint of PFS is statistically significant at the primary analysis, the following secondary endpoints ordered below will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilising a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls Type I error rate: ORR, PFS2, OS.

If the null hypothesis for any of the endpoints fails to be rejected at the primary analysis time point, then any of the subsequent endpoint(s) listed above will not be tested until the next analysis timepoint, if applicable. If the null hypothesis for an endpoint is rejected at an analysis time point, it will remain being rejected and will not be re-tested at the next analysis timepoint, if any. The significance level for each of the above secondary endpoints will be determined by the alpha spending function specific to the endpoint. The ORR will only be tested at the primary analysis time point with a 2-sided level of significance of 0.05. For PFS2, and OS, alpha spending at the primary analysis time point and the final analysis point will be determined by a linear alpha spending function based on the observed number of the events at the time, i.e., the cumulative alpha to be spent will be the total alpha (0.05) multiplied by the proportion of the observed number of the events out of the total expected number of the events. For example, if 59% targeted PFS2 events are observed at the primary analysis, the corresponding alpha level will be 0.0295 (2-sided).

Results

Participant flow

Figure 8. CONSORT Diagram (Study 54767414SMM3001)



Recruitment

Study Initiation Date: 06 November 2017 (first participant was screened).

Data Cutoff Date: 01 May 2024 (Last observation recorded as part of the database for the primary analysis).

Conduct of the study

The original protocol was dated 19 July 2017 and amended 5 times globally and 2 additional times (twice in France [prior to creation of the consolidated protocol amendment Amendment5/EEA-1] and once in Japan). Substantial changes in the conduct of the study are described in **Table 7.**

Table 7. Summary of Protocol Amendments for Study 54767414SMM3001

Amendment 1 (global; 30 January 2018)	• Amended to address feedback from Health Authorities and clarified study assessments. No changes to overall study conduct were implemented. o Clarified identification of HBV testing and management of participants o Use of local laboratories o Disease evaluation assessments and disease progression o Duration of study
Amendment 2 (global; 19 September 2018)	• Several clarifications to study conduct were implemented: no changes to study conduct o Central review of screening images to confirm participant eligibility o Biomarker assessment timepoints and a new microbiome assessment were added o Safety assessment clarifications on PRO, ECOG, FEV1 o Disease assessment clarifications for confirming disease progression
Amendment 2/FRA-1 (local amendment: France; 14 November 2018)	• Amended in France to address feedback from the local regulatory authority to modify Exclusion Criterion 1.d to prevent participants with anemia (hemoglobin <8g/dL) to be treated with daratumumab, given its known safety profile.
Amendment 3 (global; 25 January 2019)	• Amended in response to identification of a new important risk, HBV reactivation.
Amendment 3/JPN-1 (local amendment: Japan; 05 February 2019)	• Amended to add text for identification of HBV reactivation, testing, and management of participants with the potential for HBV reactivation or to modify text in response to identification of a new important risk (HBV reactivation) with Japan-specific elements.
Amendment 3/FRA-2 (local amendment: France; 12 June 2019)	• Amended to incorporate feedback from the Agence nationale de sécurité du medicament et des produits de santé (ANSM, France), who requested to add further guidance on testing for hepatitis B in participants with unknown serology status.
Amendment 4 (global; 22 June 2020) Amendment 4/FRA-2 (local amendment: France; 22 June 2020) Amendment 4/JPN-1 (local amendment: Japan; 22 June 2020)	• Amended to permit home health care and tele-health (conducted via phone or video conference) visits per the clinical judgement of the investigator, in consultation with the sponsor, and where feasible and permissible by local policy and regulations.
Amendment 5 (global; 14 January 2021) Amendment 5/FRA-2 (local amendment: France; 14 January 2021) Amendment 5/JPN-1 (local amendment: Japan; 14 January 2021)	• Amended to indicate that only the futility analysis will be performed during the interim analysis.
Amendment 5 (global/EEA-1; 14 August 2023)	• Amended to comply with EU CTR requirements and to consolidate country-specific requirements for France from 2 prior country-specific amendments into a country/territory-specific appendix.

ECOG=Eastern Cooperative Oncology Group; EU CTR=European Union Clinical Trials Regulation; FEV1=forced expiratory volume in 1 second; FRA=France; HBV=hepatitis B virus; JPN=Japan; PRO=patient-reported outcome

Protocol deviations

Major protocol deviations were reported in 8.2% of participants overall (Dara 10.3%; ACTM 6.1%; **Table 8).**

Major protocol deviations coded as 'received wrong treatment or incorrect dose' included participants that received daratumumab SC while there was a protocol-specified event for toxicity management (3 participants in the Dara arm) and participants that received post dose medication not in accordance with the protocol (5 participants in the Dara arm).

Table 8. Summary of Subjects with Major Protocol Deviations; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara	Total
Analysis set: intent-to-treat	196	194	390
Total number of subjects with major protocol deviation	12 (6.1%)	20 (10.3%)	32 (8.2%)
Subjects with major protocol deviations			
Received a disallowed concomitant treatment	4 (2.0%)	7 (3.6%)	11 (2.8%)
Received wrong treatment or incorrect dose	0	8 (4.1%)	8 (2.1%)
Entered but did not satisfy criteria	4 (2.0%)	3 (1.5%)	7 (1.8%)
Other	4 (2.0%)	3 (1.5%)	7 (1.8%)

Note: A subject can be counted in multiple categories.

Baseline data

Demographic and other baseline characteristics are summarised in **Table 9** , and baseline disease characteristics in **Table 10.**

Table 9. Summary of Demographics and Baseline Characteristics; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara	Total
Analysis set: intent-to-treat	196	194	390
Age (years)			
N	196	194	390
Mean (SD)	63.0 (10.76)	61.9 (11.17)	62.4 (10.97)
Median	64.5	63.0	64.0
Range	(36; 83)	(31; 86)	(31; 86)
18-<65	98 (50.0%)	106 (54.6%)	204 (52.3%)
65-<75	74 (37.8%)	67 (34.5%)	141 (36.2%)
>=75	24 (12.2%)	21 (10.8%)	45 (11.5%)
Sex, n (%)			
N	196	194	390
Male	93 (47.4%)	95 (49.0%)	188 (48.2%)
Female	103 (52.6%)	99 (51.0%)	202 (51.8%)
Race, n (%)			
N	196	194	390
White	162 (82.7%)	161 (83.0%)	323 (82.8%)
Black or African American	7 (3.6%)	4 (2.1%)	11 (2.8%)
Asian	13 (6.6%)	18 (9.3%)	31 (7.9%)
American Indian or Alaska Native	3 (1.5%)	0	3 (0.8%)
Native Hawaiian or Other Pacific Islander	2 (1.0%)	0	2 (0.5%)
Multiple	0	1 (0.5%)	1 (0.3%)
Not Reported	9 (4.6%)	10 (5.2%)	19 (4.9%)
Ethnicity, n (%)			
N	196	194	390
Hispanic or Latino	9 (4.6%)	14 (7.2%)	23 (5.9%)
Not Hispanic or Latino	176 (89.8%)	169 (87.1%)	345 (88.5%)
Not Reported	11 (5.6%)	11 (5.7%)	22 (5.6%)
Weight (kg)			
N	194	194	388
Mean (SD)	79.64 (18.326)	78.00 (16.045)	78.82 (17.221)
Median	78.25	78.00	78.00
Range	(41.4; 152.9)	(46.2; 159.0)	(41.4; 159.0)
≤65	46 (23.7%)	43 (22.2%)	89 (22.9%)
>65-≤85	84 (43.3%)	96 (49.5%)	180 (46.4%)
>85	64 (33.0%)	55 (28.4%)	119 (30.7%)
Height (cm)			
N	194	194	388
Mean (SD)	168.46 (11.213)	168.10 (10.317)	168.28 (10.762)
Median	168.00	168.00	168.00
Range	(143.0; 201.0)	(142.0; 192.0)	(142.0; 201.0)
Baseline ECOG score, n (%)			
N	196	194	390
0	160 (81.6%)	165 (85.1%)	325 (83.3%)
1	36 (18.4%)	29 (14.9%)	65 (16.7%)
>1	0	0	0

Note: Percentages are calculated with the number of subjects in each group with available data as the denominators.

Table 10. Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara	Total
Analysis set: intent-to-treat	196	194	390
Type of myeloma by immunofixation or serum FLC assay, n (%)			
N	196	194	390
IgG	138 (70.4%)	127 (65.5%)	265 (67.9%)
IgA	42 (21.4%)	55 (28.4%)	97 (24.9%)
IgM	0	1 (0.5%)	1 (0.3%)
IgD	2 (1.0%)	0	2 (0.5%)
IgE	0	0	0
Light chain	9 (4.6%)	9 (4.6%)	18 (4.6%)
Kappa	7 (3.6%)	6 (3.1%)	13 (3.3%)
Lambda	2 (1.0%)	3 (1.5%)	5 (1.3%)
Biclonal	5 (2.6%)	1 (0.5%)	6 (1.5%)
Serum FLC only[a]	0	1 (0.5%)	1 (0.3%)
Not detected	0	0	0
Type of measurable disease, n (%)			
N	196	194	390
Serum only	157 (80.1%)	162 (83.5%)	319 (81.8%)
Serum and urine	3 (1.5%)	3 (1.5%)	6 (1.5%)
Urine only	9 (4.6%)	4 (2.1%)	13 (3.3%)
FLC	27 (13.8%)	25 (12.9%)	52 (13.3%)
Focal lesions			
N	196	194	390
No	179 (91.3%)	172 (88.7%)	351 (90.0%)
Yes	17 (8.7%)	22 (11.3%)	39 (10.0%)
Serum M-protein (g/dL)			
N	196	194	390
<1	36 (18.4%)	29 (14.9%)	65 (16.7%)
>=1 to <=2	73 (37.2%)	84 (43.3%)	157 (40.3%)
>2 to <3	47 (24.0%)	47 (24.2%)	94 (24.1%)
>=3	40 (20.4%)	34 (17.5%)	74 (19.0%)
Plasma cell(%), bone marrow aspirate/biopsy[b]			
N	196	194	390
Mean (SD)	24.21 (11.630)	21.78 (11.416)	23.00 (11.573)
Median	20.00	20.00	20.00
Range	(10.0; 55.0)	(8.0; 59.5)	(8.0; 59.5)
<10	0	1 (0.5%)	1 (0.3%)
>=10 to <=20	102 (52.0%)	124 (63.9%)	226 (57.9%)
>20 to <40	66 (33.7%)	50 (25.8%)	116 (29.7%)
>=40	28 (14.3%)	19 (9.8%)	47 (12.1%)
Serum Free light chain (involved/uninvolved) ratio			
N	196	194	390
Mean (SD)	25.59 (25.320)	28.19 (29.898)	26.88 (27.687)
Median	15.86	16.78	16.36
Range	(0.4; 97.6)	(0.5; 160.6)	(0.4; 160.6)
<8	49 (25.0%)	54 (27.8%)	103 (26.4%)
>=8 to <=20	63 (32.1%)	53 (27.3%)	116 (29.7%)
>20	84 (42.9%)	87 (44.8%)	171 (43.8%)
Creatinine Clearance/GFR (mL/min/1.73m^2) Category, n (%)[f]			
N	196	194	390
Normal	58 (29.6%)	54 (27.8%)	112 (28.7%)
Abnormal	138 (70.4%)	140 (72.2%)	278 (71.3%)
Hepatic function[g]			
N	190	185	375
Normal	172 (90.5%)	173 (93.5%)	345 (92.0%)
Impaired	18 (9.5%)	12 (6.5%)	30 (8.0%)
ISS staging, n(%)			
N	192	191	383
I	155 (80.7%)	154 (80.6%)	309 (80.7%)
II	33 (17.2%)	33 (17.3%)	66 (17.2%)
III	4 (2.1%)	4 (2.1%)	8 (2.1%)
Time from first evidence of monoclonal gammopathy to randomization (first M-protein detection) (years)			
N	196	194	390
Mean (SD)	3.43 (4.922)	3.04 (4.170)	3.24 (4.562)
Median	1.80	1.53	1.70
Range	(0.1; 32.0)	(0.1; 26.0)	(0.1; 32.0)
<=1 year	71 (36.2%)	67 (34.5%)	138 (35.4%)
>1 year	125 (63.8%)	127 (65.5%)	252 (64.6%)
Time from initial diagnosis date of SMM to randomization (years)			
N	196	194	390

	Active Monitoring	Dara	Total
Mean (SD)	1.26 (1.301)	1.23 (1.170)	1.24 (1.236)
Median	0.67	0.80	0.72
Range	(0.0; 5.0)	(0.0; 4.7)	(0.0; 5.0)
<=1 year	114 (58.2%)	108 (55.7%)	222 (56.9%)
>1 year	82 (41.8%)	86 (44.3%)	168 (43.1%)
Risk-associated molecular subtypes			
Number of subjects with evaluable cytogenetic results (n, %)[c]	170 (86.7%)	167 (86.1%)	337 (86.4%)
Number of subjects with at least one of the following subtypes (n, %)[d]	22 (12.9%)	29 (17.4%)	51 (15.1%)
del(17p13) (n/m, %)[e]	8/166 (4.8%)	3/166 (1.8%)	11/332 (3.3%)
t(4;14) (n/m, %)[e]	11/157 (7.0%)	19/151 (12.6%)	30/308 (9.7%)
t(14;16) (n/m, %)[e]	3/145 (2.1%)	7/146 (4.8%)	10/291 (3.4%)
Mayo 2018 Risk Criteria[h]:			
N	196	194	390
Low	34 (17.3%)	45 (23.2%)	79 (20.3%)
Intermediate	76 (38.8%)	77 (39.7%)	153 (39.2%)
High	86 (43.9%)	72 (37.1%)	158 (40.5%)

Keys: NE= Not Evaluable; ISS = International staging system.
[a] not detected by immunofixation, serum free light chain only.
[b] The highest plasma cell(%) from bone marrow aspirate or biopsy.
[c] The evaluable subjects are the subjects with evaluable results with probes del(17p13), t(14, 16), and t(4,14). The denominator for the % is the ITT subjects in the treatment group. Cytogenetic abnormalities were based on FISH.
[d] The denominator for the % is the number of the subjects with evaluable cytogenetic results in the treatment group.
[e] n is the number of the subjects with the specific subtype. m is the number of the subjects with evaluable cytogenetic result for the specific probe in the treatment group.
[f] Normal: GFR (mL/min/1.73m^2) ≥90.
[g] Hepatic impairment status is classified into 4 levels per NCI Organ Dysfunction: normal (total bilirubin ≤ULN and AST ≤ULN); mild (total bilirubin ≤ULN and AST > ULN) or (ULN < total bilirubin ≤1.5xULN); moderate (1.5xULN < total bilirubin ≤3xULN); and severe (total bilirubin > 3xULN). Impaired includes mild, moderate and severe.
[h] Mayo 2018 Risk Criteria: 1) Serum M protein > 2 g/dL, 2) I/U FLC ratio > 20, 3) BMPC > 20%.
Patients with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk, ≥2 factors are considered as high risk.
Note: Values at screening visit will be taken into considerations in the derivation of the type of measurable disese if either SPEP or UPEP at baseline does not meet measurable disease definition.
Note: Percentages are calculated with the number of subjects in each group with available data as denominator.

Table 11 displays a summary of the distribution of risk factors associated with progression to multiple myeloma (as defined by the SMM3001 [AQUILA] study) between study arms.

Table 11. Summary of AQUILA Risk Factors; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara	Total
Analysis set: intent-to-treat	196	194	390
AQUILA risk factors			
Serum M protein ≥30 g/L	40 (20.4%)	34 (17.5%)	74 (19.0%)
IgA SMM	42 (21.4%)	55 (28.4%)	97 (24.9%)
Immunoparesis with reduction of at least 2 uninvolved immunoglobulin isotypes[a]	116 (59.2%)	116 (59.8%)	232 (59.5%)
Serum involved: uninvolved FLC ratio ≥8 and <100	147 (75.0%)	135 (69.6%)	282 (72.3%)
Clonal BMPCs >50% to <60% with measurable disease	4 (2.0%)	6 (3.1%)	10 (2.6%)

[a] Only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment.
Note: The risk factors were based on baseline values.
Note: One subject may meet more than one risk factors.

Subsequent Antimyeloma Therapy

The subsequent antimyeloma therapies (**Table 12**) were administered either in combination or as monotherapy depending on the subsequent treatment regimen being provided for the participant at the time.

