30 April 2020
EMA/CHMP/273138/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/X/0032

Note

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

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Administrative information

Name of the medicinal product:	Darzalex
MAH:	Janssen-Cilag International NV Turnhoutseweg 30 2340 Beerse BELGIUM
Active substance:	DARATUMUMAB
International Non-proprietary Name/Common Name:	daratumumab
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, monoclonal antibodies (L01XC24)
Therapeutic indication(s):	DARZALEX is indicated: • 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, 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. • 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.
Pharmaceutical form(s):	Solution for injection
Strength(s):	1800 mg
Route(s) of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

ADR	adverse drug reaction
ASCT	autologous stem cell transplant
CI	confidence interval
C_{max}	maximum concentration
C_{trough}	trough concentration
CTSQ	Cancer Therapy Satisfaction Questionnaire
CV	coefficient of variation
DNA	deoxyribonucleic acid
D-Rd	daratumumab, lenalidomide, and dexamethasone
D-VMP	daratumumab, bortezomib, melphalan, and prednisone
D-VRd	daratumumab, bortezomib, lenalidomide, and dexamethasone
EU	European Union
HBV	hepatitis B virus
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
IV	intravenous(ly)
HR	hazard ratio
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
rHuPH20	recombinant human hyaluronidase PH20
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
US	United States

1. Background information on the procedure

1.1. Line Extension

Pursuant to Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof, Janssen-Cilag International NV submitted to the European Medicines Agency on 19 July 2019 an Extension application for Darzalex. The MAH applied for the addition of **a new pharmaceutical form (solution for injection) associated with a new strength (1800 mg in 15-ml vial) and a new route of administration (subcutaneous injection into the abdomen)**.

Janssen-Cilag International NV is already the MAH for Darzalex 20 mg/ml concentrate for solution for infusion (EU/1/16/1101/001-003). The MAH applied for all previously authorized indications for Darzalex. No new indication is being requested for the new formulation.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e) - Extensions of marketing authorisations

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

Darzalex was designated as an orphan medicinal product EU/3/13/1153 on 17-07-2013 in the following condition: Plasma cell myeloma. The line extension, which is the subject of this application, falls within the above-mentioned orphan designation.

Similarity

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

Protocol assistance

The MAH received Protocol assistance from the CHMP on 6 March 2017 (EMEA/H/SA/2456/7/2017/PA/III). The Protocol assistance pertained to quality, non-clinical and clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Sinan B. Sarac

The application was received by the EMA on	19 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 November 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	08 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 December 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 February 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	26 March 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	07 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of marketing authorisation to Darzalex on	30 April 2020
The CHMP adopted a report on similarity of Darzalex with Imnovid, Farydak, Kyprolis and Ninlaro	30 April 2020

2. Scientific discussion

2.1. Problem statement

Darzalex (daratumumab) administered intravenously is approved in the European Union for the treatment of patients with multiple myeloma as a 20 mg/mL concentrate for solution for infusion.

This application concerns a line extension application for a 120 mg/mL liquid for subcutaneous (SC) injection (new pharmaceutical form, strength and route of administration) of daratumumab introducing the addition of recombinant human hyaluronidase PH20 (rHuPH20) at the drug substance level.

Daratumumab is a fully human monoclonal IgG1 antibody expressed by genetically engineered Chinese Hamster Ovary (CHO) cells. It binds CD38 on multiple myeloma cells with high affinity and specificity, and it harbours several effector functions including CDC and ADCC.

2.1.1. Disease or condition

The MAH applied for all previously authorized indications for Darzalex as mentioned above. No new indication is being requested in this application. DARZALEX is indicated:

- 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, 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.
- 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.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Multiple myeloma is estimated to represent 0.9% of all cancers worldwide (Bray 2018). The incidence of multiple myeloma increases steadily with age, with a median age at diagnosis of approximately 65 to 72 years (Howlader 2017; Merz 2017; Song 2016). The annual number of new cases of multiple myeloma diagnosed is estimated to be approximately 48,297 in Europe (IARC/WHO 2018). The estimated world-wide 5-year prevalence is approximately 230,000 patients (Ruzafa 2016). Major strides have been made in the treatment of multiple myeloma in the last decade. Despite the availability of new therapies, 106,105 deaths were estimated worldwide due to multiple myeloma in 2018 (Bray 2018), and annually, approximately 24,300 deaths are estimated in Europe (Ferlay 2015).

2.1.3. Biologic features-Aetiology and pathogenesis

Multiple Myeloma is a malignant disorder, characterized by uncontrolled and progressive proliferation of a plasma cell, resulting in an overabundance of monoclonal paraprotein (IgG, IgA, IgD or IgE) or Bence-Jones protein (monoclonal K or h light chains), destruction of bone, an impaired production of normal immunoglobulins and displacement of normal bone marrow hematopoietic precursors. The cause of the myeloma cell's failure to differentiate is unknown, chromosomal changes, such as translocations of chromosome 14q32, deletions (chromosome 13q, 17p) and deregulation of oncogenes and tumour suppressor genes such as the c-my oncogene play a role, as well as environmental changes in the bone marrow.

2.1.4. Clinical presentation, diagnosis prognosis

Characteristic hallmarks of multiple myeloma include osteolytic lesions, fractures, vertebral collapse and pain, anemia, recurrent or persistent infections, hypercalcemia, renal insufficiency or failure, and

in some patients, hyperviscosity syndromes, clotting abnormalities and neurological complications. Approximately 20% of patients are symptom free and diagnosed by chance (Desikan, 2000).

The disease is characterized by multiple relapses, with each successive relapse, the chance of response and duration of response typically decreases resulting in resistant disease, progressive morbidity and eventual mortality. The prognosis depends on a variety of factors including cytogenetics, age and stage of MM at time of diagnosis.

2.1.5. Management

Treatment options in Multiple Myeloma are dependent on age, performance status, comorbidity, suitability for intensive treatment as well as aggressiveness of the disease. Progress has been made over the last 15 years in the treatment of multiple myeloma, the survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years with no improvement from the years 1985 to 1998 (Kyle 2003) to 6 to 10 years today (Moreau 2015). The improvement in prognosis is primarily attributable to the adoption of high dose chemotherapy followed by autologous stem cell transplantation (ASCT) and the introduction of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) in the last decade. While newer approved medications (pomalidomide and carfilzomib) have provided some additional options for relapsed patients, both are modifications of existing agents in the same class (IMiD and PI, respectively). Lately, monoclonal antibodies like daratumumab IV and elotumumab IV have been introduced.

Despite these advances, multiple myeloma remains incurable. After relapse from PIs and IMiDs, patients are often retreated with drugs that have the same mechanism of action. Ultimately, the disease becomes refractory. Patients who are heavily pretreated and/or refractory to both a PI and IMiD have a dismal prognosis, they are difficult to get back into a durable remission, and median survival is only between 8 to 9 months (Kumar 2012; Usmani 2015, Verelst 2015). For patients who are refractory to at least 3 of the common PIs and IMiDs (bortezomib, lenalidomide, carfilzomib, or pomalidomide), the median survival decreased to only 5 months. Especially the treatment option for the majority of the MM population, i.e., the more fragile and elderly patients, is overall associated with low response rate and short survival. (Smith 2005, 2001, Palumbo 2006).