Table 12. Summary of Subsequent Antimyeloma Therapy by Therapeutic Class, Pharmacologic Class and Drug; Safety Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara	Total
Analysis set: safety	196	193	389
Total number of subjects with 1 or more subsequent antimyeloma therapies	105 (53.6%)	64 (33.2%)	169 (43.4%)
Number of subjects with stem cell transplant	44 (22.4%)	24 (12.4%)	68 (17.5%)
Therapeutic class/Pharmacologic class/Drug			
Corticosteroids for systemic use	104 (53.1%)	61 (31.6%)	165 (42.4%)
Corticosteroids for systemic use, plain	104 (53.1%)	61 (31.6%)	165 (42.4%)
Dexamethasone	101 (51.5%)	61 (31.6%)	162 (41.6%)
Prednisone	7 (3.6%)	1 (0.5%)	8 (2.1%)
Methylprednisolone	1 (0.5%)	0	1 (0.3%)
Prednisolone	2 (1.0%)	0	2 (0.5%)
Antineoplastic agents	100 (51.0%)	59 (30.6%)	159 (40.9%)
Other antineoplastic agents	87 (44.4%)	51 (26.4%)	138 (35.5%)
Bortezomib	81 (41.3%)	47 (24.4%)	128 (32.9%)
Carfilzomib	15 (7.7%)	14 (7.3%)	29 (7.5%)
Ixazomib	7 (3.6%)	9 (4.7%)	16 (4.1%)
Car t-cells nos	0	2 (1.0%)	2 (0.5%)
Ciltacabtagene autoleucel	0	1 (0.5%)	1 (0.3%)
Cisplatin	3 (1.5%)	1 (0.5%)	4 (1.0%)
Mezigdomide	1 (0.5%)	1 (0.5%)	2 (0.5%)
Nirogacestat	0	1 (0.5%)	1 (0.3%)
Selinexor	0	1 (0.5%)	1 (0.3%)
Other antineoplastic agents	1 (0.5%)	0	1 (0.3%)
Venetoclax	1 (0.5%)	0	1 (0.3%)
Alkylating agents	66 (33.7%)	33 (17.1%)	99 (25.4%)
Melphalan	54 (27.6%)	24 (12.4%)	78 (20.1%)
Cyclophosphamide	27 (13.8%)	15 (7.8%)	42 (10.8%)
Bendamustine	0	1 (0.5%)	1 (0.3%)
Busulfan	0	1 (0.5%)	1 (0.3%)
Carmustine	1 (0.5%)	0	1 (0.3%)
Monoclonal antibodies and antibody drug conjugates	58 (29.6%)	24 (12.4%)	82 (21.1%)
Daratumumab	51 (26.0%)	18 (9.3%)	69 (17.7%)
Isatuximab	5 (2.6%)	5 (2.6%)	10 (2.6%)
Daratumumab;vorhyaluronidase alfa	2 (1.0%)	1 (0.5%)	3 (0.8%)
Elotuzumab	3 (1.5%)	1 (0.5%)	4 (1.0%)
Linvoseltamab	1 (0.5%)	1 (0.5%)	2 (0.5%)
Talquetamab	0	1 (0.5%)	1 (0.3%)
Belantamab mafodotin	3 (1.5%)	0	3 (0.8%)
Elranatamab	1 (0.5%)	0	1 (0.3%)
Antimetabolites	1 (0.5%)	1 (0.5%)	2 (0.5%)
Fludarabine	1 (0.5%)	1 (0.5%)	2 (0.5%)
Cytarabine	1 (0.5%)	0	1 (0.3%)
Cytotoxic antibiotics and related substances	3 (1.5%)	1 (0.5%)	4 (1.0%)
Doxorubicin	3 (1.5%)	1 (0.5%)	4 (1.0%)
Plant alkaloids and other natural products	4 (2.0%)	1 (0.5%)	5 (1.3%)
Etoposide	3 (1.5%)	1 (0.5%)	4 (1.0%)
Vincristine	1 (0.5%)	0	1 (0.3%)
Uncoded	0	1 (0.5%)	1 (0.3%)
Investigational antineoplastic drugs	0	1 (0.5%)	1 (0.3%)
Immunosuppressants	93 (47.4%)	57 (29.5%)	150 (38.6%)
Immunosuppressants	93 (47.4%)	57 (29.5%)	150 (38.6%)
Lenalidomide	88 (44.9%)	52 (26.9%)	140 (36.0%)
Thalidomide	15 (7.7%)	12 (6.2%)	27 (6.9%)
Pomalidomide	14 (7.1%)	5 (2.6%)	19 (4.9%)
Iberdomide	0	1 (0.5%)	1 (0.3%)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Coded using WHO Drug Dictionary, March 2023 version.

Numbers analysed

Table 13. Summary of Subjects per Analysis Set; All Subjects Analysis Set (Study 54767414SMM3001)

	Active Monitoring n	Dara n	Total n
Study population			
Subjects screened			771
Intent-to-treat (ITT)	196	194	390
Safety[a]	196	193	389
Pharmacokinetic evaluable[b]		193	193
Immunogenicity evaluable		193	193
Daratumumab[c]		193	193
rHuPH20[d]		193	193

[a] Includes subjects who were assigned to active monitoring or subjects who were assigned to Dara-SC and received at least one dose of Dara-SC.
[b] Includes subjects assigned to Dara-SC group who received at least one dose of Dara-SC and have at least 1 pharmacokinetic sample concentration value after their first daratumumab administration.
[c] Includes subjects assigned to Dara-SC group who received at least one dose of Dara-SC and have at least 1 immunogenicity sample obtained after their first daratumumab administration.
[d] Includes subjects assigned to Dara-SC group who received at least one dose of Dara-SC and have appropriate plasma samples for detection of antibodies to rHuPH20.

Outcomes and estimation

Primary endpoint: PFS by IRC

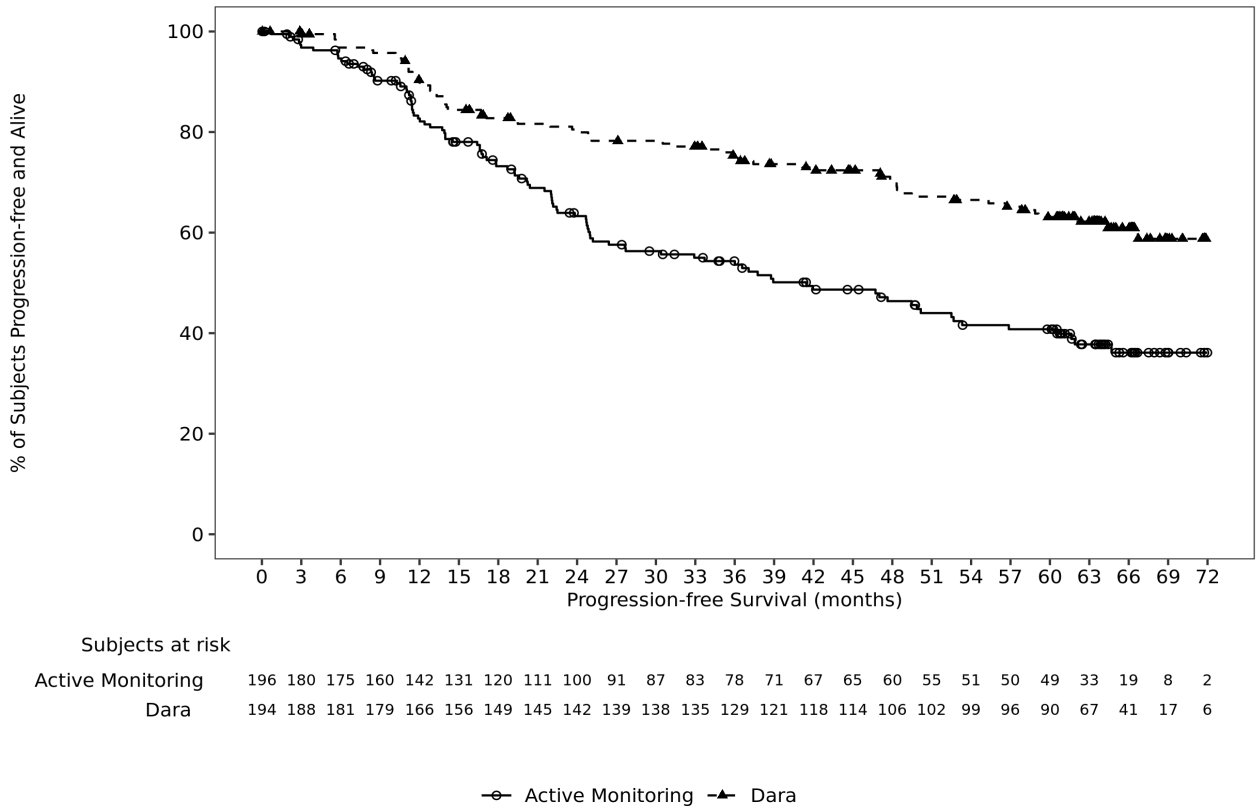
Median follow-up was 65.2 months (Dara 65.9 months; ACTM 64.8 months). A total of 166 PFS events per IRC assessment (Dara 67; ACTM 99) were observed (**Table 14** and **Figure 9**).

Table 14. Summary of progression free survival as assessed by IRC; ITT Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)	99 (50.5%)	67 (34.5%)
Number of censored (%)	97 (49.5%)	127 (65.5%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	17.12 (12.39, 21.52)	36.01 (21.95, 48.36)
Median (95% CI)	41.46 (26.41, 53.32)	NE (66.69, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.49 (0.36, 0.67)
12-month PFS rate % (95% CI)	82.7 (76.3, 87.5)	89.8 (84.5, 93.4)
24-month PFS rate % (95% CI)	63.3 (55.5, 70.0)	79.9 (73.4, 85.0)
36-month PFS rate % (95% CI)	54.3 (46.4, 61.6)	75.4 (68.4, 81.0)
48-month PFS rate % (95% CI)	46.4 (38.4, 53.9)	69.8 (62.4, 76.0)
60-month PFS rate % (95% CI)	40.8 (32.9, 48.5)	63.1 (55.3, 69.9)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Figure 9. Kaplan-Meier Plot for Progression-free Survival Based on Independent Review Committee; Intent-to-Treat Analysis Set (Study 54767414SMM3001)



A summary of the SMM3001 (AQUILA) study risk factors and their impact on progression, to multiple myeloma (as defined by the SMM3001 [AQUILA] study) or death prior to progression between study arms per IRC is provided in **Table 15**.

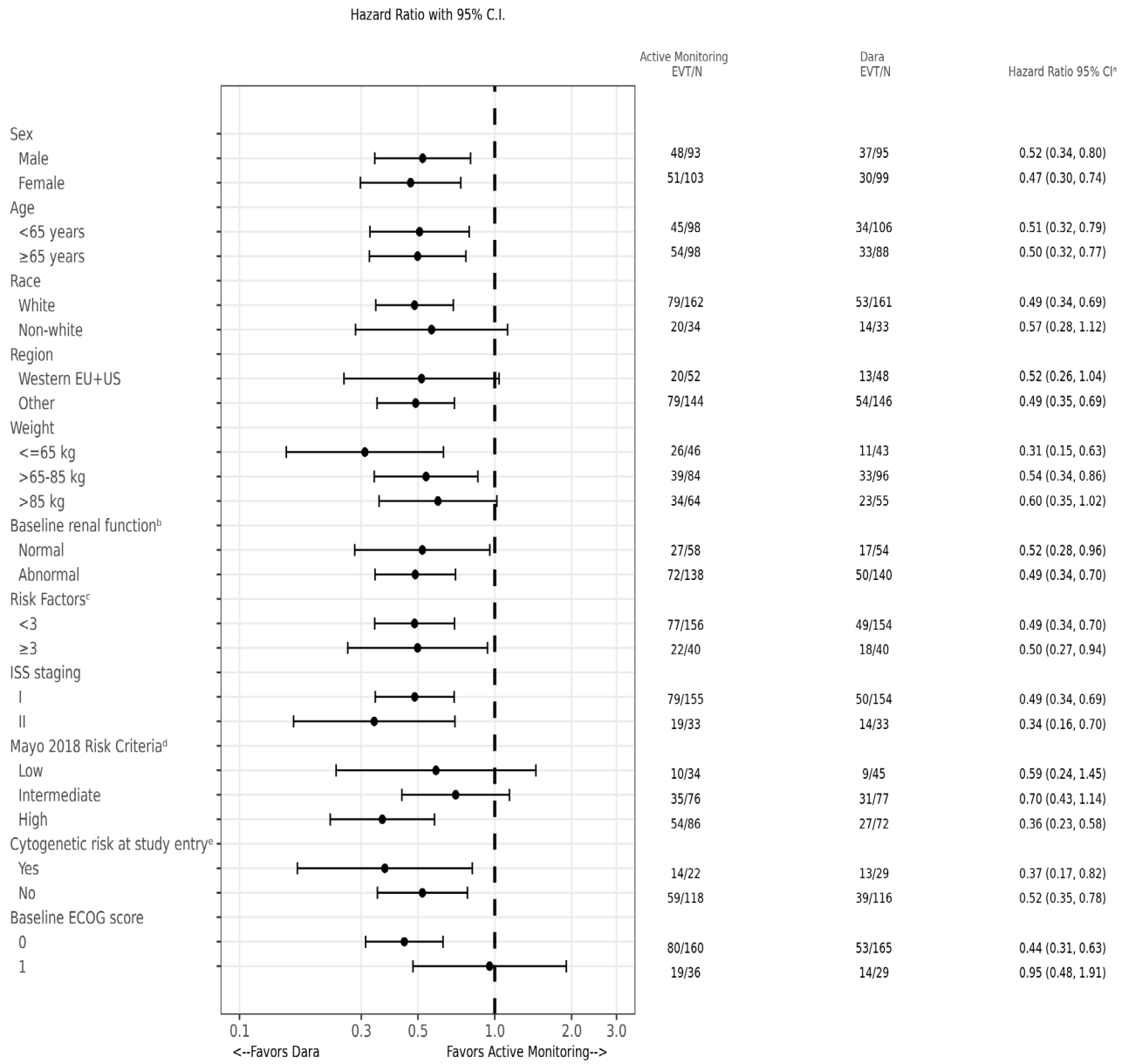
Table 15. Summary of Progression-free Survival Based on Independent Review Committee for Risk Factors; Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Subjects with progression-free survival event	99 (50.5%)	67 (34.5%)
Subjects with progressive disease [a,c]	94 (94.9%)	62 (92.5%)
Risk factors [b,d]		
Serum M protein	25 (26.6%)	9 (14.5%)
IgA	19 (20.2%)	22 (35.5%)
Immunoparesis	64 (68.1%)	42 (67.7%)
Serum involved: uninvolved FLC ratio	71 (75.5%)	51 (82.3%)
Clonal BMPCs	1 (1.1%)	2 (3.2%)
Subjects died without progressive disease [c]	5 (5.1%)	5 (7.5%)
Risk factors [b,c]		
Serum M protein	0	0
IgA	2 (40.0%)	3 (60.0%)
Immunoparesis	2 (40.0%)	1 (20.0%)
Serum involved: uninvolved FLC ratio	4 (80.0%)	3 (60.0%)
Clonal BMPCs	0	0

Keys: FLC = free light chain; PD = progressive disease.
[a] A subject may show PD based on more than one criterion.
[b] The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. Serum involved: uninvolved FLC ratio ≥8 and <100, or e. Clonal BMPCs >50% to <60% with measurable disease.
[c] Percentages are based on number of subjects with PFS event in each treatment group.
[d] Percentages are based on number of subjects with progressive disease in each treatment group.
Note: One subject may meet more than one risk factors.

Subgroup Analysis of Progression-free Survival per IRC Assessment

Figure 10. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Independent Review Committee; Intent-to-Treat Analysis Set (Study 54767414SMM3001)



Keys: CI = confidence interval; EU = European Union; GFR = glomerular filtration rate; ISS = International staging system; US = United States; EVT=Event.

a: Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory. A hazard ratio <1 indicates an advantage for Dara-SC.

b: Normal: GFR (mL/min/1.73m^2) ≥90.

c: The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.

d: Mayo 2018 risk criteria: Serum M protein > 2 g/dL, I/U FLC ratio > 20 and BMPC > 20%. Patients with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk and ≥2 factors are considered as high-risk.

e: Yes: presence of del(17p13), t(4;14), or t(14;16) at baseline; No: tested for these probes but did not have any abnormality.

Note: The subgroups with less than 10 subjects in either treatment group are suppressed in this figure.

Supplementary Analyses of Progression-free Survival per IRC Assessment

Additional supplementary analyses of PFS per IRC assessment were conducted including no censoring for start of subsequent therapy (**Table 16**), censoring for death due to COVID-19 (**Table 17**), censoring for participants who missed 2 or more consecutive disease evaluations prior to the PFS event date (**Table 18**) and not censored for patients which withdrew consent from the study (**Table 19**).

Table 16. Summary of Progression-free Survival as Assessed by Independent Review Committee (Not Censored for Subsequent Antimyeloma Therapy); Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)	104 (53.1%)	68 (35.1%)
Number of censored (%)	92 (46.9%)	126 (64.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	16.82 (12.81, 21.52)	36.01 (21.95, 48.36)
Median (95% CI)	41.46 (27.63, 52.57)	NE (66.69, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.48 (0.35, 0.66)
12-month PFS rate % (95% CI)	82.9 (76.6, 87.7)	89.8 (84.5, 93.4)
24-month PFS rate % (95% CI)	63.7 (56.0, 70.3)	80.0 (73.5, 85.1)
36-month PFS rate % (95% CI)	55.1 (47.3, 62.2)	75.5 (68.5, 81.1)
48-month PFS rate % (95% CI)	46.0 (38.2, 53.5)	69.9 (62.6, 76.1)
60-month PFS rate % (95% CI)	39.1 (31.4, 46.8)	62.6 (54.9, 69.4)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Table 17. Summary of Progression-free Survival as Assessed by Independent Review Committee (Censored for Deaths Due to COVID-19); Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)	99 (50.5%)	65 (33.5%)
Number of censored (%)	97 (49.5%)	129 (66.5%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	17.12 (12.39, 21.52)	36.27 (21.95, 49.48)
Median (95% CI)	41.46 (26.41, 53.32)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.47 (0.35, 0.65)
12-month PFS rate % (95% CI)	82.7 (76.3, 87.5)	89.8 (84.5, 93.4)
24-month PFS rate % (95% CI)	63.3 (55.5, 70.0)	79.9 (73.4, 85.0)
36-month PFS rate % (95% CI)	54.3 (46.4, 61.6)	75.9 (69.0, 81.5)
48-month PFS rate % (95% CI)	46.4 (38.4, 53.9)	70.9 (63.6, 77.0)
60-month PFS rate % (95% CI)	40.8 (32.9, 48.5)	64.1 (56.3, 70.8)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Table 18. Summary of Progression-free Survival as Assessed by Independent Review Committee (Censored for Patients Who Missed 2 or More Consecutive Disease Evaluations Prior to PFS Event Date); Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)	98 (50.0%)	65 (33.5%)
Number of censored (%)	98 (50.0%)	129 (66.5%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	16.82 (12.39, 21.52)	36.01 (21.95, 48.85)
Median (95% CI)	38.93 (26.41, 52.67)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.48 (0.35, 0.66)
12-month PFS rate % (95% CI)	82.6 (76.2, 87.5)	89.8 (84.5, 93.4)
24-month PFS rate % (95% CI)	63.1 (55.3, 69.9)	79.9 (73.4, 85.0)
36-month PFS rate % (95% CI)	54.1 (46.1, 61.3)	75.3 (68.3, 80.9)
48-month PFS rate % (95% CI)	46.0 (38.1, 53.7)	70.2 (62.9, 76.4)
60-month PFS rate % (95% CI)	40.4 (32.5, 48.2)	64.1 (56.3, 70.9)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Table 19. Summary of Progression-Free Survival as Assessed by Independent Review Committee (Not censored for Patients Who Withdrawal of Consent to Study Participation); Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)	113 (57.7%)	76 (39.2%)
Number of censored (%)	83 (42.3%)	118 (60.8%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	16.39 (11.56, 19.25)	34.99 (19.48, 44.78)
Median (95% CI)	35.81 (24.87, 46.72)	NE (62.03, NE)
75% quantile (95% CI)	NE (64.69, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.48 (0.36, 0.64)
12-month PFS rate % (95% CI)	80.3 (73.8, 85.4)	89.8 (84.5, 93.4)
24-month PFS rate % (95% CI)	60.6 (53.0, 67.4)	79.4 (72.8, 84.6)
36-month PFS rate % (95% CI)	49.7 (42.0, 56.9)	74.3 (67.3, 80.1)
48-month PFS rate % (95% CI)	41.3 (33.7, 48.6)	66.0 (58.6, 72.5)
60-month PFS rate % (95% CI)	36.3 (28.9, 43.7)	59.2 (51.5, 66.1)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. Serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Key secondary endpoint: ORR by computerised algorithm

Table 20. Summary of Overall Best Confirmed Response based on Computerised Algorithm; Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring		Dara			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: Intent-to-treat	196		194			
Response category						
Stringent complete response (sCR)	0	(NE,NE)	5 (2.6%)	(0.8%, 5.9%)		
Complete response (CR)	0	(NE,NE)	12 (6.2%)	(3.2%, 10.6%)		
Very good partial response (VGPR)	2 (1.0%)	(0.1%, 3.6%)	41 (21.1%)	(15.6%, 27.6%)		
Partial response (PR)	2 (1.0%)	(0.1%, 3.6%)	65 (33.5%)	(26.9%, 40.6%)		
Stable disease (SD)	180 (91.8%)	(87.1%, 95.3%)	67 (34.5%)	(27.9%, 41.7%)		
Progressive disease (PD)[c]	4 (2.0%)	(0.6%, 5.1%)	0	(NE,NE)		
Not evaluable[d]	8 (4.1%)	(1.8%, 7.9%)	4 (2.1%)	(0.6%, 5.2%)		
CR or better (sCR + CR)	0	(NE,NE)	17 (8.8%)	(5.2%, 13.7%)	NE (NE, NE)	<0.0001
VGPR or better (sCR + CR + VGPR)	2 (1.0%)	(0.1%, 3.6%)	58 (29.9%)	(23.5%, 36.9%)	41.41 (9.93, 172.70)	<0.0001
Overall response (sCR+CR+VGPR+PR)	4 (2.0%)	(0.6%, 5.1%)	123 (63.4%)	(56.2%, 70.2%)	83.80 (29.69, 236.54)	<0.0001

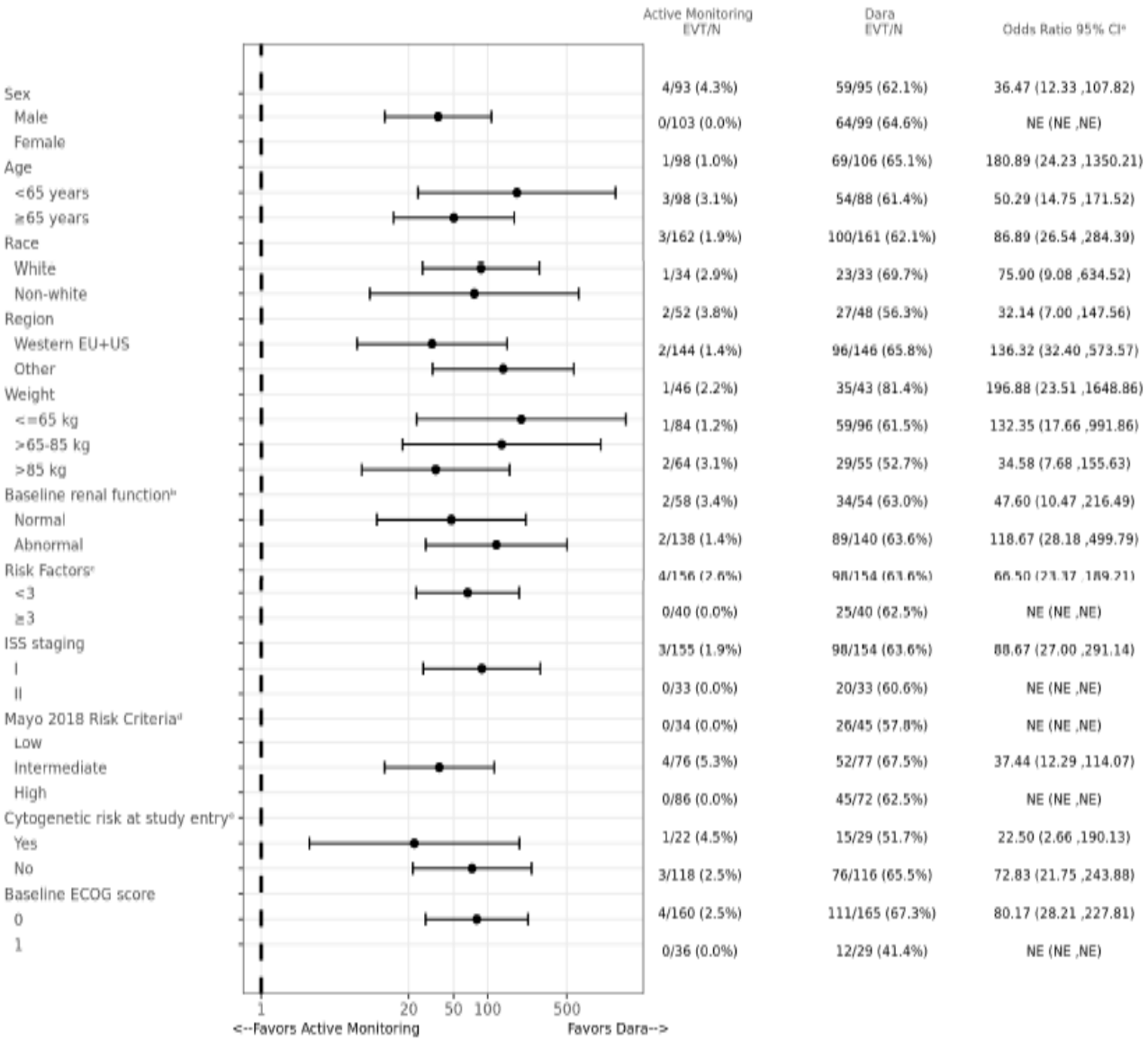
Keys: CI = confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factor is number of risk factors associated with progression to multiple myeloma (<3 vs ≥3). An odds ratio > 1 indicates an advantage for Dara-SC.
[b] p-value was calculated using Cochran Mantel-Haenszel Chi-Squared test.
[c] Progression to MM is based on the SLiMCRAB criteria, defined as, ≥60% bone marrow plasma cells, free light chain involved/uninvolved ratio ≥100, > 1 focal bone lesions on MRI, calcium elevation, renal insufficiency by creatinine clearance, anemia or bone disease due to lytic bone lesions.
[d] Not evaluable includes subjects : a) who have missing post-baseline assessments for the components they had measurable disease in, and b) those who were already diagnosed with multiple myeloma per baseline central imaging review.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as the denominator.

Table 21. Summary of Duration of Response based on Computerized Algorithm; Responders in the Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: responders (PR or better) in the intent-to-treat analysis set	4	123
Duration of response[a]		
Number of events (%)	1 (25.0%)	25 (20.3%)
Number of censored (%)	3 (75.0%)	98 (79.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	42.66 (27.4, NE)	NE (44.9, NE)
Median (95% CI)	NE (27.4, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (27.4, NE)	NE (NE, NE)

Keys: CI = confidence interval; NE = not estimable; MM=Multiple Myeloma.
[a] First response PR or better.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to disease progression.

Figure 11. Forest Plot of Subgroup Analysis on Overall Response Rate Based on Computerised Algorithm; Intent-to-treat Analysis Set (Study 54767414SMM3001)



Keys: CI = confidence interval; EU = European Union; ISS = International staging system; Overall response = sCR, CR, VGPR, or PR; US = United States, EVT = Event.
[a] Mantel-Haenszel estimate of the common odds ratio for un-stratified tables is used. An odds ratio > 1 indicates an advantage for Dara-SC.
[b] Normal: GFR (mL/min/1.73m^2) ≥90.
[c] The risk factors were: a. Serum M protein ≥30 g/L; b. IgA SMM; c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[d] Mayo 2018 risk criteria: Serum M protein > 2 g/dL, I/U FLC ratio > 20 and BMPC > 20%. Patients with presence of 0 factors are considered as low risk, 1 factor are considered as intermediate risk and ≥2 factors are considered as high risk.
[e] Yes: presence of del(17p13), t(4;14), or t(14;16) at baseline; No: tested for these probes but did not have any abnormality .
Note: The subgroups with less than 10 subjects in either treatment group are suppressed in this table.

Key secondary endpoint: PFS2

Median PFS2 was not reached in either arm (60-month PFS2 rate: Dara 85.9%; ACTM 78.0% (**Table 22**).

Table 22. Summary of Progression-free Survival on First-line Therapy for MM(PFS2) Based on Investigator Assessment; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival (PFS)		
Number of events (%)[a]	38 (19.4%)	25 (12.9%)
Number of censored (%)	158 (80.6%)	169 (87.1%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (55.89, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[b]		0.0318
Hazard ratio (95% CI)[c]		0.58 (0.35, 0.96)
12-month PFS rate % (95% CI)	99.5 (96.3, 99.9)	99.5 (96.3, 99.9)
24-month PFS rate % (95% CI)	94.4 (89.8, 96.9)	98.4 (95.1, 99.5)
36-month PFS rate % (95% CI)	92.5 (87.4, 95.6)	95.0 (90.6, 97.4)
48-month PFS rate % (95% CI)	85.4 (79.0, 90.0)	90.9 (85.5, 94.3)
60-month PFS rate % (95% CI)	78.0 (70.7, 83.7)	85.9 (79.7, 90.3)

Keys: CI = confidence interval; MM = Multiple Myeloma; NE = not estimable.
[a] Disease progression (investigator assessment) on study treatment and progress on the 1st line of next therapy or any death
[b] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[c] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Key secondary endpoint: OS

Median OS was not reached in either arm (60-month OS rate: Dara 93.0%; ACTM 86.9%;**Table 23**).

Table 23. Summary of Overall Survival; Intent-to-Treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Overall survival		
Number of events (%)	26 (13.3%)	15 (7.7%)
Number of censored (%)	170 (86.7%)	179 (92.3%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[a]		0.52 (0.27, 0.98)
12-month survival rate % (95% CI)	99.5 (96.4, 99.9)	99.5 (96.4, 99.9)
24-month survival rate % (95% CI)	97.3 (93.7, 98.9)	99.0 (95.9, 99.7)
36-month survival rate % (95% CI)	94.5 (90.0, 97.0)	97.9 (94.5, 99.2)
48-month survival rate % (95% CI)	90.4 (85.1, 93.9)	96.3 (92.4, 98.2)
60-month survival rate % (95% CI)	86.9 (81.0, 91.1)	93.0 (88.2, 95.8)

Keys: CI = confidence interval; NE = not estimable.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

Ancillary analyses

Time to Biochemical or Diagnostic (SLiM-CRAB) Progression per Computerised Algorithm Analyses

Table 24. Summary of Progression-free Survival Time as Assessed by Biochemical or SLiM-CRAB Progression Based on Computer Algorithm; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Progression-free survival		
Number of events (%)	139 (70.9%)	116 (59.8%)
Number of censored (%)	57 (29.1%)	78 (40.2%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	8.44 (7.85, 11.04)	19.48 (13.96, 24.67)
Median (95% CI)	17.81 (14.39, 22.01)	44.06 (38.87, 55.23)
75% quantile (95% CI)	49.87 (38.74, 66.3)	NE (66.33, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.51 (0.40, 0.66)
12-month PFS rate % (95% CI)	65.1 (57.7, 71.5)	86.6 (80.8, 90.7)
24-month PFS rate % (95% CI)	40.2 (32.9, 47.3)	69.1 (61.9, 75.2)
36-month PFS rate % (95% CI)	32.2 (25.3, 39.2)	61.8 (54.3, 68.4)
48-month PFS rate % (95% CI)	25.2 (18.8, 32.1)	48.1 (40.5, 55.2)
60-month PFS rate % (95% CI)	22.2 (16.1, 29.0)	38.8 (31.5, 46.0)

Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on the log-rank test stratified by the stratification factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). The risk factors were: a. serum M protein ≥30 g/L; b. IgA SMM; c. immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG were considered in determination for immunoparesis, IgD and IgE were not considered in this assessment); d. serum involved: uninvolved FLC ratio ≥8 and <100, or e. clonal BMPCs >50% to <60% with measurable disease.
[b] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratification factor. A hazard ratio < 1 indicates an advantage for Dara-SC.