Therefore, besides from novel therapeutic strategies to improve and deepen ORR, treatment modalities minimising the toxicities and treatment duration that are associated with current treatment options are needed.

About the product

Daratumumab is a targeted immunotherapy that binds with high affinity to tumor cells that overexpress CD38, a transmembrane glycoprotein. Multiple mechanisms of action have been described. Daratumumab IV received marketing authorization in the EU in May 2016 and is now approved in many countries worldwide for the treatment of multiple myeloma. Based on the cumulative total of 915,039,200 mg of daratumumab distributed from launch (cumulative to 31 October 2018), the estimated cumulative exposure to daratumumab IV in marketed use is 34,316 person-years. Daratumumab administered IV (DARZALEX) has been well-tolerated with manageable side effects, the most common side effect associated with daratumumab is infusion-related reactions (IRRs), which are experienced by approximately half of subjects receiving daratumumab IV-based regimens, with most (>90%) IRRs occurring during the first infusion. To minimize the risk of IRRs, the IV infusion requires a large infusion volume (500 to 1000 mL) with an infusion rate of approximately 7 hours for the first infusion, and subsequent infusions of 3 to 4 hours.

The MAH has developed a subcutaneous (SC) formulation containing 1800 mg daratumumab (120 mg/mL) co-formulated with 30,000 U recombinant human hyaluronidase PH20 (rHuPH20; 2000 U/mL) in a single vial (hereafter referred to as daratumumab SC). The SC formulation is given as a flat dose (1800 mg), injected into the SC tissue of the abdomen over approximately 3 to 5 minutes. The rHuPH20 used in the daratumumab SC formulation is the same as that approved in combination with other protein therapeutics for SC administration HyQvia, Rituxan Hycela, Herceptin Hylecta in the US; HyQvia, Herceptin SC, and MabThera SC in the European Union [EU]) and in the commercial product Hylenex recombinant (hyaluronidase human injection) approved in the US.

The goal in developing daratumumab SC was to demonstrate comparable efficacy and safety to the existing IV formulation but providing faster administration and lower rates of IRRs and to extrapolate the extensive data already generated for daratumumab IV to the new SC formulation.

Type of Application and aspects on development

This submission provides data supporting the approval of a subcutaneous (SC) formulation of daratumumab (daratumumab SC), a co-formulated drug product containing daratumumab and recombinant human hyaluronidase PH20 (rHuPH20) in a single vial. Daratumumab SC is given as a flat dose (1800 mg), injected into the SC tissue of the abdomen over approximately 3 to 5 minutes. Hyaluronidase increases permeability of the SC tissue by depolymerizing hyaluronan. rHuPH20 increases the tissue dispersion and absorption of other injected drugs and fluids by acting locally and transiently within the SC space.

In support of the non-clinical part of this application the results of the nonclinical program for daratumumab, as submitted in the initial Marketing Authorisation Application for DARZALEX, can be applied to daratumumab SC. In addition, the nonclinical program for rHuPH20, submitted in support of line extensions procedures for MabThera and Herceptin® are provided and can also be applied to daratumumab SC. Emphasis is placed on the assessment of Non-clinical studies of the combination of dara-rHuPH20 which are also being submitted. Clinical data submitted are derived from 4 studies in subjects treated with daratumumab as an 1800 mg flat dose (co-formulated with rHuPH20) and injected SC into the abdomen. Quality aspects of the product development are also being assessed

2.2. Quality aspects

2.2.1. Introduction

Darzalex is currently authorised as a 20 mg/mL concentrate for solution for infusion in 5 mL and 20 mL glass vials containing 100 mg and 400 mg of daratumumab, respectively. It is formulated with glacial acetic acid, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride and water for injections.

The scope of this application is the introduction of a new dosage form: 1800 mg solution for subcutaneous (SC) injection in a 15 mL single-use vial (120 mg daratumumab per mL). It is formulated with recombinant human hyaluronidase enzyme (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, sorbitol, L-methionine, polysorbate 20 and water for injections. RHuPH20 acts as a skin permeation enhancer that facilitates SC delivery. It is produced in genetically engineered CHO cells. Detailed information on the manufacture and control is presented in the dossier. RHuPH20 has already been approved as an excipient in other antibody-based medicinal products for SC injection.

The active substance manufacturing process has been optimised for the more concentrated 120 mg/mL daratumumab active substance for SC injection and is run at a new manufacturing facility.

2.2.2. Active Substance

General Information

Daratumumab is a fully human monoclonal glycosylated immunoglobulin G1κ (IgG1κ). The antibody is produced by genetically engineered CHO cells and binds with high affinity and specificity to the extracellular domain of human CD38.

Manufacture, characterisation and process controls

Manufacturing process

A new manufacturing site (Biogen (Denmark) Manufacturing ApS) has been proposed for the manufacture of daratumumab used for the SC presentation. A second-generation active substance manufacturing process optimised for the more concentrated 120 mg/mL active substance has been established. Valid GMP certificates for Biogen Denmark and all active substance quality control sites are provided.

The adapted process is not considered to constitute an alternate process, but rather changes introduced to increase antibody titer while maintaining the batch scale. The working cell bank and the bioreactor scale (15,000 L) are identical to the currently approved process for 20 mg/mL daratumumab active substance. Changes have been made to the cell culture media and the bioreactor duration has been decreased from 15 days for 20 mg/mL daratumumab to 13 days for 120 mg/mL daratumumab.

None of the culture media contain components of animal origin.

The 120 mg/mL active substance purification process has been adjusted compared to the 20 mg/mL active substance in order to manage the increased antibody titer. The Protein A affinity and cation-exchange column resins, as well as the virus removal filter, have been replaced. Virus validation confirmed adequate viral clearance capacity of the purification process using the new resins and virus filter. In addition, where the 20 mg/mL active substance manufacturing process has a virus inactivated and neutralised intermediate (VIN intermediate) which can be stored frozen, the 120 mg/mL manufacturing process uses a straight-through process without this option. Additionally, the final UF/DF step has been modified to achieve the higher active substance concentration in a different formulation buffer. The final formulation (except for the addition of rHuPH20 during finished product manufacturing) is made at the active substance level.

The harvest from the bioreactor is confirmed to be free of microbial growth by testing for microbial detection, mycoplasma and adventitious viruses (all are IPCs with acceptance criteria). IPCs control for the levels of bioburden and endotoxin throughout purification, and by the end of the purification the sterile-filtered active substance is tested for its content of host cell proteins. The proposed controls are all considered appropriate and do not call for comments.

Control of critical steps and intermediates

Critical and non-critical output parameters are defined in the dossier for the individual manufacturing steps. Adequate justifications for the respective acceptance criteria have been provided.

Control of materials

No change.

Process validation

The 120 mg/mL active substance manufacturing process has been re-evaluated and re-validated due to the introduced process changes. Consistency of the daratumumab manufacturing process was demonstrated by manufacture and analysis of five consecutive commercial-scale process validation batches. Residual host cell DNA and residual Protein A was consistently shown to be removed to

sufficiently low levels within these process validation batches, as well as in other clinical batches, which makes the Applicant's proposal of omitting in-process control (IPC) testing of these two process-related impurities acceptable. The residual host cell DNA and Protein A levels will, however, still be measured, with established alerts limits, in association with the monitoring of the resin lifetimes.

Virus removal re-filtration at Stage 8, re-concentration of pre-formulated bulk at Stage 9 and re-filtration of the active substance at Stage 10 has been validated at reduced scale. To further support the reprocessing at commercial scale (one step per batch), verification studies will be performed on the first commercial scale batches that require reprocessing. The proposed reprocessing steps are found acceptable and in line with the CHMP process validation guideline (EMA/CHMP/BWP/187338/2014).

Manufacturing process development

In comparability studies, 20 mg/mL daratumumab active substance batches were compared to 120 mg/mL daratumumab active substance batches used in the clinical development. The analytical program encompasses both the release assays as well as extended characterisation and demonstrates that 120 mg/mL daratumumab active substance batches have physicochemical and biological characteristics, as well as impurity levels, that are comparable to the 20 mg/mL daratumumab active substance.

Characterisation

The elucidation of structure confirmed that the change in the manufacturing method did not result in any significant structural change.

The 120 mg/ml daratumumab active substance batch was used for all characterisation studies. The protein structure of daratumumab was characterised using a wide variety of orthogonal techniques. The characterisation results, presented in Table 3, are in general identical or highly similar to those presented in the 20 mg/mL Darzalex solution for infusion.

No detectable differences in biological activity was found between the two active substance batches.

The head-to-head comparability study presented showed that, in general, the 120 mg/mL daratumumab active substance corresponds to the 20 mg/mL daratumumab active substance. Product-related impurities in the active substance were characterised. It can be concluded that the adaptations introduced to the daratumumab manufacturing process for production of 120 mg/mL daramtumumab active substance is without negative impact on the impurity profile.

Specification

The specification for the active substance includes control of identity, purity and impurities, potency and other general tests**.**

Analytical methods

All analytical methods, except for identity, are identical to the methods used for release and stability testing of 20 mg/mL daratumumab active substance. The identity test has been adequately validated.

Batch analysis

Analysis data on 12 batches of the active substance were provided. Batch analysis results confirm that the manufacturing process is capable of producing 120 mg/mL daratumumab active substance of an acceptable and consistent quality.

Reference materials

No change

Stability

The shelf life of the active substance is 24 months when stored frozen at the recommended storage conditions of -70 (±10°C) or -40 (±10°C), which allows more flexibility compared to the approved storage temperature of the 20 mg/mL daratumumab active substance at -70ºC. The shelf life claim is

based on an ongoing stability program for clinical, process validation, and post-process validation batches. The stability program is designed to follow ICH guidelines.

Statistical trending analyses of the real-time stability data (-40 ±10 °C) were performed when applicable as per ICH Q1E guidance. Stability data from storage at -70°C is support the lower storage condition.

The proposed shelf life and storage conditions for the active substance are considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of the dosage form

The daratumumab finished product is supplied as a sterile 120 mg/mL solution for injection, intended for administration by the SC route. The solution is clear to opalescent, colourless to yellow. Each vial contains 1800 mg of daratumumab in a 15 mL nominal fill volume and an excess volume of at least 1.3 mL. The finished product contains no preservatives and is for single use only.

The nominal composition of the finished product along with the function and grade of the excipients used in preparation of the finished product are provided.

All excipients used in the finished product formulation are of non-animal origin and, with the exception of rHuPH20, all the excipients are of pharmacopoeial grade. RHuPH20 is a skin permeation enhancer that facilitates SC delivery; it is a known excipient used in the formulation of other centrally authorised monoclonal antibody products; further details are provided below.

Pharmaceutical development

The primary reason for developing and optimising the SC formulation was to significantly reduce the burden of administration time associated with IV administration. To facilitate SC delivery, the finished product was formulated with rHuPH20.

The selection of the formulation composition was based on the results of a high throughput formulation screening, a short-term stability study, and other development studies. The lead formulation was further tested for robustness against manufacturing, processing, and shipping stress. Based on the outcome of all these studies, the finished product formulation was optimised to achieve a daratumumab concentration of 120 mg/mL allowing SC delivery and a single vial liquid dosage form presentation (1800 mg/vial of daratumumab).

The applicant has applied QbD principles in the development of the finished product and their manufacturing process.

A Quality Target Product Profile (QTPP) has been presented including the derived Critical Quality Attributes (CQAs).

The manufacturing process for the 120 mg/mL daratumumab finished product and its associated control strategy were developed based on the QTPP and the manufacturing experience gained with the approved product at the commercial manufacturing facility. A formal risk assessment was performed to establish an appropriate set of controls for the CQAs constituting of parametric controls, material controls, IPC tests, release testing, stability testing, characterisation testing, process validation, and process controls.

Criticality assessment was performed on all the parameters of the finished product manufacturing process steps that could potentially impact the CQAs. These steps (e.g. compounding, sterile filtration, aseptic filling, stoppering and capping, and their critical process parameters (CPPs) were identified and proven acceptable ranges (PARs) were set.

Acceptable justifications for the IPC acceptance criteria are provided in the dossier. IPC tests were performed on all Phase 3 and process validation batches at the critical steps in the finished product manufacturing process. The number of process validation batches has been justified.

The primary packaging material consisting of a type 1 glass vial with an elastomeric closure and an aluminium seal with a flip off button comply with Ph. Eur. and EC requirements and is considered suitable for a solution for injection intended to be administered subcutaneously. Additionally, the secondary packaging is protecting the finished product against light exposure, as the finished product is light sensitive. The stability data for the finished product demonstrates that the container closure also provide adequate protection from microbial contamination, as has been shown for all the clinical and process validation batches placed on stability at 2-8 °C after 0, 12 and 24 months of storage. This is supported by container closure integrity tests.

Studies to determine the extractables and potential leachables from the bromobutyl stoppers have been conducted and are justified.

The finished product was evaluated for compatibility with different types of syringes, plungers and types of SC administration sets. The results from these studies show that the finished product is compatible with the claimed components and studies are justified.

Excipient - recombinant human hyaluronidase (rHuPH20)

The rHuPH20 is a glycosylated single chain protein. rHuPH20 acts locally and transiently to depolymerise the substrate hyaluronan at the site of injection in the skin. This facilitates the absorption and dispersion of the injected monoclonal antibody by temporarily reducing viscosity and resistance to flow in the subcutaneous space.

The rhuPH20 is produced in genetically engineered CHO cells. Detailed information on the manufacture and control is presented in the dossier. rHuPH20 from the same supplier has already been commercially registered within the EU as a biological excipient when co-formulated with other biological therapeutics (see above). Therefore, the assessment of the manufacture and control of rhuPH20 is only shortly summarised in the assessment report.