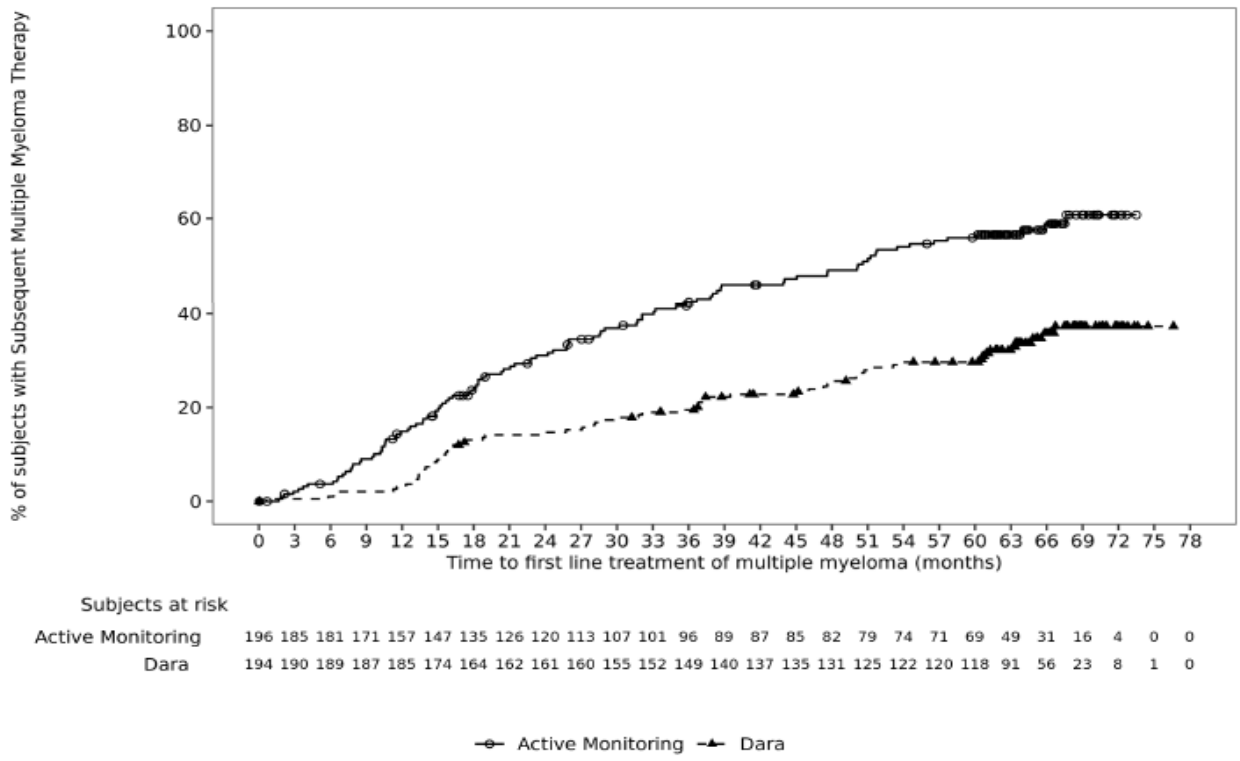
Time to First Subsequent Treatment for Multiple Myeloma

Table 25. Summary of Time to First Line Treatment of Multiple Myeloma; Intent-to-treat Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Intent-to-treat	196	194
Time to subsequent anticancer therapy		
Number of events (%)[a]	102 (52.0%)	64 (33.0%)
Number of censored (%)	94 (48.0%)	130 (67.0%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	18.37 (14.78, 24.21)	47.64 (32.10, 60.81)
Median (95% CI)	50.20 (36.70, 63.93)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[b]		<0.0001
Hazard ratio (95% CI)[c]		0.46 (0.33, 0.62)

Keys: CI = confidence interval; NE = not estimable.
[a] Number of events refers to number of subjects who started subsequent anticancer therapy or died due to progressive disease, whichever occured first.
[b] p-value is based on the log-rank test stratified by number of risk factors associated with progression to multiple myeloma (<3 vs ≥3).
[c] Hazard ratio and 95% CI was calculated using the Cox proportional hazards model with treatment as the sole explanatory variable and stratified by the stratifaction factor (number of risk factors associated with progression to multiple myeloma [<3 vs ≥3]). A hazard ratio < 1 indicates an advantage for Dara-SC.

Figure 12. Kaplan-Meier Plot for Time to First Line Treatment of Multiple Myeloma; Intent-to-Treat Analysis Set (Study 54767414SMM3001)



Incidence of Multiple Myeloma with Adverse Prognostic Factors

Table 26. Incidence of Progression to MM with Adverse Prognostic Features; Subjects Progressed to MM (Study 54767414SMM3001)

	Active Monitoring		Dara	
	n (%)	95% CI for %	n (%)	95% CI for %
Number of subjects progressed to MM (based on IRC assessment)	94		62	
Progressed to MM with stage III of ISS staging	7 (7.4%)	(3.0%, 14.7%)	2 (3.2%)	(0.4%, 11.2%)
Progressed to MM with ISS stage unknown[a]	23 (24.5%)	(16.2%, 34.4%)	14 (22.6%)	(12.9%, 35.0%)
Progressed to MM with stage III of r-ISS staging	1 (1.1%)	(0.0%, 5.8%)	0	(NE, NE)
Progressed to MM with r-ISS stage unknown[a]	43 (45.7%)	(35.4%, 56.3%)	26 (41.9%)	(29.5%, 55.2%)
Progressed to MM with additional adverse cytogenetic characteristics[c]	1 (1.1%)	(0.0%, 5.8%)	2 (3.2%)	(0.4%, 11.2%)
Progressed to MM without additional adverse cytogenetic characteristics[b]	48 (51.1%)	(40.5%, 61.5%)	31 (50.0%)	(37.0%, 63.0%)
Progressed to MM with cytogenetic characteristics unknown[a]	44 (46.8%)	(36.4%, 57.4%)	27 (43.5%)	(31.0%, 56.7%)
Progressed to MM with stage III of ISS staging or stage III of r-ISS staging, or with additional adverse cytogenetic characteristics	8 (8.5%)	(3.7%, 16.1%)	4 (6.5%)	(1.8%, 15.7%)

Keys: MM=Multiple Myeloma, NE= not estimable.
[a] cannot be determined due to missing assessments.
[b] No additional adverse cytogenetic characteristics at the time of MM diagnosis compared to the adverse cytogenetic characteristics at the baseline.
[c] Additional adverse cytogenetic characteristics found at the time of MM diagnosis compared to the adverse cytogenetic characteristics at the baseline.
Note: Adverse cytogenetic characteristics: FISH findings of del(17p13), t(4;14), t(14;16) at the time of MM diagnosis. Stage III of r-ISS staging: Beta-2 microglobulin of 5.5 mg/L or more, and either High risk for chromosomal abnormalities (Presence of del(17p13), and/or t(4;14), and/or t(14,16)) or high LDH(above upper normal limit).
Note: Percentages calculated with the number of subjects progressed to MM in each treatment group as the denominator.
Note: Subject may have more than one adverse prognostic features.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27. Summary of Efficacy for trial SMM3001 (Acquila)

Title: A Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects with High-risk Smouldering Multiple Myeloma		
Study identifier	EU Trial Number: 2023-507143-11 EudraCT Number: 2016-001205-16 NCT No.: NCT03301220	
Design	A randomized (1:1), open-label, multicenter, Phase 3 study comparing Dara monotherapy vs. active monitoring (ACTM) in patients with high-risk smouldering multiple myeloma.	
	Duration of main phase:	06 November 2017 (date first participant was screened) to 01 May 2024 (date of last observation recorded as part of the database for the primary analysis)

Hypothesis	Superiority of Dara over ACTM		
Treatments groups	Dara sc		Daratumumab SC 1800 mg was administered weekly in Cycles 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and every 4 weeks thereafter until 39 cycles or up to 36 months or until PD, or other reasons as outlined in the protocol, whichever occurred first. Each cycle was 28 days.
	Active monitoring (ACTM)		No disease-specific treatment administered.
Endpoints and definitions	Primary endpoint	PFS by IRC	the time from the date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurred first. Assessed by IRC.
	Key Secondary endpoint	ORR by computerized algorithm	the proportion of participants with a PR or better as defined by the IMWG response criteria
	Key Secondary endpoint	PFS2	time from the date of randomization to the date of documented PD on the first-line treatment for MM or death, whichever comes first
	Key Secondary endpoint	OS	the time from the date of randomization to the date of death
Database lock	01 May 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (n=390) Median duration of follow up of 65.2 months (Dara 65.9 months vs. ACTM 64.8 months) (01 May 2024)		
Descriptive statistics and estimate variability	Treatment group	**ACTM**	**Dara**
	Number of subjects	196	194
	Median PFS by IRC (months)	41.46	NE
	95% CI	(26.41, 53.32)	(66.69, NE)
	PFS events (n)	99	67
	%	50.5%	34.5%
	ORR (%)	2%	63.4%
	95% CI	(0.6%, 5.1%)	(56.2%, 70.2%)
	PFS2 events (n)	38	25
	(%)	19.4%	12.9%
	OS events (n)	26	15
	(%)	13.3%	7.7%
Effect estimate per comparison	Primary endpoint: PFS by IRC	Comparison groups	Dara vs ACTM
		Hazard ratio	0.49
		95% CI	(0.36, 0.67)
		P-value	<0.0001
	Key Secondary endpoint:	Comparison groups	Dara vs ACTM

	ORR	Odds ratio	83.8
		95% CI	(29.69, 236.54)
		P-value	<0.0001
	Key Secondary endpoint: PFS2	Comparison groups	Dara vs ACTM
		Hazard ratio	0.58
		95% CI	(0.35, 0.96)
		P-value	0.0318
	Key Secondary endpoint: OS	Comparison groups	Dara vs ACTM
		Estimated hazard ratio	0.52
		95% CI	(0.27, 0.98)
		P-value	Not calculated

Supportive study

Study SMM2001 was a Phase 2, randomized, open-label, 3-arm, multicentre study in participants at least 18 years old with intermediate or high-risk SMM. Randomization was stratified based on the number of risk factors for progression to symptomatic MM (<2 vs ≥2). The study comprised a Screening Phase (up to 28 days before Cycle 1, Day 1), a Treatment Phase, and a Follow-up Phase.

Eligible participants were randomized to 1 of 3 treatment arms:

- Arm A (Long Intense): Daratumumab 16 mg/kg IV: weekly in Cycle 1, every 2 weeks in Cycles 2 and 3, every 4 weeks in Cycles 4 to 7, and every 8 weeks in Cycles 8 to 20.
- Arm B (Intermediate): Daratumumab 16 mg/kg IV: weekly in Cycle 1 and every 8 weeks in Cycles 2 to 20.
- Arm C (Short Intense): Daratumumab 16 mg/kg IV: weekly in Cycle 1.

The co-primary endpoints were:

- CR rate, defined as the proportion of participants with a CR, as defined in the protocol.
- PD/Death rate, defined as the proportion of participants that have progressed to MM or died per patient-year (number of events (PD or death)/total follow-up for all participants).

The type I error rate planned for one of the co-primary endpoints (CR) rate) was 1-sided alpha of 0.05 and for the other co-primary endpoint of PD/death rate was 1-sided alpha of 0.1. However, there were not adjustments for multiplicity the readout of primary and secondary efficacy objective can only be regarded as exploratory.

In Treatment Arm A, a CR or better (sCR+CR) assessed by IMWG criteria was reported in 2 (4.9%) participants.

The PD/death rate was 0.096 (90% CI: 0.0684, 0.1233) in Treatment Arm A.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study SMM3001

Study SMM3001 is a Phase 3, randomised, open-label, 2-arm, multicentre study comparing active monitoring and daratumumab SC in participants with high-risk SMM. Randomisation was stratified based on the number of risk factors associated with progression to MM (<3 vs ≥3). The factors were (1) involved:uninvolved FLC ratio ≥8 (yes vs no), (2) serum M protein ≥30 g/L (yes vs no), (3) IgA SMM (yes vs no), (4) immunoparesis (reduction of 2 uninvolved Ig isotypes [yes vs no]), and (5) BMPCs (>50% to <60% vs ≤50%). The study comprises a Screening Phase, an Active Monitoring Phase (Arm A; hereafter referred to as ACTM) or a Treatment Phase with daratumumab SC (Arm B; hereafter referred to as Dara) for up to 39 cycles or 36 months, and a Follow-up Phase. High-risk was determined by having at least 1 of the following risk factors: Serum M protein ≥30 g/L, IgA SMM, Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG should be considered in determination for immunoparesis; IgD and IgE are not considered in this assessment), Serum involved: uninvolved FLC ratio ≥8 and <100, or Clonal BMPCs >50% to <60% with measurable disease.

In Study SMM3001, the inclusion criteria might not adequately reflect the target population because there is not a consensus yet about high-risk SMM definition. The high-risk criteria employed in this study were those available at the time of this development initiation, in 2015. However, the risk factors stated in the inclusion criteria are not fully aligned with the risk factors associated with an increased risk of progression of SMM to active myeloma (high-risk SMM) included in the EHA-ESMO Guideline, which are those that the clinicians refer to at present and published by the International Myeloma Working Group (IMWG) in 2020. This IMWG risk stratification model for SMM is the result of updating previously existing models to ensure homogeneous risk evaluation in this setting. Although these models are mainly based on clinical parameters, genomic predictors of progression have lately been defined for SMM. In the case of Study SMM3001, the MAH used the combination of two models (Mayo Clinic and PETHEMA) and other risk factors in order to establish the high-risk criteria for enrolment. Nevertheless, these two models presented significant limitations (they only applied to SMM diagnosis and assumed that progression risk remains constant over time) and included some discordances between them. As a result, some patients could be classified as high-risk by one model and as intermediate or low risk by the other.

The difficulties to identify the risk profile for progression to MM and correctly define the patients with this precursor state who are at a higher risk of progression to symptomatic disease are well-known. However, in order to guide treatment decisions, the right identification of these patients is crucial so patients at a lower risk are not exposed to the toxicity of a treatment which might offer a rather limited benefit. For this reason, the CHMP requested that the indication proposed by the applicant was amended to specify that daratumumab in patients with SMM is intended as monotherapy and the indication refers to the exact inclusion risk criteria used in the study as reflected in Section 5.1 of the SmPC. These changes were accepted by the MAH.

Even though the high-risk definition employed is not based on a single accepted risk classification, the overall inclusion and exclusion criteria used in the study are acceptable. SMM was defined by IMWG criteria.

The primary endpoint was PFS by IRC. This is considered acceptable. Key secondary endpoints include ORR by computerised algorithm, PFS2 and OS.

The statistical methods used in this trial are generally robust and appropriate. For PFS, subjects were censored at the last disease assessment prior to the start of subsequent anti-myeloma therapy, study discontinuation, or clinical cut-off if progression or death had not occurred. Treatment discontinuation itself was ignored, and patients who initiated new therapy or left the study without documented progression were censored. To ensure robustness, supplementary analyses were conducted by modifying censoring rules: patients starting subsequent anti-myeloma therapy, dying due to COVID-19, or missing two or more consecutive disease assessments were not censored.

Multiple secondary endpoints were assessed, including PFS2 which was defined as the time from randomization to progression on first-line therapy or death, with investigator-assessed progression events. The censoring rules for PFS2 raise concerns that may lead to underestimating events and misrepresenting true progression-free survival. Specifically, censoring patients who start first-line therapy without documented progression or those who start first-line of next therapy after progression on study treatment but before progressing on first-line therapy risks excluding meaningful clinical events. This is particularly important since progression evaluation is based solely on investigator assessment, which may introduce variability or bias. Although PFS2 had not matured at the time of the primary analysis and did not cross the prespecified stopping boundary based on the predefined testing order, this risk is mitigated by a planned sensitivity analysis assessing the robustness of PFS2, considering patients who initiate first-line therapy without documented progression or after progression on study treatment but before progression on first-line therapy, which will be performed at study end alongside the final PFS2 and OS analyses.

The interim analysis was conducted solely for futility using a non-binding boundary, with no alpha spent. As a result, the full alpha was preserved for the final PFS analysis, and no adjustment to the significance threshold was required. A hierarchical testing approach was implemented to control the overall type I error rate at a two-sided alpha of 0.05. Testing began with the primary endpoint of PFS, and if significant, secondary endpoints (ORR, PFS2, OS) were sequentially tested in the specified order. ORR was tested only at the primary analysis with a fixed alpha of 0.05. For PFS2 and OS, alpha was allocated across analysis timepoints using a linear alpha spending function proportional to the observed number of events, ensuring cumulative alpha control and rigorous hypothesis testing. However, at the time of the primary analysis, PFS2 data were immature and not formally tested, and OS was not tested as it was to follow PFS2 per the prespecified hierarchy.

Protocol amendments have been described in acceptable detail and are not believed to have impacted trial integrity. Protocol deviations were generally balanced between arms and are not assessed to have contributed any major impact on trial conduct or results.

Baseline demographic characteristics were well balanced. Disease characteristics were also balanced except for more patients with IgA SMM being randomized to the Dara-arm. The impact of this is uncertain but will likely, if anything, have put the Dara-arm at a slight disadvantage.