The rHuPH20 manufacturing process is based on a cell bank system. The manufacturing process is described in satisfactory detail. There are no materials of animal origin used in the process.

- Suitable in-process controls and release controls are proposed.

The proposed rHuPH20 Bulk Enzyme specification has been applied throughout clinical development (Phase 1 to Phase 3) and is found acceptable.

Viral safety is confirmed for the rHuPH20 MCB, WCB, and end-of-production cells.

Manufacture of the product and process controls

Manufacturing process

The 120 mg/mL daratumumab finished product, is manufactured by Cilag AG Schaffhausen, Switzerland, where also primary packaging, secondary packaging and quality control of the drug product is performed. Quality control is also performed at Janssen Sciences Ireland UC, and batch release and quality control is performed at Janssen Biologics B.V., in the Netherlands. Secondary packaging and physical importation are performed by Janssen Pharmaceutica NV, Belgium.

The commercial manufacturing process of daratumumab finished product consists of receiving and storage of frozen active substance, thawing, compounding, and pre-filtration to create the finished product solution. The finished product solution is sterile filtered and aseptically filled into vials, which are stoppered and capped to achieve the final finished product. The vials are 100% optically inspected, and stored at 2-8°C. The manufacturing process has been described in sufficient details in the dossier.

A risk assessment for the potential presence of elemental impurities in the finished product was conducted in accordance with ICH Q3D guideline, taking into account potential contributions from the active substance, excipients, manufacturing equipment, container closure system (primary packaging), and processing water. No elemental impurities above the calculated permitted daily exposure for parenteral finished products were identified in 120 mg/mL daratumumab finished product.

Process validation

Validation of the process steps was performed to demonstrate control of the finished product manufacturing process. The following steps were evaluated as part of the process validation: thawing and holding, compounding, pre-filtration, sterile filtration, aseptic filling, stoppering and capping, optical inspection, secondary packaging, and other possible post-fill process steps (e.g., 100% container closure integrity test), and the results met the pre-established acceptance criteria.

Those aspects of the process that were validated met one or more of the following five types of pre-determined criteria: acceptance criteria for IPCs, acceptable ranges for CPPs, acceptance criteria for all finished product release tests, acceptance criteria for all process characterisation testing and/or additional acceptance criteria for product characterisation testing (qualified, non-routine tests used to characterise the finished product).

Reproducibility is demonstrated by the manufacturing of three consecutive finished product process validation batches. Additionally, the results of the release and characterisation tests used to evaluate the consistency of these batches confirmed that the manufacturing process reliably produces the finished product with consistent biochemical, biological, and physical properties.

All process characterisation, finished product release and characterisation sampling tests met the release acceptance criteria and process validation specifications for all quality attributes including microbial control. The proposed holding times are considered acceptable.

Media fills were performed to qualify the aseptic filling process and demonstrate that the procedures and environmental conditions in the commercial manufacturing facility were capable of supporting aseptic processing of the finished product, as demonstrated by the results of the three most recent semi-annual re-qualification runs of 2017/2018.

Satisfactory validation reports on filters used during the manufacturing process, as well as validation reports on sterilisation of equipment, components and stoppers, depyrogenation of glass vials and decontamination of filling isolators has been provided in the dossier.

Qualification of finished product shipping was evaluated through qualification of the shipping systems used for transportation through the supply chain and is found acceptable.

Ongoing process verification is in place where data from commercial manufactured batches are reviewed periodically to verify that the validated state is maintained. This is acceptable.

Product specification

The specification for the finished product includes control of identity, purity and impurities, potency and other general tests. The tests listed on the finished product specification for release and stability is acceptable and in line with ICH Q6B.

Process-related impurities in the finished product are the same as those listed and evaluated for the active substance.

Analytical methods

Many analytical procedures are identical to the procedures used to analyse Darzalex 20 mg/mL. All analytical procedures have been adequately described and have been revalidated in the proposed new SC formulation, and are thus suitable for analysis of the 120 mg/mL daratumumab finished product.

Batch analysis

Batch analysis results have been presented for a justified number of batches of 120 mg/ml daratumumab finished product; justified number of clinical batches and justified number of process validation batches. The batch results are all well within specification limits, and the results confirm consistency and uniformity of the product, indicating that the manufacturing process is under control.

Reference materials

No change.

Stability of the product

The acceptable shelf life of 120 mg/mL daratumumab finished product is 12 months when stored at the recommended storage condition of 2-8 °C and protected from light.

Stability results from batches manufactured according to commercial process as well as pilot scale batches have been provided. The studies are performed in accordance with ICH Q5C (Stability testing of Biotechnological/Biological products). Results from accelerated and stress studies have been provided.

All stability data for batches stored at recommended storage conditions remained within specification acceptance criteria at all time points tested.

A photostability study has been performed showing degradation, aggregation and decrease in potency of the finished product during light exposure, thus supporting the storage condition "protect from light". Additionally, a temperature cycling study on two finished product batches was performed, showing that 120 mg/mL daratumumab finished product remains stable following possible temperature fluctuations during transportation.

During the shelf-life, the product in unpunctured vial may be stored at room temperature ($\leq 30^0$C) and ambient light for a single period of up to 24 hours in the original carton to protect from light. Once the product has been taken out of the refrigerator, the product must not be returned to the refrigerator.

Once transferred from the vial into the dosing syringe (provided separately), the Darzalex solution for subcutaneous injection can be stored for up to 4 hours at ambient temperature and ambient light.

Adventitious agents

During cell line development, fetal bovine serum was used. No animal-derived materials have, however, been used to prepare the master cell bank or working cell banks or have been used during antibody manufacturing.

Mycoplasma and microbial bioburden are controlled through use of a sanitary process design and appropriate testing. Bioburden and endotoxin contamination is also evaluated as part of routine release testing.

Viral clearance is achieved through two orthogonal steps; viral inactivation (low-pH treatment), and physical removal by virus removal filtration. Five manufacturing steps were evaluated for their virus reducing capacity.

A viral safety factor for retrovirus-like particles (RVLP) in the manufacturing process was calculated from viral clearance values using XMuLV, a specific model virus for the RVLP in the production CHO cell line used for clinical and commercial manufacturing. Unprocessed cell culture supernatant in the production bioreactor was found to contain a maximum of 2.5×10^9 RVLP/mL. The manufacturing process was calculated to provide sufficient removal capacity to assure a level of less than 1 lipid-enveloped RVLP per 5.3×10^{11} doses.

With regard to non-specific model virus studies, cumulative minimum clearances of 13.5 $\log_{10}$ for mouse virus minute, 28.3 $\log_{10}$ for pseudorabies virus, and 19.8 $\log_{10}$ for reovirus type 3 were demonstrated.

Overall, the study on the virus reduction capacity of the manufacturing process is acceptable.

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been demonstrated.

Post approval change management protocol(s)

PACMPs to the daratumumab manufacturing process

The Applicant has included three PACMPs in the line extension application where the validation of reprocessing at commercial scale batches is deferred until a time when it is required. Separate PACMPs are provided for reprocessing at Stage 8, Stage 9 and Stage 10. All three PACMPs are found acceptable.

PACMP to the excipient rHuPH20 manufacturing process

A PACMP has been proposed to support implementation of new manufacturing equipment and process changes at the rHuPH20 active substance manufacturing site. A process validation campaign consisting of suitable number of consecutive rHuPH20 Bulk Enzyme lots will be conducted to support comparability of pre- and post-change rHuPH20 Bulk Enzyme. In-process control and release testing results from the process validation lots will be compared to the results from a suitable number of historical lots using the currently approved process and evaluated using pre-established assessment limits. The PACMP includes a plan to evaluate comparability of the finished product manufactured using the pre-changes and post-changes rHuPH20 Bulk Enzyme. The proposed strategy is acceptable The PACMP is found acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The overall quality documentation provided in this line extension application to introduce a new pharmaceutical form, Darzalex 1800 mg solution for injection for subcutaneous use, is considered to be adequate.

The active substance manufacturing process has been successfully optimised to produce the more concentrated 120 mg/mL daratumumab active substance in the new manufacturing facility. The changes have been adequately explained and supported by data. An appropriate control strategy is in place to guarantee consistent quality of the active substance, finished product, including the non-compendial excipient rHuPH20. Data has been presented to give reassurance on viral and TSE safety.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality point of view, the line extension application for Darzalex is considered approvable.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The results of the nonclinical program for daratumumab, as submitted in the initial Marketing Authorisation Application (MAA) for DARZALEX IV for multiple myeloma, can be applied to daratumumab SC. In addition, the nonclinical program for rHuPH20, submitted in support of line extensions procedures for MabThera and Herceptin® are provided and can also be applied to daratumumab SC.

In this nonclinical assessment report, only newly performed studies in support of the combination formulation are assessed in detail.

The new studies submitted in this application are:

- Two new studies on rHuPH20 alone carried out to investigate the local effects at the infusion site following SC delivery in Yucatan mini-pigs and Sprague-Dawley rats.
    - Local skin reactions were assessed after ID administration of rHuPH20 to Sprague Dawley rats (study R09090).
    - Induration and local infusion site evaluations were performed after SC administration of rHuPH20 to Yucatan mini-pigs (studies 11028, 11018 and 11125).
- Three non-GLP studies in Yucatan mini pig were performed to evaluate infusion rate, injection pressure and the effect of needle size on SC infusion of dara-rHuPH20. (Studies 15036, 16020, 16093)
- Three tissue distribution studies following ID, SC, or intravenous (IV) administration of ^{125}I-labeled rHuPH20 in mice (12214-B, 13128, 13184).
- A single-dose GLP rabbit local tolerance study was performed to support the safety of dara rHuPH20 when administered by SC infusion (Study T-2014-031).

Safety pharmacology endpoints were evaluated as part of the repeated dose toxicity studies in cynomolgus monkeys. The previously performed studies are summarised in brief where appropriate.

2.3.2. Pharmacology

Daratumumab (dara) is a human immunoglobulin (Ig)G1κ antibody based therapeutic agent that has already been approved for the treatment of multiple myeloma for the IV formulation as Darzalex.

The applicant has developed a new subcutaneous (SC) formulation containing dara which is co-formulated with recombinant human hyaluronidase (rHuPH20), and this is applied as an extension to the IV Darzalex formulation. rHuPH20 is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered by a SC route. PH20 hyaluronidase depolymerizes Hyaluronan (HA) which results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix, and in this way, PH20 temporarily facilitates dispersion, and allows for larger volumes to be administered via the SC route.

Only chimpanzee has been identified as the relevant toxicological species, as daratumumab only binds to human and chimpanzee CD38, but not that of other common toxicological species. Due to ethical reasons, further studies on the SC formulation was not conducted in chimpanzee. Only local tolerance studies in rabbits and Yucatan mini-pigs were conducted on daratumumab and rHuPH20 combined via

SC administration to assess local tolerability and feasibility of route of administration. It is agreed that the results of the nonclinical program for daratumumab, as submitted in the initial Marketing Authorisation Application for Darzalex IV formulation, can be applied to daratumumab SC, as the intended target concentration is similar following both SC and IV administration. Furthermore, some of the data regarding rHuPH20 submitted in support of the dara-rHuPH20 application is the same as that approved for subcutaneous administration of MabThera (H/C/165/X/0083, approved in 2014) and Herceptin (H/C/278/X/0060, approved in 2013), and reference is given respectively to the EPAR for these products where the studies have already been assessed.

Studies on the primary pharmacology of daratumumab have already been assessed in connection with the authorisation of the IV formulation of Darzalex. The dispersive properties of rHuPH20 was also already assessed previously. It was concluded that rHuPH20 has locally-acting dispersive properties in the skin.

In reviewing the submitted studies, it was apparent that the company behind rHuPH20 has performed additional studies not previously assessed. The new studies on rHuPH20 alone were carried out to investigate the local effects at the infusion site following SC delivery in Yucatan mini-pigs and Sprague-Dawley rats.

Local skin reactions as a function of delivery volume and buffer composition following intradermal administration of rHuPH20 was investigated in Sprague-Dawley rats. No histologic findings were observed at the injection sites that were attributed to the buffer, human serum albumin (HSA), rHuPH20, or volume injected in the rat intradermal space.

When immunoglobulin G (IgG) was subcutaneously infused to Yucatan mini-pigs, concomitant infusion with rHuPH20 resulted in reduction of the local effects of SC administration as measured by local swelling, skin surface temperature, histological changes as well as induration, which corresponded with greater maintenance of normal cutaneous blood pressure. Furthermore, reduced changes in infusion pressure with increased volumetric dispersion and skin pliability was observed as well as a maintained cutaneous blood perfusion in the presence of rHuPH20 during large volume infusions of IgG.

No stand-alone safety pharmacology studies were conducted with either daratumumab or rHuPH20. Safety pharmacology endpoints were incorporated into the design of the repeat-dose toxicology studies as suggested in ICH S6(R1).

With reference to the assessment performed in connection with the authorisation of Darzalex IV formulation there were no treatment-related adverse effects on cardiovascular, respiratory, or central nervous system parameters in the 6-week repeat-dose toxicology studies in chimpanzees administered daratumumab.

Previously, a 39 week study in cynomolgus monkeys using rHuPH20 has been provided in support of another SC formulation containing rHuPH20, where safety pharmacology endpoints were included. No treatment-related adverse effects of once weekly SC administered rHuPH20 were observed on cardiovascular, respiratory, or central nervous system parameters at up to 2 mg/kg/day.

2.3.3. Pharmacokinetics

The information provided by the applicant regarding the bioanalytical methods is considered acceptable. Both GLP compliant and non-GLP compliant studies were submitted which were either validated or qualified according to current guidelines.