Efficacy data and additional analyses

At the primary analysis of PFS (01 May 2024), with a median duration of follow up of 65.2 months (Dara 65.9 months vs. ACTM 64.8 months), treatment of high-risk SMM with Dara SC conferred a significantly higher PFS compared to ACTM (HR=0.49; 95% CI: 0.36, 0.67; 2-sided p<0.0001). Median PFS was not reached in the Dara arm and was 41.5 months (95% CI: 26.4-53.3) in the ACTM arm. Importantly, positive trends for both PFS2 and OS were observed at the data cut-off of 01 May 2024. Of note, not a single patient progressed with renal insufficiency in either arm and only one case of fracture was observed (in the ACTM arm). A slight imbalance between arms is observed regarding censoring, with the number of censored subjects of 127 (65.5%) in the Dara arm and 97 (49.5%) in

the ACTM arm. Among these imbalances, there were patients censored as 'withdrawal of consent to study participation' [12 (12.1%) in the ACTM arm and 9 (7.1%) in the Dara arm]. The MAH provided a composite strategy to handle intercurrent events of failures for treatment – related events (e.g., start any subsequent anti-cancer therapy, withdrawal of consent to study participation and no postbaseline disease assessment). The result corroborates the original results of the primary analysis (HR=0.49; 95% CI: 0.36, 0.67; p-value <0.0001).

In a post-hoc subgroup analysis employing the contemporary Mayo 2018 high risk criteria for SMM, it was observed that 54 of 86 patients with high risk SMM in the ACTM-arm had a PFS event vs. 27 of 72 patients in the Dara-arm, corresponding to HR for PFS of 0.36 (95 CI: 0.23;0.58). This seems to suggest that the observed PFS benefit in the Aquila trial could potentially be expected to be observed in patients meeting the Mayo 2018 criteria for high risk SMM as well. In addition, this subgroup analysis by the Mayo 2018 Risk Criteria includes three categories (low, intermediate and high risk), which does not seem to match the inclusion criteria used for study enrolment that should define only a "high risk" population. The MAH has clarified that some patients enrolled in this study who were classified as high-risk by AQUILA risk factors could be patients with low or intermediate risk according to any of the models integrated within the risk criteria employed in this study, such as the patients included in the subgroup analysis of Mayo 2018 Risk Criteria.

Supplementary analyses with modifying censoring rules consistently confirmed the robustness of the primary results, with hazard ratios favouring daratumumab compared to active monitoring and maintaining statistical significance across all scenarios. Withdrawals were slightly imbalanced between the active monitoring arm (12 patients, 12.4%) and the daratumumab arm (9 patients, 7.1%). A worst-case sensitivity analysis was conducted in which these withdrawals were treated as progression events rather than censored. The resulting hazard ratio was 0.48 (95% CI: 0.36–0.64; $p < 0.0001$), consistent with the primary analysis (HR = 0.49), indicating no material impact from the imbalance. This adequately addresses the request and supports the robustness of the primary PFS findings.

The key secondary endpoint of ORR also demonstrated a significant increase in the Dara-arm (63.4%, 95% CI: 56.2%, 70.2%) vs 2 (95% CI:0.6%, 5.1%) compared to ACTM. This is not surprising in a trial comparing an active anti-myeloma agent with observation. In addition, the odds ratio crossed the planned boundary type I error rate. The MAH found a high level of agreement between investigator assessment and computerized algorithm, which is acceptable.

The PFS2 and OS data were not yet mature, with 47.01% and 24.3% events observed, respectively. However, the fact that the positive results of the primary endpoint of PFS are supported by a a trend toward a positive effect of Daratumumab on PFS2 and OS is reassuring.

Finally, other secondary endpoints analyses (i.e. time to biochemical progression, depth of response, time to 1st treatment for active MM, duration of response, time to response, incidence of multiple myeloma with adverse prognostic factors) are also considered important. Results for these endpoints appear to favour the Dara arm compared to the ACTM arm and this is acknowledged as further supportive evidence of benefit.

As there are no other approved treatments in the setting of SMM, it is believed to be important to substantiate the benefits on PFS with results from OS and PFS2. Final results of both these analyses will be provided by the MAH when available.

2.4.3. Conclusions on the clinical efficacy

The pivotal trial SMM3001 demonstrated a statistically significant improvement in PFS by IRC with daratumumab monotherapy treatment of high-risk SMM compared to ACTM. This is considered

clinically significant and is further supported by statistically significant improvement in ORR for subjects treated with daratumumab compared to ACTM. Other secondary endpoints such as PFS2 and OS data were not yet mature but also showed a positive trend in favour of treatment with daratumumab versus active monitoring.

2.5. Clinical safety

Introduction

The most frequent adverse reactions of any grade ≥ 20% patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, atrial fibrillation and syncope.

Patient exposure

The pivotal safety data in support of this application come from the Phase 3 Study SMM3001. At the time of the CCO (01 May 2024), 390 participants were enrolled and randomized to either treatment with daratumumab or active monitoring in Study SMM3001; 193 of 194 participants who were assigned to daratumumab received the treatment and 196 participants were assigned to active monitoring.

The median duration of treatment was 35.0 months (range: 0.03 to 36.1), median number of treatment cycles was 38 cycles (range: 1 to 39), median number of injections was 48 (range: 1 to 49), median dose was 2273.7 mg/cycle (range: 1800.0 to 7200.0), and median relative dose intensity was 100% (range: 25% to 100%).

The median duration of active monitoring in the ACTM arm was 25.9 months (range 0.1 to 36.0).

Data from study SMM2001 are considered supportive only, as these patients received daratumumab IV at various doses.

In SMM2001, a total of 122 participants received daratumumab. The median duration of treatment was 44.0 months (range: 1.0 to 91.6 months) in Treatment Arm A (long intense), 35.2 months (range: 1.9 to 90.6 months) in Treatment Arm B (intermediate), and 1.6 months (range: 0.1 to 1.9 months) in Treatment Arm C (short intense). The median number of cycles received was 22.0 cycles (range: 1 to 47 cycles) for Treatment Arm A (long intense), 20.0 cycles (range: 2 to 47 cycles) for Treatment Arm B (intermediate), and 1.0 cycle (range: 1 to 1 cycle) for Treatment Arm C (short intense).

Adverse events

Adverse events

An overview of the treatment emergent adverse events (TEAEs) reported in studies SMM3001and SMM2001 are summarised in **Table 28** and **Table 29** respectively.

Table 28. Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: safety	196	193
Any TEAE	162 (82.7%)	187 (96.9%)
At least one related		138 (71.5%)
Maximum toxicity grade		
Grade 1	32 (16.3%)	17 (8.8%)
Grade 2	70 (35.7%)	92 (47.7%)
Grade 3	51 (26.0%)	67 (34.7%)
Grade 4	5 (2.6%)	9 (4.7%)
Grade 5	4 (2.0%)	2 (1.0%)
Any serious TEAE	38 (19.4%)	56 (29.0%)
At least one related		15 (7.8%)
TEAEs leading to discontinuation of daratumumab		11 (5.7%)
At least one related to daratumumab		6 (3.1%)
TEAEs leading to dose modification[a]		90 (46.6%)
At least one related		36 (18.7%)
TEAE with outcome of death	4 (2.0%)	2 (1.0%)
At least one related		2 (1.0%)
Death due to COVID-19	0	2 (1.0%)
TEAE of COVID-19	10 (5.1%)	17 (8.8%)
Serious TEAE of COVID-19	1 (0.5%)	5 (2.6%)

Keys: TEAE = treatment-emergent adverse event.
[a] Dose modification includes dose delay within cycle, cycle delay and dose skipped.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1

Table 29. Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study Study 54767414SMM2001)

	Long Intense	Intermediate	Short Intense
Analysis set: safety	41	41	40
Any treatment-emergent adverse event	41 (100.0%)	41 (100.0%)	37 (92.5%)
At least one reasonably related to daratumumab	34 (82.9%)	34 (82.9%)	28 (70.0%)
Maximum toxicity grade			
Grade 1	3 (7.3%)	4 (9.8%)	9 (22.5%)
Grade 2	11 (26.8%)	19 (46.3%)	22 (55.0%)
Grade 3	22 (53.7%)	17 (41.5%)	4 (10.0%)
Grade 4	5 (12.2%)	0	2 (5.0%)
Grade 5	0	1 (2.4%)	0
Any serious treatment-emergent adverse event	20 (48.8%)	14 (34.1%)	4 (10.0%)
At least one reasonably related to daratumumab	1 (2.4%)	1 (2.4%)	1 (2.5%)
Treatment-emergent adverse events leading to dose delay	16 (39.0%)	13 (31.7%)	1 (2.5%)
At least one reasonably related to daratumumab	3 (7.3%)	3 (7.3%)	0
Treatment-emergent adverse events leading to discontinuation of daratumumab	3 (7.3%)	1 (2.4%)	2 (5.0%)
At least one reasonably related to daratumumab	1 (2.4%)	0	1 (2.5%)

Note: Adverse events are reported using MedDRA version 25.1.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Common adverse events

Study SMM3001

Table 30. Most common (at least 10% in either arm) Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: safety	196	193
Total number of subjects with TEAE	162 (82.7%)	187 (96.9%)
MedDRA system - organ class/preferred term		
Infections and infestations	88 (44.9%)	154 (79.8%)
Upper respiratory tract infection	15 (7.7%)	58 (30.1%)
Nasopharyngitis	23 (11.7%)	49 (25.4%)
Pneumonia	10 (5.1%)	22 (11.4%)
General disorders and administration site conditions	57 (29.1%)	126 (65.3%)
Fatigue	26 (13.3%)	66 (34.2%)
Pyrexia	6 (3.1%)	33 (17.1%)
Injection site erythema	0	31 (16.1%)
Oedema peripheral	3 (1.5%)	20 (10.4%)
Musculoskeletal and connective tissue disorders	89 (45.4%)	121 (62.7%)
Arthralgia	35 (17.9%)	52 (26.9%)
Back pain	38 (19.4%)	46 (23.8%)
Pain in extremity	15 (7.7%)	28 (14.5%)
Myalgia	9 (4.6%)	20 (10.4%)
Gastrointestinal disorders	52 (26.5%)	119 (61.7%)
Diarrhoea	10 (5.1%)	53 (27.5%)
Nausea	9 (4.6%)	37 (19.2%)
Nervous system disorders	43 (21.9%)	94 (48.7%)
Headache	13 (6.6%)	35 (18.1%)
Respiratory, thoracic and mediastinal disorders	41 (20.9%)	85 (44.0%)
Cough	12 (6.1%)	33 (17.1%)
Dyspnoea	10 (5.1%)	29 (15.0%)
Psychiatric disorders	16 (8.2%)	68 (35.2%)
Insomnia	5 (2.6%)	43 (22.3%)
Vascular disorders	23 (11.7%)	51 (26.4%)
Hypertension	19 (9.7%)	20 (10.4%)

Keys: TEAE = treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1.

Study SMM2001

Table 31. Most common (at least 10% in either arm) Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study Study 54767414SMM2001)

Analysis set: safety	Long Intense 41	Intermediate 41	Short Intense 40
Total number of subjects with treatment-emergent adverse events	40 (97.6%)	40 (97.6%)	37 (92.5%)
System organ class/Preferred term			
General disorders and administration site conditions	32 (78.0%)	29 (70.7%)	22 (55.0%)
Fatigue	16 (39.0%)	25 (61.0%)	9 (22.5%)
Influenza like illness	7 (17.1%)	2 (4.9%)	1 (2.5%)
Pyrexia	6 (14.6%)	3 (7.3%)	3 (7.5%)
Chest discomfort	4 (9.8%)	3 (7.3%)	4 (10.0%)
Asthenia	1 (2.4%)	2 (4.9%)	4 (10.0%)
Infections and infestations	30 (73.2%)	23 (56.1%)	12 (30.0%)
Upper respiratory tract infection	11 (26.8%)	11 (26.8%)	4 (10.0%)
Musculoskeletal and connective tissue disorders	26 (63.4%)	22 (53.7%)	11 (27.5%)
Arthralgia	10 (24.4%)	6 (14.6%)	0
Back pain	10 (24.4%)	5 (12.2%)	4 (10.0%)
Myalgia	7 (17.1%)	5 (12.2%)	2 (5.0%)
Musculoskeletal pain	5 (12.2%)	3 (7.3%)	2 (5.0%)
Pain in extremity	5 (12.2%)	7 (17.1%)	2 (5.0%)
Musculoskeletal chest pain	0	4 (9.8%)	4 (10.0%)
Respiratory, thoracic and mediastinal disorders	26 (63.4%)	24 (58.5%)	24 (60.0%)
Cough	14 (34.1%)	13 (31.7%)	11 (27.5%)
Dyspnoea	10 (24.4%)	8 (19.5%)	3 (7.5%)
Nasal congestion	7 (17.1%)	4 (9.8%)	6 (15.0%)
Oropharyngeal pain	3 (7.3%)	8 (19.5%)	4 (10.0%)
Dysphonia	0	1 (2.4%)	5 (12.5%)
Gastrointestinal disorders	22 (53.7%)	23 (56.1%)	15 (37.5%)
Diarrhoea	10 (24.4%)	7 (17.1%)	4 (10.0%)
Nausea	8 (19.5%)	10 (24.4%)	3 (7.5%)
Vomiting	7 (17.1%)	4 (9.8%)	1 (2.5%)
Constipation	3 (7.3%)	5 (12.2%)	2 (5.0%)
Nervous system disorders	20 (48.8%)	21 (51.2%)	15 (37.5%)
Headache	11 (26.8%)	8 (19.5%)	13 (32.5%)
Dizziness	6 (14.6%)	4 (9.8%)	1 (2.5%)
Somnolence	5 (12.2%)	4 (9.8%)	0
Paraesthesia	3 (7.3%)	6 (14.6%)	2 (5.0%)
Psychiatric disorders	16 (39.0%)	18 (43.9%)	6 (15.0%)
Insomnia	11 (26.8%)	13 (31.7%)	5 (12.5%)
Skin and subcutaneous tissue disorders	16 (39.0%)	10 (24.4%)	11 (27.5%)
Rash	6 (14.6%)	2 (4.9%)	2 (5.0%)
Vascular disorders	15 (36.6%)	7 (17.1%)	7 (17.5%)
Hypertension	6 (14.6%)	1 (2.4%)	2 (5.0%)
Flushing	4 (9.8%)	5 (12.2%)	1 (2.5%)

Long-Intense=Treatment Arm A; Intermediate=Treatment Arm B; Short Intense=Treatment Arm C
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Grade 3 or 4 Adverse Events

Study SMM3001

Table 32. Most common (at least 2% in either arm) Grade 3-4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: safety	196	193
Total number of subjects with Grade 3-4 TEAE	59 (30.1%)	78 (40.4%)
MedDRA system - organ class/preferred term		
Infections and infestations	9 (4.6%)	31 (16.1%)
Pneumonia	2 (1.0%)	9 (4.7%)
General disorders and administration site conditions	5 (2.6%)	5 (2.6%)
Fatigue	1 (0.5%)	5 (2.6%)
Musculoskeletal and connective tissue disorders	7 (3.6%)	3 (1.6%)
Back pain	4 (2.0%)	0 (0%)
Gastrointestinal disorders	6 (3.1%)	10 (5.2%)
Diarrhoea	1 (0.5%)	4 (2.1%)
Nervous system disorders	4 (2.0%)	8 (4.1%)
Syncope	3 (1.5%)	5 (2.6%)
Blood and lymphatic system disorders	6 (3.1%)	11 (5.7%)
Neutropenia	4 (2.0%)	8 (4.1%)
Vascular disorders	9 (4.6%)	12 (6.2%)
Hypertension	9 (4.6%)	11 (5.7%)

Keys: TEAE = treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1.

Study SMM2001

The incidence of Grades 3 or 4 TEAEs were 65.9% of participants in Treatment Arm A (long intense), 41.5% of participants in Treatment Arm B (intermediate), and 15.0% of participants in Treatment Arm C (short intense).

The most frequently reported Grade 3 or 4 TEAEs (≥5%) were:

- Treatment Arm A (long intense): Hypertension (14.6%), Pneumonia (7.3%)
- Treatment Arm B (intermediate): Hypertension (9.8%)
- Treatment Arm C (short intense): none

Adverse Drug Reactions

Adverse drug reactions in Study SMM3001 were evaluated according to the following internal criteria:

• All TEAEs reported in ≥10% of participants and that occurred at a higher incidence (≥5% difference) in the Dara arm compared with the ACTM arm were considered to have met the ADR threshold. The comparison of incidence of TEAEs between arms was completed after rounding incidence to the nearest whole numbers for all events (i.e., 4.9% is rounded to 5%).

• All laboratory parameters were reviewed. No laboratory parameters had an incidence of Grade 3 or 4 values ≥10%.

• Thrombocytopenia, Neutropenia, Lymphopenia, Leukopenia, and Anaemia were listed in a separate haematology laboratory table based on haematology laboratory parameters regardless of the incidence and difference between arms.

• Treatment-emergent SAEs that occurred at a higher incidence (≥2% difference) in the Dara arm as compared with the ACTM arm were considered to have met the ADR threshold. The comparison of incidence was completed after rounding incidence to whole numbers for all events.

Based on this analysis, the MAH identified the following ADRs:

Myalgia

The myalgia incidence was higher in the Dara group compared to the ACTM group (Dara 10.4%; ACTM 4.6%). Considering other known musculoskeletal ADRs of daratumumab (e.g., arthralgia, muscle spasms, musculoskeletal chest pain) and based on the imbalance in the incidence, myalgia was assessed as a new ADR for daratumumab. One participant, in the Dara arm, reported Grade 3 Myalgia; the event was assessed as not related to daratumumab and resolved without dose modification of daratumumab. No Grade 4, serious, or fatal events of Myalgia were reported in either arm. Myalgia led to dose modification of daratumumab for 1 participant and discontinuation of daratumumab for 1 participant.

Pain in Extremity

The incidence of Pain in extremity was higher in the Dara arm compared to the ACTM arm (Dara 14.5%; ACTM 7.7%). Considering other known musculoskeletal ADRs of daratumumab (e.g., arthralgia, muscle spasms, musculoskeletal chest pain) and based on the imbalance in the incidence, pain in extremity was assessed as a new ADR for daratumumab. One participant in the Dara arm reported Grade 3 Pain in extremity; the event was assessed as not related to daratumumab and resolved without dose modification of daratumumab. No Grade 4, serious, or fatal events of Pain in extremity were reported in either arm.

The frequency of the known ADRs associated with daratumumab use were updated with data from the SMM3001study which were combined with other daratumumab monotherapy and combination studies to obtain ADR frequencies from a pooled safety data (Table 33).

Table 33. Adverse Reactions in Multiple Myeloma, including high-risk smouldering myeloma and AL Amyloidosis Patients Treated With Daratumumab IV or Daratumumab SC

	Any Grades	Any Grades	Grade 3-4
Infections and infestations			
Upper respiratory tract infection[a]	Very Common	46%	3%
COVID-19[a,g]	Very Common	31%	8%
Pneumonia[a]	Very Common	19%	11%
Bronchitis[a]	Very Common	14%	1%
Urinary tract infection	Common	7%	1%
Sepsis[a]	Common	4%	4%
Cytomegalovirus infection[a]	Uncommon	<1%	<1%[#]
Hepatitis B reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders			
Neutropenia[a]	Very Common	42%	36%
Thrombocytopenia[a]	Very Common	30%	18%
Anaemia[a]	Very Common	26%	11%
Lymphopenia[a]	Very Common	12%	10%
Leukopenia[a]	Very Common	11%	6%
Immune system disorders			
Hypogammaglobulinaemia[a]	Common	3%	<1%[#]
Anaphylactic reaction[b]	Rare		
Metabolism and nutrition disorders			
Decreased appetite	Very Common	10%	<1%
Hypokalaemia[a]	Very Common	10%	3%
Hyperglycaemia	Common	6%	3%
Hypocalcaemia	Common	6%	1%
Dehydration	Common	2%	1%[#]
Psychiatric disorders			
Insomnia	Very Common	17%	1%[#]
Nervous system disorders			
Peripheral neuropathy[a]	Very Common	31%	4%
Headache	Very Common	11%	<1%[#]
Dizziness	Common	9%	<1%[#]
Paraesthesia	Common	9%	<1%
Syncope	Common	3%	2%[#]
Cardiac disorders			
Atrial fibrillation	Common	4%	1%
Vascular disorders			
Hypertension[a]	Common	9%	4%
Respiratory, thoracic and mediastinal disorders			
Cough[a]	Very Common	22%	<1%[#]
Dyspnoea[a]	Very Common	18%	2%
Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders			
Diarrhoea	Very Common	33%	5%
Constipation	Very Common	28%	1%
Nausea	Very Common	22%	1%[#]
Abdominal pain[a]	Very Common	14%	1%
Vomiting	Very Common	13%	1%[#]
Pancreatitis[a]	Common	1%	<1%

	Any Grades	Any Grades	Grade 3-4
Skin and subcutaneous tissue disorders			
Rash	Very Common	12%	1%[#]
Pruritus	Common	6%	<1%[#]
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[a]	Very Common	35%	3%
Arthralgia	Very Common	14%	1%
Muscle spasms	Very Common	12%	<1%[#]
General disorders and administration site conditions			
Fatigue	Very Common	24%	4%
Oedema peripheral[a]	Very Common	24%	1%
Pyrexia	Very Common	22%	1%
Asthenia	Very Common	19%	2%
Injection site reactions[d,f]	Very Common	10%	0
Chills	Common	8%	<1%[#]
Injury, poisoning and procedural complications			
Infusion related reactions[c]			
Daratumumab IV[e]	Very Common	39%	5%
Daratumumab SC[f]	Common	9%	1%

[#] No grade 4.
[a] Indicates a grouping of terms.
[b] Based on post-marketing adverse reactions.
[c] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab IV studies only (N=2324).
[f] Frequency based on daratumumab SC studies only (N=1573).
[g] Frequency based on MMY3014, MMY3019 and SMM3001 studies only (N=741) due to the onset of the pandemic during the studies.
Note: Based on 3897 multiple myeloma and AL amyloidosis patients treated with daratumumab IV or daratumumab SC (daratumumab + rHuPH20).
Note: Studies included are AMY3001, MMY1001, MMY1002, MMY1004, MMY1008, MMY2002, MMY2040, MMY3003, MMY3004, MMY3006, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, SMM3001, GEN501, GEN503

Serious adverse event/deaths/other significant events

Serious Adverse Events

Study SMM3001

Table 34. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: safety	196	193
Total number of subjects with serious TEAEs	38 (19.4%)	56 (29.0%)
MedDRA system - organ class/preferred term		
Infections and infestations	10 (5.1%)	32 (16.6%)
Pneumonia	1 (0.5%)	7 (3.6%)
COVID-19	0	3 (1.6%)
Cellulitis	0	2 (1.0%)
COVID-19 pneumonia	1 (0.5%)	2 (1.0%)
Pyelonephritis	0	2 (1.0%)
Sepsis	2 (1.0%)	2 (1.0%)
Corneal infection	0	1 (0.5%)
Diverticulitis	1 (0.5%)	1 (0.5%)
Erysipelas	0	1 (0.5%)
Gastroenteritis norovirus	0	1 (0.5%)
Lower respiratory tract infection	0	1 (0.5%)
Metapneumovirus infection	0	1 (0.5%)
Pharyngitis	0	1 (0.5%)
Pneumonia bacterial	1 (0.5%)	1 (0.5%)
Pneumonia streptococcal	0	1 (0.5%)
Pneumonia viral	0	1 (0.5%)
Septic arthritis staphylococcal	0	1 (0.5%)
Septic shock	1 (0.5%)	1 (0.5%)
Sinusitis	0	1 (0.5%)
Urinary tract infection	1 (0.5%)	1 (0.5%)
West Nile viral infection	0	1 (0.5%)
Appendicitis	1 (0.5%)	0
Bacteraemia	1 (0.5%)	0
Pneumonia pneumococcal	1 (0.5%)	0
Vestibular neuronitis	1 (0.5%)	0
Injury, poisoning and procedural complications	4 (2.0%)	9 (4.7%)
Rib fracture	1 (0.5%)	2 (1.0%)
Ankle fracture	0	1 (0.5%)
Fall	0	1 (0.5%)
Hip fracture	0	1 (0.5%)
Humerus fracture	0	1 (0.5%)
Incisional hernia	0	1 (0.5%)
Shoulder fracture	0	1 (0.5%)
Spinal compression fracture	2 (1.0%)	1 (0.5%)
Subdural haematoma	0	1 (0.5%)

	Active Monitoring	Dara
Traumatic fracture	0	1 (0.5%)
Femoral neck fracture	1 (0.5%)	0
Splenic injury	1 (0.5%)	0
Gastrointestinal disorders	2 (1.0%)	8 (4.1%)
Diarrhoea	1 (0.5%)	2 (1.0%)
Inguinal hernia	0	2 (1.0%)
Small intestinal obstruction	1 (0.5%)	2 (1.0%)
Dysphagia	0	1 (0.5%)
Haemorrhoids	0	1 (0.5%)
Intestinal obstruction	0	1 (0.5%)
Volvulus	0	1 (0.5%)
Abdominal pain	1 (0.5%)	0
Haemorrhoidal haemorrhage	1 (0.5%)	0
Obstruction gastric	1 (0.5%)	0
General disorders and administration site conditions	5 (2.6%)	4 (2.1%)
Non-cardiac chest pain	0	2 (1.0%)
Gait disturbance	0	1 (0.5%)
Pyrexia	2 (1.0%)	1 (0.5%)
Chest pain	1 (0.5%)	0
Pain	1 (0.5%)	0
Pelvic mass	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	4 (2.0%)	4 (2.1%)
Asthma	0	2 (1.0%)
Chronic obstructive pulmonary disease	0	1 (0.5%)
Dyspnoea	0	1 (0.5%)
Emphysema	0	1 (0.5%)
Pulmonary embolism	1 (0.5%)	1 (0.5%)
Acute respiratory failure	1 (0.5%)	0
Organising pneumonia	1 (0.5%)	0
Pneumothorax	1 (0.5%)	0
Pulmonary oedema	1 (0.5%)	0
Cardiac disorders	5 (2.6%)	3 (1.6%)
Angina pectoris	1 (0.5%)	1 (0.5%)
Atrial fibrillation	0	1 (0.5%)
Sinus tachycardia	0	1 (0.5%)
Cardiac arrest	1 (0.5%)	0
Cardiac failure	1 (0.5%)	0
Myocardial ischaemia	2 (1.0%)	0
Eye disorders	1 (0.5%)	2 (1.0%)
Cataract	0	1 (0.5%)
Lacrimation increased	0	1 (0.5%)
Glaucoma	1 (0.5%)	0
Musculoskeletal and connective tissue disorders	1 (0.5%)	2 (1.0%)
Intervertebral disc protrusion	0	1 (0.5%)
Osteoarthritis	0	1 (0.5%)
Back pain	1 (0.5%)	0
Nervous system disorders	4 (2.0%)	2 (1.0%)
Brain oedema	0	1 (0.5%)
Intracranial aneurysm	0	1 (0.5%)
Transient ischaemic attack	0	1 (0.5%)
Cerebellar stroke	1 (0.5%)	0
Cerebral ischaemia	1 (0.5%)	0
Dizziness	1 (0.5%)	0
Ischaemic stroke	1 (0.5%)	0
Skin and subcutaneous tissue disorders	0	2 (1.0%)
Dermal cyst	0	1 (0.5%)
Diabetic foot	0	1 (0.5%)
Neurodermatitis	0	1 (0.5%)
Surgical and medical procedures	0	2 (1.0%)
Breast prosthesis removal	0	1 (0.5%)

	Active Monitoring	Dara
Radical prostatectomy	0	1 (0.5%)
Blood and lymphatic system disorders	1 (0.5%)	1 (0.5%)
Iron deficiency anaemia	1 (0.5%)	1 (0.5%)
Ear and labyrinth disorders	1 (0.5%)	1 (0.5%)
Vertigo positional	0	1 (0.5%)
Hypoacusis	1 (0.5%)	0
Hepatobiliary disorders	2 (1.0%)	1 (0.5%)
Cholecystitis acute	0	1 (0.5%)
Cholecystitis	2 (1.0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.5%)	1 (0.5%)
Breast cancer	0	1 (0.5%)
Invasive ductal breast carcinoma	1 (0.5%)	0
Neoplasm of appendix	1 (0.5%)	0
Plasmacytoma	1 (0.5%)	0
Vascular disorders	0	1 (0.5%)
Deep vein thrombosis	0	1 (0.5%)
Metabolism and nutrition disorders	1 (0.5%)	0
Hyperkalaemia	1 (0.5%)	0
Pregnancy, puerperium and perinatal conditions	1 (0.5%)	0
Abortion spontaneous	1 (0.5%)	0
Renal and urinary disorders	4 (2.0%)	0
Acute kidney injury	2 (1.0%)	0
Haematuria	1 (0.5%)	0
Renal injury	1 (0.5%)	0
Reproductive system and breast disorders	2 (1.0%)	0
Benign prostatic hyperplasia	1 (0.5%)	0
Pelvic organ prolapse	1 (0.5%)	0

Keys: TEAE = treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1.

Study SMM2001

Table 35. Number of subjects with 1 or more Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study Study 54767414SMM2001)

	Long Intense	Intermediate	Short Intense
Analysis set: safety	41	41	40
Total number of subjects with serious treatment-emergent adverse events	20 (48.8%)	14 (34.1%)	4 (10.0%)
MedDRA system organ class / Preferred term			
Infections and infestations	6 (14.6%)	3 (7.3%)	2 (5.0%)
Pneumonia	4 (9.8%)	1 (2.4%)	1 (2.5%)
Sepsis	1 (2.4%)	0	1 (2.5%)
Streptococcal sepsis	1 (2.4%)	0	0
Babesiosis	0	1 (2.4%)	0
COVID-19	0	1 (2.4%)	0

Deaths

Study SMM3001

Table 36. Summary of Death and Cause of death; Safety Analysis Set (Study Study 54767414SMM3001)

	Active Monitoring	Dara
Analysis set: Safety	196	193
Deaths during study	26 (13.3%)	15 (7.8%)
Adverse event	4 (2.0%)	2 (1.0%)
COVID-19	0	2 (1.0%)
Progressive disease	9 (4.6%)	3 (1.6%)
Other	13 (6.6%)	10 (5.2%)
COVID-19	0	0
Deaths within 30 days of end of treatment or active monitoring	4 (2.0%)	0
Adverse event	4 (2.0%)	0
COVID-19	0	0
Progressive disease	0	0
Other	0	0
COVID-19	0	0
Deaths within 60 days of first treatment dose or active monitoring	1 (0.5%)	0
Adverse event	1 (0.5%)	0
COVID-19	0	0
Progressive disease	0	0
Other	0	0
COVID-19	0	0

Note: Percentages are calculated with the number of subjects in each group as denominators.

The causes of death indicated as Other were reported as such because the event occurred outside the AE reporting window.

Study SMM2001

Table 37. Summary of Death and Cause of death; Intent-to-treat Analysis Set (Study Study 54767414SMM2001)

	Long Intense	Intermediate	Short Intense
Analysis set: intent-to-treat	41	41	41
Total number of subject who died during study	7 (17.1%)	5 (12.2%)	4 (9.8%)
Primary cause of death			
Adverse Event	1 (2.4%)	2 (4.9%)	0
Related	0	0	0
Unrelated	1 (100.0%)	2 (100.0%)	0
Progressive Disease	1 (2.4%)	1 (2.4%)	2 (4.9%)
Other	5 (12.2%)	2 (4.9%)	2 (4.9%)
Total number of subjects who died within 30 days of last dose	0	1 (2.4%)	0
Primary cause of death			
Adverse Event	0	1 (2.4%)	0
Related	0	0	0
Unrelated	0	1 (100.0%)	0

Note: Percentages are calculated with the number of subjects in each group as denominator.

Adverse Events of Clinical Interest (study SMM3001)

Systemic Administration-related Reactions (sARRs) and Infusion-related Reactions (IRR)

Both sARRs and IRRs were defined as systemic reactions related to daratumumab administration, regardless of the route of administration (IV or SC). These terms are interchangeable.

Systemic administration-related reactions were reported in 16.6% of participants. Grade 3 or 4 sARRs were reported in 2 (1.0%) participants

Twenty-nine (15.0%) participants reported sARRs with the first administration of daratumumab SC, 4 (2.1%) participants with the second administration, and 5 (2.6%) with subsequent administrations (Attachment TSFAEIRR04). Five (2.6%) participants had recurrent sARRs.

Measures to prevent IRRs included predose medication with methylprednisolone, paracetamol, and antihistamines. Montelukast was also permitted as a predose medication at the investigator's discretion and was recommended on Cycle 1 Day 1. Pre-injection medications were administered to all participants (100%) in the Dara arm as required per protocol. Post-injection medications were administered to 97.9% of participants in the Dara arm as described per protocol. Post-injection medications administered to ≥10% of participants in the Dara arm were dexamethasone (52.3%), methylprednisolone (21.8%), and prednisone (19.2%).

Local Injection-site Reactions

Local injection-site reactions were reported in 27.5% of participants. Local injection-site reactions reported in ≥5% of participants were Injection site erythema (15.5%) and Erythema (5.2%). No Grade 3 or 4 local injection-site reactions were reported.