Regarding tissue distribution of rHuPH20, this was further investigated in CD-1 mice after single IV, ID or SC administration of ^{125}I-rHuPH20 at different doses. The studies showed a similar rate of distribution for the different administration pathways, where radioactivity in tissues was well distributed after 2-5 minutes post-dose. Cmax was obtained after 15 min-2 h. The elimination half-life was similar between

the different administration routes and ranged from 3.5-5.9 h. In terms of total radioactivity dose administered, apart from the injection site, the highest proportions were associated with liver, lungs, urinary bladder content, kidneys, thyroid/parathyroid glands and gall bladder/bile.

Excretion studies on rHuPH20 showed a rapid excretion mainly via urine with similar recoveries across administration routes; 70-80 % and >98 % for ID, IV and SC administration, respectively. Smaller proportions was recovered in faeces.

2.3.4. Toxicology

No new toxicological studies have been performed with daratumumab or rHuPH20 besides a GLP compliant local tolerance study in NZW rabbits as well as three non-GLP studies in Yucatan minipigs.

A study in juvenile mice were submitted in support of rHuPH20. However, the indication for Darzalex SC formulation is in the adult population only. Therefore, the juvenile study with rHuPH20 is considered not relevant and has not been assessed in detail. For future application for use in children, an assessment of the juvenile population must be performed.

In a GLP compliant local tolerance study NZW rabbits received 14 mL of rHuPH20 SC alone or in combination with daratumumab (20 mg/mL) at a rate of 5 mL/min. The following parameters were evaluated during the in-life phase of the study: clinical signs, body weights, body weight changes, food consumption, dermal scoring, and body temperatures. Animals were euthanized on day 4 and further examined. Dosing with rHuPH20 did not result in any findings besides barely perceptible erythema, flaking, and purple discolorations at the injection site which were observed in all groups. No daratumumab related macroscopic or microscopic findings were observed. This is endorsed.

Three studies were conducted with female Yucatan mini-pigs via SC administration to investigate local reactions at the injection site as a function of differing concentrations of human IgG or daratumumab, differing concentrations of rHuPH20, rate of injection and needle size. The volume used in the nonclinical studies were identical to the clinically used volume (15 mL).

There were no statistical differences between different concentrations on rHuPH20 on degree of erythema, swelling and local infusion site swelling, however, injection pressure was reduced in a dose-dependent trend with increasing concentration of rHuPH20. The higher flow rate of 4 mL/min resulted in less reactions than the lower rate. Furthermore, it was shown that the 23-gauge needle produced the smallest bleb with manual injection.

Non-clinical investigations of the potential impact of ADA on fertility and offspring development were investigated in reproductive and developmental studies in CD-1 mice and NZW rabbits. In mice, exposure to ADA in offspring was confirmed throughout development from late gestation through adulthood. Male and female fertility investigations in rabbits showed that persistent exposure to ADA prior to mating had no impact on mating behaviour and fertility. Furthermore, ADA did not show effects on the offspring pre-weaning or post-weaning through maturity and mating. NZW rabbit was shown to be a relevant species for the safety assessment of rRbPH20 ADA impact.

Endogenous PH20 expression patterns were characterized in human tissue. The study concluded that the human anti-PH20/rHuPH20 antibodies demonstrated specific binding only to the testis. Gene expression studies in mice, rabbit and human tissue furthermore showed that SPAM1/PH20 is primarily expressed in the adult male reproductive tract.

Darzalex is however not indicated during pregnancy. Therefore, the information on the effect of ADA on fertility and offspring development is not considered relevant for this application.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment for rHuPH20 and daratumumab have already been addressed in previous market authorisations and are not further addressed in this assessment report, as the indication for the SC formulation is to simply substitute the IV administration. Hence, no increase in the exposure of daratumumab to the environment is foreseen.

2.3.6. Discussion on non-clinical aspects

Only chimpanzee has been identified as the relevant toxicological species, as daratumumab only binds to human and chimpanzee CD38, but not that of other common toxicological species. Due to ethical reasons, further studies on the SC formulation was not conducted in chimpanzee, which is accepted and supported.

Only local tolerance studies in rabbits and Yucatan mini-pigs were conducted on daratumumab and rHuPH20 combined via SC administration to assess local tolerability and feasibility of route of administration. It is agreed that the results of the nonclinical program for daratumumab, as submitted in the initial Marketing Authorisation Application for Darzalex IV formulation, can be applied to daratumumab SC, as the intended target concentration is similar following both SC and IV administration. Furthermore, some of the data regarding rHuPH20 submitted in support of the dara-rHuPH20 application is the same as that approved for subcutaneous administration of previously authorized products.

No adverse findings was observed in the conducted local tolerance studies and as the documentation submitted in support of the extension was considered adequate, no nonclinical Other Concerns have been raised.

2.3.7. Conclusion on the non-clinical aspects

The nonclinical data submitted for the new SC formulation of Darzalex is considered sufficient to support authorisation from a nonclinical point of view. The conclusions from the nonclinical assessment is considered sufficiently reflected in section 4.6 and 5.3 in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

The submission for daratumumab SC consists of 4 clinical studies in subjects with multiple myeloma. Details of Study MMY1004, MMY1008, MMY3012 and MMY2040 are provided in Table 7

GCP

The Clinical trials were performed in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council for Harmonisation of technical Requirements and GCP guidelines 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

Table 1 Overview of Clinical Pharmacology Studies and data included in PopPK analysis

Table 9: Overview of Clinical Pharmacology Studies and Data Included in the Population Pharmacokinetics Analysis

Study ID	Study Title and Design (including doses administered)	Brief Description of Pharmacokinetics Sampling Schedule (including how many subjects, rich or sparsely sampled)
MMY1004	An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab With the Addition of Recombinant Human Hyaluronidase PH20 (rHuPH20) for the Treatment of Subjects With Relapsed or Refractory Multiple Myeloma Doses: 1200 mg and 1800 mg. Dosing schedule: Dosing every week for Cycles 1 and 2 followed by every 2 weeks for Cycle 3 to 6, then every 4 weeks thereafter. A cycle was 4 weeks.	Part 1 (53 subjects): Formulation: mixed-and-deliver 1200 mg (8 subjects) 1800 mg (45 subjects) Part 2 (25 subjects): Formulation: co-formulant 1800 mg (25 subjects) PK: Sparse sampling for all subjects and additional rich sampling during the first and last weekly dose on Cycle 1 Day 1 and Cycle 2 Day 22 (EOI, EOI+2 hours, and EOI+12 hours), and on non-dosing days on Cycle 1 Days 2, 3, 4 and Cycle 2 Days 23 and 25.
MMY1008	A Phase 1 Study of Subcutaneous Delivery of JNJ-54767414 (Daratumumab) in Japanese Subjects With Relapsed or Refractory Multiple Myeloma Dose: 1800 mg Dosing Schedule: Dosing every week for Cycles 1 and 2 followed by every 2 weeks for Cycle 3 to 6, then every 4 weeks thereafter. A cycle was 4 weeks.	6 subjects Formulation: co-formulant PK: Sparse sampling for all subjects and additional rich sampling during the first and last weekly dose on Cycle 1 Day 1 and Cycle 2 Day 22 (EOI, EOI+2 hours, and EOI+12 hours), and on non-dosing days on Cycle 1 Days 2, 3, 4 and Cycle 2 Days 23 and 25.
MMY3012	A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma.	480 subjects (planned; 240 in each arm) Formulation: SC Arm: co-formulant