Cytopenia Adverse Events

Table 38. Treatment-emergent Cytopenia by Preferred Term and Grade 3 or 4; Safety Analysis Set (Study 54767414SMM3001)

	Active Monitoring		Dara	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: safety	196		193	
Total number of subjects with treatment-emergent Cytopenia	24 (12.2%)	6 (3.1%)	23 (11.9%)	9 (4.7%)
Neutropenia[a]	5 (2.6%)	4 (2.0%)	13 (6.7%)	8 (4.1%)
Neutropenia	5 (2.6%)	4 (2.0%)	13 (6.7%)	8 (4.1%)
Febrile neutropenia	1 (0.5%)	1 (0.5%)	0	0
Anaemia[a]	19 (9.7%)	2 (1.0%)	9 (4.7%)	0
Anaemia	19 (9.7%)	2 (1.0%)	9 (4.7%)	0
Thrombocytopenia[a]	3 (1.5%)	0	4 (2.1%)	1 (0.5%)
Thrombocytopenia	3 (1.5%)	0	4 (2.1%)	1 (0.5%)
Lymphopenia[a]	1 (0.5%)	0	3 (1.6%)	2 (1.0%)
Lymphopenia	1 (0.5%)	0	3 (1.6%)	2 (1.0%)

Keys: TEAE = treatment-emergent adverse event.
[a] Preferred term grouping.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1.

Haemorrhagic events

Haemorrhagic TEAEs (SMQ, excluding injection site reactions) were experienced by 15.0% of participants in the Dara arm and 10.7% of participants in the ACTM arm. Grade 3 or 4 haemorrhagic TEAEs were experienced by 1 (0.5%) participant in the Dara arm (Subdural haematoma) and 2 (1.0%) participants in the ACTM arm (Rectal haemorrhage and Uterine haemorrhage).

Infections and Infestations

The overall incidence of treatment-emergent Infections and Infestations (SOC) was higher in the Dara arm (79.8%) compared with the ACTM arm (44.9%). The majority of any grade Infections and Infestations had resolved at the time of the CCO (Dara 97.8%; ACTM 96.3%). The median duration of any grade Infections and Infestations was 14.0 days in both groups.

The most common any grade Infections and Infestations (≥10% in either arm) were:

- Upper respiratory tract infection (Dara 30.1%; ACTM 7.7%)
- Nasopharyngitis (Dara 25.4%; ACTM 11.7%)
- Pneumonia (Dara 11.4%; ACTM 5.1%)

Most Infections and Infestations were Grade 1 or 2 in both arms.

The incidence of treatment-emergent Grade 3 or 4 Infections and Infestations (SOC) was higher in the Dara arm (16.1%) compared with the ACTM arm (4.6%). The majority of Grade 3 or 4 Infections and Infestations had resolved at the time of the CCO (Dara 94.6%; ACTM 72.7%). The median duration of Grade 3 or 4 Infections and Infestations was 5.0 days in the Dara arm and 9.0 days in the ACTM arm. The only Grade 3 or 4 treatment-emergent Infections and Infestations reported in >1% of participants in either arm was Pneumonia (Dara 9 [4.7%], ACTM 2 [1.0%]).

The incidence of treatment-emergent SAEs of Infections and Infestations (SOC) was higher in the Dara arm (16.6%) compared with the ACTM arm (5.1%)

Treatment-emergent Infections and Infestations that led to discontinuation of daratumumab SC were reported in 2 (1.0%) participants.

Viral infections including COVID-19

The overall incidence of treatment-emergent viral infections was higher in the Dara arm (25.9%) compared with the ACTM arm (9.7%). Most treatment-emergent viral infections were Grade 1 or 2 in both arms. The incidence of Grade 3 or 4 treatment-emergent viral infections was 7 (3.6%) participants in the Dara arm and 1 (0.5%) participant in the ACTM. No Grade 3 or 4 treatment-emergent viral infection was reported in >1 participant in either arm.

The most common any grade treatment-emergent viral infections (≥5% in either arm) were:

- COVID-19 (Dara 8.3%; ACTM 5.1%)
- Influenza (Dara 5.2%; ACTM 0.5%)

Hepatitis B reactivation

No participants experienced treatment-emergent HBV reactivation or a new HBV infection in either arm.

New Malignancies

The overall incidence of new malignancies (previously known as second primary malignancies) was similar between arms (Dara 9.3%; ACTM 10.2%).

Laboratory findings (Study SMM3001)

Haematologic laboratory results were consistent between the arms. No clinically meaningful changes over time were observed in haematological values for either arm. There were no Grade 3 haematological laboratory abnormalities reported at a frequency ≥10% in either arm. Grade 4 haematological abnormalities were reported by no participants in the Dara arm and 2 (1.0%) participants in the ACTM arm. Clinically relevant changes in haematological values were reported by investigators as AEs.

Chemistry laboratory results were consistent between the arms. No clinically meaningful changes over time were observed in chemistry values for either arm. There were no Grade 3 or 4 chemistry laboratory abnormalities reported at a frequency ≥10% in either arm. Clinically relevant changes in chemistry values were reported by investigators as AEs.

Safety in special populations

Adverse events analyses by age group are summarised in **Table 39** and **Table 40** for studies SMM3001 and SMM2001 respectively.

Table 39. Overview of Treatment-emergent Adverse Events by age; Safety Analysis Set (Study 54767414SMM3001)

	Active Monitoring n (%)				Dara n (%)			
	<65 years n (%)	65-<75 years n (%)	>=75 years n (%)	Total n (%)	<65 years n (%)	65-<75 years n (%)	>=75 years n (%)	Total n (%)
Analysis set: safety	98	74	24	196	105	67	21	193
Any TEAE	81 (82.7%)	60 (81.1%)	21 (87.5%)	162 (82.7%)	101 (96.2%)	66 (98.5%)	20 (95.2%)	187 (96.9%)
At least one related					78 (74.3%)	49 (73.1%)	11 (52.4%)	138 (71.5%)
Maximum severity of any TEAE								
Grade 1	18 (18.4%)	9 (12.2%)	5 (20.8%)	32 (16.3%)	14 (13.3%)	2 (3.0%)	1 (4.8%)	17 (8.8%)
Grade 2	39 (39.8%)	29 (39.2%)	2 (8.3%)	70 (35.7%)	54 (51.4%)	28 (41.8%)	10 (47.6%)	92 (47.7%)
Grade 3	20 (20.4%)	22 (29.7%)	9 (37.5%)	51 (26.0%)	27 (25.7%)	31 (46.3%)	9 (42.9%)	67 (34.7%)
Grade 4	3 (3.1%)	0	2 (8.3%)	5 (2.6%)	5 (4.8%)	4 (6.0%)	0	9 (4.7%)
Grade 5	1 (1.0%)	0	3 (12.5%)	4 (2.0%)	1 (1.0%)	1 (1.5%)	0	2 (1.0%)
Any serious TEAE	12 (12.2%)	14 (18.9%)	12 (50.0%)	38 (19.4%)	26 (24.8%)	24 (35.8%)	6 (28.6%)	56 (29.0%)
At least one related					5 (4.8%)	8 (11.9%)	2 (9.5%)	15 (7.8%)
TEAEs leading to discontinuation of daratumumab					2 (1.9%)	6 (9.0%)	3 (14.3%)	11 (5.7%)
At least one related to daratumumab					2 (1.9%)	3 (4.5%)	1 (4.8%)	6 (3.1%)
TEAEs leading to dose modification[a]					35 (33.3%)	44 (65.7%)	11 (52.4%)	90 (46.6%)
At least one related					15 (14.3%)	17 (25.4%)	4 (19.0%)	36 (18.7%)
TEAE with outcome of death	1 (1.0%)	0	3 (12.5%)	4 (2.0%)	1 (1.0%)	1 (1.5%)	0	2 (1.0%)
At least one related					1 (1.0%)	1 (1.5%)	0	2 (1.0%)
Death due to COVID-19	0	0	0	0	1 (1.0%)	1 (1.5%)	0	2 (1.0%)
TEAE of COVID-19	9 (9.2%)	1 (1.4%)	0	10 (5.1%)	12 (11.4%)	5 (7.5%)	0	17 (8.8%)
Serious TEAE of COVID-19	1 (1.0%)	0	0	1 (0.5%)	4 (3.8%)	1 (1.5%)	0	5 (2.6%)

Keys: TEAE = treatment-emergent adverse event.
[a] Dose modification includes dose delay within cycle, cycle delay and dose skipped.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.
Note: If a subject has a missing subgroup value, the subject is only counted in the total column.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE. For active monitoring group, AEs with onset on or after the randomization are considered TEAE through 3 years on study and up to 30 days thereafter.
Note: Adverse events are reported using MedDRA version 26.1

Table 40 Overview of Treatment-emergent Adverse Events by age; Safety Analysis Set (Study 54767414SMM2001)

	Long Intense + Intermediate		
	< 65	65 - 74	>=75
	n (%)	n (%)	n (%)
Analysis set: safety	44	32	6
Any TEAE	44 (100.0%)	32 (100.0%)	6 (100.0%)
Drug-related	42 (95.5%)	22 (68.8%)	4 (66.7%)
Any serious TEAE	17 (38.6%)	15 (46.9%)	2 (33.3%)
Drug-related	2 (4.5%)	0	0
Maximum severity of any TEAE			
Grade 1	4 (9.1%)	2 (6.3%)	1 (16.7%)
Grade 2	18 (40.9%)	10 (31.3%)	2 (33.3%)
Grade 3	20 (45.5%)	16 (50.0%)	3 (50.0%)
Grade 4	1 (2.3%)	4 (12.5%)	0
Grade 5	1 (2.3%)	0	0
TEAEs leading to discontinuation of daratumumab	1 (2.3%)	2 (6.3%)	1 (16.7%)
Drug-related	1 (2.3%)	0	0
TEAEs leading to dose modification[a]	21 (47.7%)	13 (40.6%)	2 (33.3%)
Drug-related	6 (13.6%)	2 (6.3%)	0
TEAE with outcome of death	1 (2.3%)	0	0
At least one related	0	0	0
Death due to COVID-19[b]	0	1 (3.1%)	0
COVID-19 AEs[c]	11 (25.0%)	3 (9.4%)	1 (16.7%)
COVID-19 SAEs	0	1 (3.1%)	0
COVID-19 non-serious AEs	11 (25.0%)	2 (6.3%)	1 (16.7%)

Keys: TEAE = treatment-emergent adverse event.
[a] Dose modification includes dose delay within cycle, cycle delay and dose skipped.
[b] Includes subject(s) where death occurred outside the AE reporting window.
[c] Excludes subject(s) where death occurred outside the AE reporting window.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.
Note: If a subject has a missing subgroup value, the subject is only counted in the total column.
Note: Adverse events are reported using MedDRA version 25.1.

Sex

In Study SMM3001, a higher percentage of males (n=95) compared with females (n=98) in the Dara arm experienced Grade 3 or 4 TEAEs (males: 51.6%; females: 29.6%). A higher percentage of males compared with females experienced treatment-emergent SAEs in both arms (Dara males 36.8%, females 21.4%; ACTM males 22.6%, females 16.5%). Grade 5 TEAEs were reported in 2 (2.1%) male participants and 0 female participants in the Dara arm.

No subgroup analysis by sex was conducted for Study SMM2001.

Race

In Study SMM3001, a higher percentage of treatment-emergent SAEs was observed in non-White participants compared with White participants in both arms (Dara non-White, 39.4% [n=33], White, 26.9% [n=160]; ACTM non-White, 29.4% [n=34]; White, 17.3% [n=162]).

Interpretation of the subgroup analysis by race in Study SMM2001 is limited due to the small number of enrolled participants from the non-White group (n=10).

Weight

In Study SMM3001, no safety concerns were observed in participants with a baseline weight of ≤65 kg in either arm.

No subgroup analysis by baseline body weight was conducted for Study SMM2001 as the study was performed with daratumumab IV.

Baseline renal function

In Study SMM3001, in the Dara arm, a higher percentage of participants with abnormal baseline renal function compared with participants with normal baseline renal function status experienced TEAEs leading to discontinuation (abnormal 7.1% [10/40]; normal 1.9% [1/53]) and TEAEs leading to dose modification (abnormal 49.3% [69/140]; normal 39.6% [21/53]).

No subgroup analysis by baseline renal function was conducted in Study SMM2001.

Baseline hepatic function

In Study SMM3001, interpretation of the subgroup analysis by baseline hepatic function is limited due to the small number of participants with impaired hepatic function enrolled in the study (Dara 12 participants; ACTM 18 participants).

No subgroup analysis by baseline hepatic function was conducted in Study SMM2001.

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies were performed for daratumumab SC.

Discontinuation due to adverse events

Study SMM3001

Table 41. Treatment-emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term and Grade 3 or 4; Safety Analysis Set-Dara SC subjects only (Study 54767414SMM3001)

	Dara	
	Any Grade	Grade 3 or 4
Analysis set: safety	193	
Total number of subjects with treatment discontinuation due to TEAEs	11 (5.7%)	5 (2.6%)
MedDRA system - organ class/preferred term		
Infections and infestations	2 (1.0%)	2 (1.0%)
Pneumonia bacterial	1 (0.5%)	1 (0.5%)
Septic arthritis staphylococcal	1 (0.5%)	1 (0.5%)
Pneumonia	1 (0.5%)	0
Viral rash	1 (0.5%)	0
General disorders and administration site conditions	3 (1.6%)	1 (0.5%)
Fatigue	2 (1.0%)	1 (0.5%)
Asthenia	1 (0.5%)	0
Investigations	2 (1.0%)	1 (0.5%)
Blood alkaline phosphatase increased	1 (0.5%)	1 (0.5%)
Aspartate aminotransferase increased	1 (0.5%)	0
Psychiatric disorders	2 (1.0%)	1 (0.5%)
Anxiety	2 (1.0%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	3 (1.6%)	1 (0.5%)
Dyspnoea	2 (1.0%)	1 (0.5%)
Asthma	1 (0.5%)	0
Nasal congestion	1 (0.5%)	0
Blood and lymphatic system disorders	1 (0.5%)	0
Anaemia	1 (0.5%)	0
Cardiac disorders	1 (0.5%)	0
Palpitations	1 (0.5%)	0
Musculoskeletal and connective tissue disorders	1 (0.5%)	0
Myalgia	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	0
Adenocarcinoma	1 (0.5%)	0

Keys: TEAE = treatment-emergent adverse event.
Note: Adverse events reported as the reason for action 'Study drug permanently discontinued' on the Daratumumab injection CRF page are summarized.
Note: Percentages are calculated with the number of subjects in Dara SC group as denominators.
Note: For daratumumab treatment group, AEs with onset date and time on or after that of the first dose through 30 days after the last study drug administration are considered TEAE.
Note: Adverse events are reported using MedDRA version 26.1.

Dose modification of daratumumab SC (increase or decrease) was not permitted per protocol. Dose delay was recommended as the primary method for managing daratumumab-related toxicities.

The incidence of dose delays, cycle delays, or dose skipped due to TEAEs was 46.6%. The most common (≥5%) TEAEs leading to treatment dose delays, cycle delays, or dose skipped were Upper respiratory tract infection (14 [7.3%]), Pneumonia (11 [5.7%]), and COVID-19 (10 [5.2%]).

The incidence of dose delays, cycle delays, or dose skipped due to Grade 3 or 4 TEAEs was 18.7%. Grade 3 or 4 TEAEs leading to dose delays, cycle delays, or dose skipped in ≥2 participants were:

- Pneumonia (5 [2.6%])
- Neutropenia (4 [2.1%])

- Fatigue (3 [1.6%])
- Cellulitis (2 [1.0%])
- Sepsis (2 [1.0%])
- Dyspnoea (2 [1.0%])
- Hypophosphatemia (2 [1.0%])

Injection interruption or abortion due to TEAEs was reported in 3 (1.6%) participants. No TEAEs leading to injection interruption or abortion were reported in >1 participant. No Grade 3 or 4 TEAEs leading to injection interruption or abortion were reported.

Study SMM2001

The incidence of TEAEs leading to study treatment discontinuation was 7.3% in Treatment Arm A (long intense), 2.4% in Treatment Arm B (intermediate), and 5.0% in Treatment Arm C (short intense). No TEAE leading to treatment discontinuation was reported in more than 1 participant in any treatment arm.

Post marketing experience

A cumulative review was performed for all medically confirmed post-marketing spontaneous cases (serious and nonserious) of daratumumab received in the GMS global safety database through 31 July 2024.

Based on the total 14,739,507,922 milligrams distributed worldwide from launch to 31 July 2024 (*IV and SC*), the estimated exposure to IV and SC daratumumab is 446,262 person-years.

The cumulative search of the GMS global safety database through 31 July 2024 retrieved a total of 19,439 cases. Of these, 1,285 cases were identified as medically unconfirmed cases and 748 cases concerned multiple unidentifiable patients; therefore, these 2007 cases were not further reviewed. Of the 17,432 remaining cases, among the cases reporting sex, more than half (54.6%) concerned males and where age or age group was reported, most concerned elderly patients (≥65 years of age) (59.2%). The patients' age ranged from 0.1 to 100 years (median age: 68 years).

Of the 17,572 cases, 8,789 reported 15,198 serious events. Among these serious cases, the most frequently reported serious PTs (≥2% of the reported serious events) were Infusion-related reaction (7.48%), Plasma cell myeloma (7.23%), Neutropenia (2.97%), Death (2.81%), Disease progression (2.64%), Pneumonia (2.53%), Dyspnoea (2.26%), and Thrombocytopenia (2.4%).

A total of 1,176 cases reported 1,474 events with a fatal outcome. Among these cases, the most frequently reported fatal PTs (≥2% of the reported fatal events) were Death (29.0%), Plasma cell myeloma (9.1%), Disease progression (6.2%), Pneumonia (3.8%), Sepsis (3.3%), COVID-19, (2.8%), and Septic shock (2.2%).

2.5.1. Discussion on clinical safety

The pivotal safety population in this application included the 193 patients who received at least one dose of daratumumab in study SMM3001; a Phase 3, randomised, open-label, 2-arm, multicenter study of active monitoring (ACTM, N=196) and daratumumab SC (Dara) in participants with high-risk SMM.

In study SMM2001, patients received daratumumab IV at various doses, with treatment arm A (long intense) and B (intermediate) most closely resembling the pivotal study SMM3001 and thus results from this study are not included in the discussion.

In study SMM3001 the median duration of treatment was 35.0 months in the Dara arm and 25.9 months in the ACTM arm (active monitoring). The percentage of patients that completed 39 months of treatment was higher in the Dara arm compared to the ACTM arm; 65.5% vs 40.8%. This was mainly due to a higher frequency of PD in the ACTM arm (41.8%) versus the Dara arm (21.8%) and to some extent refusal of continued treatment (11.2% vs 2.6%, respectively).

The AE profile of daratumumab SC was consistent with the known safety profile of daratumumab. AEs with a frequency of ≥20% and a ≥10% higher frequency in the Dara arm compared with the ACTM arm were fatigue (Dara 34.2%; ACTM 13.3%), upper respiratory tract infection (Dara 30.1%; ACTM 7.7%), diarrhoea (Dara 27.5%; ACTM 5.1%), nasopharyngitis (Dara 25.4%; ACTM 11.7%), and insomnia (Dara 22.3%; ACTM 2.6%).

Corticosteroids were administered in the Dara arm (methylprednisolone 100 mg PO or IV or equivalent for the first 2 doses and 60 mg for all subsequent doses, if there had been no IRR events), and this is expected to be a contributing factor for some of the adverse events particularly insomnia and fatigue and potentially also infections.

The frequency of grade 3-4 adverse events was 40.4% in the Dara arm and 30.1% in the ACTM arm with only vascular disorders (SOC) presenting with a PT with a frequency of more than 5% mainly due to Hypertension (5.7% in the Dara arm and 4.6% in the ACTM arm). In addition, there was a significant difference in Grade 3-4 AEs in the SOC Infections and infestations (16.1% in the Dara arm and 4.6% in the ACTM arm), with the most frequent PT being pneumonia (4.7% and 1.0%, respectively).

Two new ADRs for daratumumab have been identified from this study: myalgia and pain in extremity, which have been grouped under the group term of musculoskeletal pain, which is agreed. Back pain and musculoskeletal chest pain have also been included in this group. Similarly, other ADRs have been grouped such as influenza under the group term upper respiratory tract infection, and peripheral sensory neuropathy under peripheral neuropathy.

Twenty-six patients (13.3%) in the ACTM arm and 15 patients (7.8%) in the Dara arm died during the study (Table 8/SCS). No patients in the Dara arm died within 30 days of the last dose of daratumumab or within 60 days of the first dose of daratumumab, whereas four patients in the ACTM arm died due to an AE within 30 days of the end of active monitoring (death on Day 21, 442, 543, and 685, respectively), and one patient died within 60 days of the start of active monitoring.

The incidence of SAEs was higher in the Dara arm compared with the ACTM arm (29.0% vs 19.4%, respectively). The difference was mainly due to events in the SOC infections and infestations (16.6% vs 5.1%, respectively).

Although as many as 27.5% of patients in the Dara arm experienced local injection-site reactions, none of these were Grade 3-4.

Neutropenia was more frequent in the Dara arm (6.7% vs 2.6% in the ACTM arm), whereas anaemia was observed with a higher frequency in the ACTM arm (9.7% vs 4.7% in the Dara arm).

The incidence of thrombocytopenia (grouped term) was low and there was 1 incident of Grade 3-4 hemorrhagic event in either arm.

The overall incidence of Infections (by SOC) was higher in the Dara arm (79.8%) compared to the ACTM arm (44.9%). The corresponding Grade 3-4 AEs were 16.1% and 4.6%, respectively and there were 2 deaths due to infection (COVID-19) in the Dara arm.

The incidence of viral infections was higher in the Dara arm (25.9%) compared to the ACTM arm (9.7%) and Grade 3-4 viral infections occurred in 3.6% and 0.5%, respectively. COVID-19 infections (grouped term) were reported in 8.8% in the Dara arm and 5.1% in the ACTM arm. Grade 3 COVID-19 infections were reported in 1 (0.5%) participant in both arms. No Grade 4 COVID-19 infections were reported, but two deaths, as described.

Haematology and clinical chemistry laboratory results were consistent between the arms and no clinically meaningful changes over time were observed.

For the≥65-75 years subgroup a higher frequency of infections was observed in the Dara arm mainly relating to pneumonia. This difference was not observed in the ACTM arm. AE frequencies for the ≥75 years subgroup are unreliable due to the low number of patients (N=21).

The post-marketing experience of daratumumab remains generally consistent with the known safety profile.

2.5.2. Conclusions on clinical safety

Safety findings from the pivotal study SMM3001 in support of this application are consistent with the known safety profile of daratumumab as characterised previously from other clinical studies.

Two new ADRs (pain in extremity and myalgia) for daratumumab were identified and are now included in the SmPC under 'musculoskeletal pain' and the frequency of some already known ADRs have also been updated based on the totality of the data.

Overall, submitted safety information supports the use of daratumumab for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Ongoing	Primary objective is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Draft Protocol: Interim report: Final report:	Aug 2021 2nd Quarter 2024 1st Quarter 2026

Risk minimisation measures

Summary Table of Risk Minimisation Activities

Safety Concern	Risk Minimization Measures
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4, which advises that patients should be typed and screened, and phenotyping or genotyping be considered prior to starting daratumumab treatment; • SmPC Sections 4.4, which advises HCPs to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommend that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommend mitigating daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; • SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; • SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection; Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.

Key: AL amyloidosis = light chain amyloidosis; DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, MAH took the opportunity to update the PI in accordance with the latest EMA excipients guideline.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

With the currently proposed indication extension, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet. The use of lay language for additional symptoms and side effects is consistent with the current approved leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present application is in the therapeutic area of "high-risk" smouldering multiple myeloma. The MAH has accepted the following amended indication: *DARZALEX as monotherapy is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma.*

Smouldering multiple myeloma (SMM) is diagnosed in persons who meet the following criteria

- Serum monoclonal (M) protein ≥3 g/dL and/or 10 to 59 percent bone marrow clonal plasma cells.
- Absence of lytic lesions, anaemia, hypercalcemia, and kidney impairment (end-organ damage) that can be attributed to the plasma cell proliferative disorder and the absence of biomarkers associated with near inevitable progression to end-organ damage (≥60 percent clonal plasma cells in the marrow; involved/uninvolved free light chain [FLC] ratio of ≥100 with involved FLC >100 mg/dL; or more than one focal bone lesion on magnetic resonance imaging [MRI]).

In current clinical practice, the Mayo 2018/International Myeloma Working Group (IMWG) risk stratification system (Lakshman, Blood Cancer J, 2018) is commonly used and recommended in the ESMO guideline on multiple myeloma (2021). They are also called the 20/2/20 criteria and include the following three risk factors for progression:

- Bone marrow plasma cells >20 percent
- Monoclonal (M) protein >2 g/dL

- Involved/uninvolved free light chain (FLC) ratio >20

Low risk SMM is defined as having none of the three risk factors. Intermediate SMM risk is defined as having one of the three risk factors. High risk SMM is defines as ≥2 of the three risk factors.

3.1.2. Available therapies and unmet medical need

There are no authorised medicinal products in the indication targeted by the applicant. Clinical guidelines recommend observation rather than treatment for patients with SMM.

3.1.3. Main clinical studies

Study SMM3001 (Aquila) is a Phase 3, randomised, open-label, 2-arm, multicentre study comparing active monitoring to daratumumab SC in participants with high-risk SMM. Randomisation was stratified based on the number of risk factors associated with progression to MM (<3 vs ≥3). The factors were (1) involved:uninvolved FLC ratio ≥8 (yes vs no), (2) serum M protein ≥30 g/L (yes vs no), (3) IgA SMM (yes vs no), (4) immunoparesis (reduction of 2 uninvolved Ig isotypes [yes vs no]), and (5) BMPCs (>50% to <60% vs ≤50%). The study comprises a Screening Phase, an Active Monitoring Phase (Arm A; hereafter referred to as ACTM) or a Treatment Phase with daratumumab SC (Arm B; hereafter referred to as Dara) for up to 39 cycles or 36 months, and a Follow-up Phase.

A total of 390 patients were enrolled (196 in the ACTM-arm and 194 in the Dara-arm).

The primary endpoint was PFS (progression to MM) by IRC. Key secondary endpoints were ORR, PFS2 and OS.

3.2. Favourable effects

At the primary analysis of PFS (01 May 2024), with a median duration of follow up of 65.2 months (Dara 65.9 months vs. ACTM 64.8 months), treatment with daratumumab SC conferred a significantly higher PFS in patients with high-risk SMM (as defined in the Aquila trial) compared to ACTM (HR=0.49; 95% CI: 0.36, 0.67; 2-sided p<0.0001). Median PFS was not reached in the daratumumab arm and was 41.5 months (95% CI: 26.4-53.3) in the ACTM arm.

The key secondary endpoint of ORR also demonstrated a significant increase in the daratumumab arm: 63.4% (95% CI: 56.2%, 70.2%) vs 2% (95% CI:0.6%, 5.1%) in the ACTM arm.

Key secondary endpoints of OS and PFS2 were not mature (47.01% and 24.3% of events respectively). observed but seemed to demonstrate trends in favour of the Dara-arm.

3.3. Uncertainties and limitations about favourable effects

One uncertainty is how representative of the targeted indication of high risk of progressing to MM was the population enrolled in the study. The most commonly employed risk stratification tool in SMM, the IMWG 20/2/20 tool, has high-risk category with a 2-year risk of progression of 44.2% (Mateos et al., Blood Cancer J, 2020). As this guideline was not available at the time of the trial initiation, high-risk SMM, was defined differently. In the statistical assumptions, a median PFS in the ACTM-arm of 30 months before progression to frank MM was assumed, while the actual results from the ACTM-arm of the pivotal study found a median PFS of 41.5 months (median follow-up in the ACTM-arm was 64.8

months). The 2-year risk of progression in the control arm was 36.7%. Based on the observed results. it seems that a higher risk population for progressing to MM could have been enrolled. However, in a post-hoc subgroup analysis employing the contemporary Mayo 2018 high risk criteria for SMM, results still favoured daratumumab treated patients, with a HR for PFS of 0.36 (95 CI: 0.23;0.58).

SMM is asymptomatic and progression to MM can also be entirely asymptomatic (i.e., based only on lab results/imaging). Therefore, it is uncertain exactly how clinically relevant a gain in PFS is when treating an asymptomatic condition like SMM. Regardless of whether a progression event is symptomatic or not, it can be considered clinically valuable that the time to need of frank anti-myeloma treatment (typically triplet or quadruplet combination therapy) is postponed. Additionally, the fact that the positive results of the primary endpoint of PFS are supported by an apparently also positive trendb on PFS2 and OS is reassuring.

Given the concerns on the clinical applicability of the primary endpoint mentioned above, it will be crucial to be able to support the demonstrated PFS gain by OS data and to be able to substantiate that early monotherapy treatment does not compromise the ability to deliver efficacious anti-myeloma (almost invariably combination treatment) at the time of progression to MM. The CHMP recommended that the final PFS2 and OS analyses are submitted when available.

3.4. Unfavourable effects

The incidence of TEAEs was higher in the Dara arm compared with the ACTM arm (Dara 96.9%; ACTM 82.7%). The incidence of Grade 3 or 4 TEAEs was higher in the Dara arm compared with the ACTM arm (Dara 40.4%; ACTM 30.1%). There was a significant clinically relevant difference in Grade 3-4 AEs in the SOC Infections and infestations (16.1% in the Dara arm and 4.6% in the ACTM arm), with the most frequent PT being pneumonia (4.7%). The incidence of SAEs was higher in the Dara arm compared with the ACTM arm (29.0% vs 19.4%, respectively) mainly due to infections (16.6% vs 5.1% by SOC, respectively). The incidence of TEAEs with an outcome of death (Grade 5) was low and balanced in both arms (Dara 1.0%; ACTM 2.0%). The rate of TEAEs leading to discontinuation of daratumumab was 5.7%.

3.5. Uncertainties and limitations about unfavourable effects

The main limitation of the study is that the comparison of the effects of daratumumab versus active monitoring is subject to bias and could lead to imbalances in TEAEs reporting.

As glucocorticoids are administered concomitantly with daratumumab monotherapy it is not always possible to adjudicate AEs to daratumumab or glucocorticoids with certainty.

3.6. Effects Table

Table 42 . Effects Table for Darzalex for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma (data cut-off:01 May 2024).

Effect	Short description	Unit	Dara N=194	ACTM N=196	Uncertainties / Strength of evidence	Reference
Favourable Effects						
PFS	Median time from randomisation to first disease progression (according to the IMWG response criteria) or death	Months (95% CI)	NE (66.69-NE)	41.46 (26.41,53.52)	HR: 0.49 (0.36-0.67) ORR: 63.4 (95% CI: 56.2%, 70.2%) in the Dara arm vs 2 (95% CI:0.6%, 5.1%) in the control arm PFS2 and OS not mature yet but with a favorable trend for the Dara arm	Aquila
Unfavourable Effects						
Death	Due to any reason	%	7.8	13.3	Median follow-up 65 months Low number of grade 5 TEAEs	Aquila
SOC Infections	Grade 3-4		16.6	5.1	PT Pneumonia 4.7% and 1.0%, respectively	
Fatigue	All events		34.2	13.3	Possible confounding from glucocorticoid administration	
Insomnia	All events		22.3	2.6		

Abbreviations: ACTM= active monitoring; CI= confidence interval; IMWG= International Myeloma Working Group; HR = Hazard ratio; NE=not estimable; ORR= overall response rate; PT= preferred term; SOC=system organ class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant improvement in the risk of progression to MM (or death), in particular if supported by (at least) no detriment of PFS2 and OS, could be considered clinically meaningful as this could be translated to a postponement of the added morbidity that may be associated with frank progression to MM (both in terms of deleterious effects of the disease as well as toxicity associated with treatment) without sacrificing the ability to receive and benefit from established anti-myeloma treatment upon progression. PFS as an endpoint is important even if progression was asymptomatic. PFS is a surrogate parameter of clinical benefit in the context of preventability / postponement of additional treatment. This is because progression means that frank MM is diagnosed which is an absolute indication for treatment with multi-agent regimens +/- ASCT which will necessarily be more toxic than daratumumab monotherapy used to prevent this. Decreasing the number of patients who need the multi-agent treatment within two or three years is a key aspect of determining a positive B/R.

Administering daratumumab monotherapy to trial-eligible patients not yet requiring anti-myeloma therapy was generally well tolerated albeit with an increased risk of infections which is in line with the known safety profile of daratumumab.

3.7.2. Balance of benefits and risks

The benefit-risk balance of daratumumab monotherapy treatment in the proposed patient population is positive, since the demonstrated clinically relevant benefits of daratumumab monotherapy for the treatment of adult patients with smouldering multiple myeloma at a high risk for progression to multiple myeloma are considered to outweigh the toxicity of the treatment. The toxicities from daratumumab monotherapy are considered manageable in the current clinical setting.

These benefits outweigh the risks associated with its use. Furthermore, considering that this is an early treatment setting and it is not curative, the goal is the prevention of end-organ damage (renal dysfunction and bone disease) and improvement in long-term survival.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Darzalex as monotherapy for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include daratumumab for the treatment of adult patients with smouldering multiple myeloma (SMM) at high risk of developing multiple myeloma based on results from study 54767414SMM3001 (AQUILA): a Phase 3 randomised, multicentre study of subcutaneous daratumumab Versus Active Monitoring in Subjects with High-risk Smouldering Multiple Myeloma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet was also updated in accordance. Version 12.1 of the RMP was also submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to update the PI in accordance with the latest EMA excipients guideline.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Talvey, Carvykti, Abecma, Farydak, Ninlaro and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘‘Darzalex-EMEA/H/C/004077/II/0077’.