	Doses: SC Arm :1800 mg; IV Arm: 16 mg/kg Dosing Schedule: Dosing every week for Cycles 1 and 2 followed by every 2 weeks for Cycle 3 to 6, then every 4 weeks thereafter. A cycle was 4 weeks.	IV Arm: IV formulation PK: Sparse sampling for all subjects. One sample before infusion for Day 1 and Day 15 of Cycle 1, Day 1 of Cycles 2, 3, 5, 7, and 12, and EOT (eg, 4 weeks after the last dose) and 8 weeks after last daratumumab dose for both IV and SC cohorts; 1 sample immediately after end of infusion for Day 1 of Cycle 1 and Cycle 3 for IV cohort, and 1 sample after injection for Day 4 of Cycle 1 and Cycle 3 for SC cohort.
MMY2040	A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens Dose: 1800 mg Dosing Schedule: D-VRd cohort: Dosing every week for Cycles 1 to 3 followed by every 3 weeks thereafter. A cycle is 3 weeks. D-VMP cohort: Dosing every week for Cycles 1 followed by every 3 weeks for Cycle 2 to 9, then every 4 weeks thereafter. A cycle is 6 weeks for Cycle 1-9 and 4 weeks thereafter. D-Rd cohort: Dosing every week for Cycles 1 and 2 followed by every 2 weeks for Cycles 3 to 6, then every 4 weeks thereafter. A cycle was 4 weeks.	199 subjects Formulation: co-formulant PK: D-VRd cohort: Sparse sampling for all subjects on Cycle 1 Days 1 and 4, Cycle 3 Day 1 and Cycle 4 Day 1 and 4. D-VMP cohort: Sparse sampling for all subjects on Cycle 1 Days 1 and 4, Cycle 2 Days 1 and 4, and on Day 1 of Cycle 3, 6 and 9. D-Rd cohort: Sparse sampling for all subjects on Cycle 1 Days 1 and 4, Cycle 3 Days 1 and 4, and on Day 1 of Cycle 6, 9 and 12.

D-Rd= daratumumab SC, lenalidomide, and dexamethasone; D-VMP=daratumumab SC, bortezomib, melphalan, and prednisone; D-VRd=daratumumab SC, bortezomib, lenalidomide, and dexamethasone; EOI=end of infusion; EOT=end of treatment; IV=intravenous; PK=pharmacokinetics; SC=subcutaneous.
Source: Mod5.3.5.2/MMY1004; Mod5.3.5.2/MMY1008; Mod5.3.5.1/MMY3012; Mod5.3.5.2/MMY2040

2.4.2. Pharmacokinetics

Analytical Methods

A validated electrochemiluminescence-based immunoassay was used for quantitation of daratumumab in serum samples. Carry-over was not investigated. Bioanalysis of daratumumab SC in studies MMY1004, MMY1008, MMY2040 and MMY3012 was performed at a CRO or in-house at Janssen. The method was cross-validated between sites. The in-study performance of the daratumumab assay was overall considered acceptable for daratumumab SC. Immunogenicity of daratumumab SC will be reassessed following reanalysis with an improved screening ADA assay. The tissue permeability enhancer rHuPH20 was not measurable in serum according to the Applicant and no bioanalysis of rHuPH20 was performed. rHuPH20 immunogenicity was assessed by use of validated assay.

Evaluation and Qualification of Models

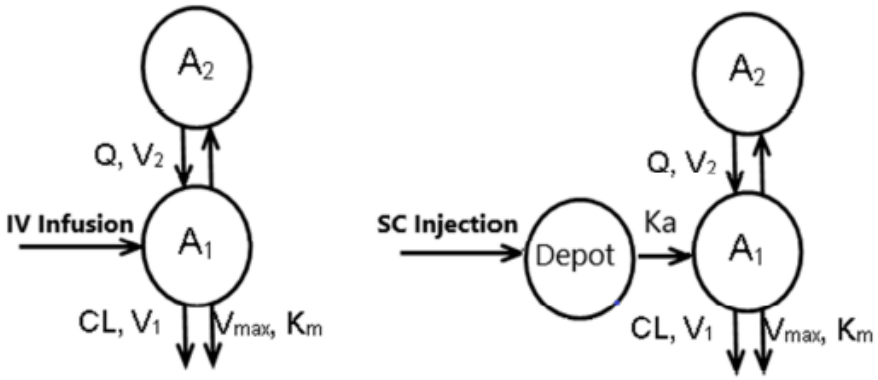
An exploratory analysis on concentration-time data and covariates was performed to compare the PK of daratumumab SC and IV. Data from studies MMY3012, MMY1004 part 2 and MMY1008 were fitted using the datatumumab model derived for IV infusion with the absorption of the SC formulation modelled as a first-order absorption process.

Pop PK population

Only subjects using the SC formulation (MMY1004 Part 2, MMY1008, MMY3012, and MMY2040) were included in the population pharmacokinetics analyses. Subjects using the mixed-and-deliver formulation in MMY1004 Part 1 were not included. All serum samples, with available actual time of blood collection as well as daratumumab dose administration, were used for the population pharmacokinetics analysis.

The Pop PK model for SC administration was similar to the previous model for IV administration but with an additional depot compartment to account for the first-order SC absorption process.

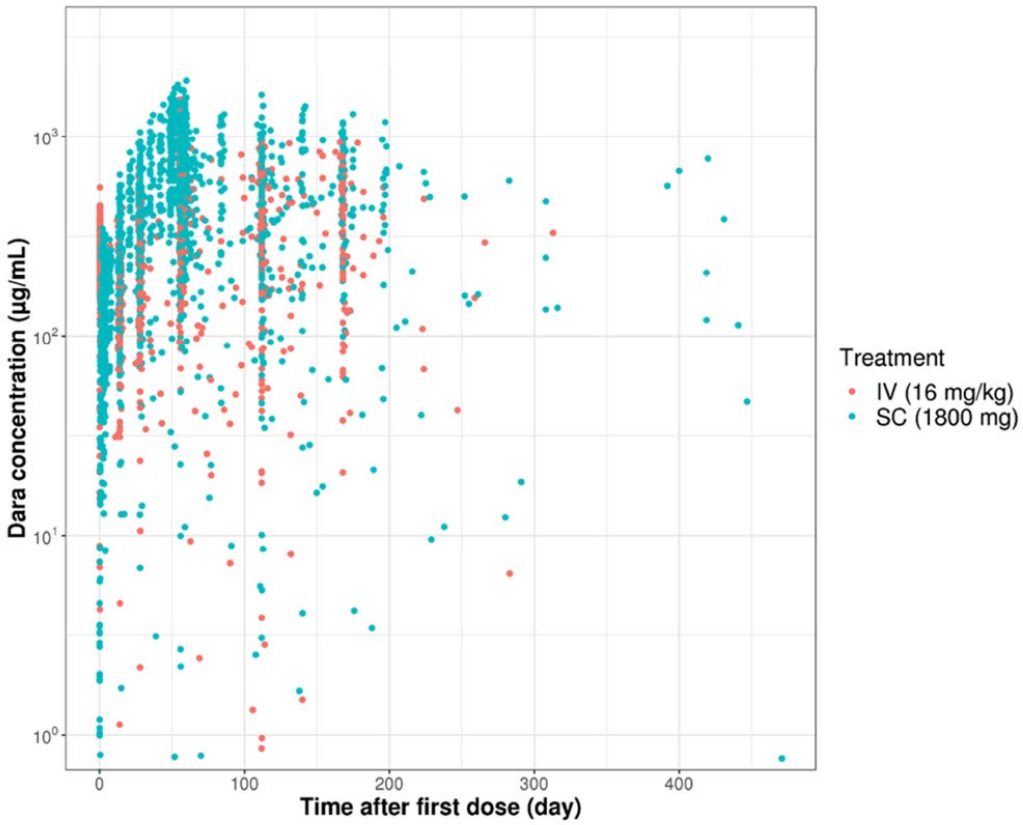
Figure 1 Michaelis Menten PK model for Daratumumab



A_1=daratumumab amount in the central compartment; A_2=daratumumab amount in the peripheral compartment; CL=linear clearance; IV=intravenous; Ka=absorption rate; K_m=Michaelis-Menten constant; Q=inter-compartmental clearance; PK=pharmacokinetics; 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}).
Source: Mod5.3.3.5/PPK/Fig2

The Pop PK population consisted of data from 742 patients or 5305 data points. BLQ data (less than 3% of the data set) was excluded by the M1 method for parameter estimation but included in the final dataset.

Figure 2 Daratumumab Monotherapy serum Concentrations after Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration



Abbreviations: Dara=daratumumab; IV=intravenous; SC=subcutaneous.

The exponents for weight on clearance and volume are 1.24 and 0.91; which are different to those expected for allometry (0.75 and 1, respectively). The intra-individual variability is moderate, 34.8%. The inter-individual variability is high (>36%) for all PK parameters. Sex, IgG myeloma, baseline albumin and weight were identified as significant covariates for daratumumab SC exposure.

Table 2 **Parameter Estimates of the PPK Model of Daratumumab Based on Combined Daratumumab SC and Daratumumab IV Data**

Parameter, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)
CL (L/h)	0.00496	8.4	58.7	4.9
ALB on CL	-1.85	12.1	-	-
WT on CL	1.24	10.6	-	-
TPMM on CL	1.26	14.4	-	-
V_1 (L)	5.25	4.1	36.9	3.7
WT on V1	0.91	11.5	-	-
Sex on V1	-0.105	45.4	-	-
V_2 (L)	3.78	7.0	-	-
Q (L/h)	0.00955	8.0	-	-
V_{max} (mg/h)	1.15	9.7	67.4	8.4
K_{DES} (1/h)	0.0000783	33.3	145.9	20.8
K_m (µg/mL)	2.56	16.0		
Ka (1/h)	0.0117	5.8	36.1	12.4
F1	0.689	2.7	-	-
ADD ERR (%CV)	34.8	0.3	-	-

Abbreviations: ALB=serum albumin concentration; ADD ERR=additive error term on the log-scale; BW=body weight; CL=linear clearance; CV=coefficient of variation; F1=bioavailability; IgG=immunoglobulin G; IV=interindividual variability; IV=intravenous; Ka=first-order absorption; K_m=Michaelis-Menten constant; K_{DES}=first-order rate for decrease of V_{max}; PPK=population pharmacokinetics; Q=intercompartmental clearance; RSE=relative standard error; SC=subcutaneous; TPMM=type of myeloma, IgG versus non-IgG; TVCL=typical value; 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; WT=body weight.
Note: Objective function value=-1759.836. Conditional number=42.8. Conditional number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate.
For IIV, RSE% is given for %CV and is an approximate value.
The typical values of PK parameters in Subject j,

$TVCLj = 0.00496 \bullet \left(\frac{BWj}{78.6}\right)^{1.24} \bullet \left(\frac{ALBj}{37}\right)^{-1.85} \bullet TPMMCL$ where TPMMCL is a shift factor of 1 for non-IgG subjects with multiple myeloma and 1+1.26 for IgG subjects with multiple myeloma. $TVV1j = 5.25 \bullet \left(\frac{BWj}{78.6}\right)^{0.91} \bullet SEXV1$ where SEXV1 is a shift factor of 1 for female and 1 to 0.105 for male.

Source: Appendix 3<<Provided as .lst file, will need help from doc specialist>>

Table 3: Comparison of Parameter Estimates of Daratumumab for the Final Population Pharmacokinetic Model Without / with Outliers (run121 / run122)

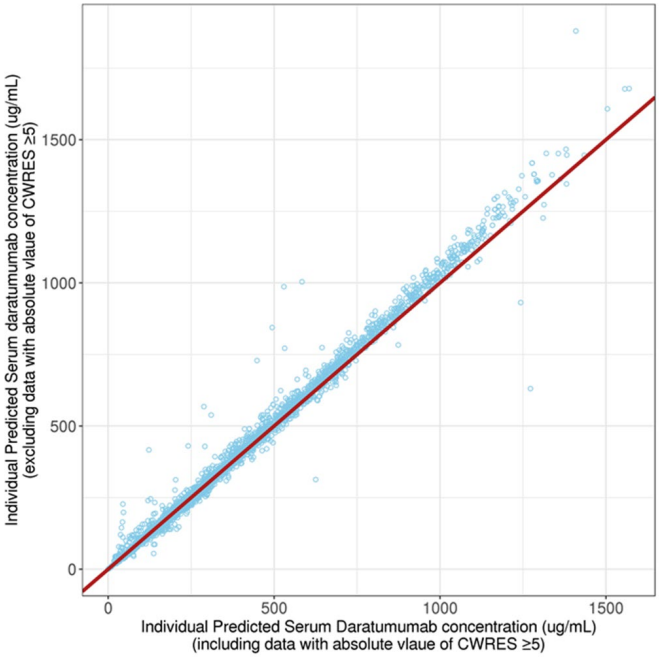
Parameter, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)
CL (L/hr)	0.00496 / 0.00508	8.4 / 7.4	58.7 / 60.6	4.9 / 3.7
ALB on CL	-1.85 / -1.81	12.1 / 11.2		
WT on CL	1.24 / 1.21	10.6 / 9.8		
TPMM on CL	1.26 / 1.11	14.4 / 14.2		
V1 (L)	5.52 / 5.06	4.1 / 3.0	36.9 / 29.8	3.7 / 3.3
WT on V1	0.91 / 0.8	11.5 / 10.0		
SEX on V1	-0.105 / -0.0959	45.4 / 36.7		
V_2 (L)	3.78 / 2.77	7.0 / 6.0		
Q (L/hr)	0.00955 / 0.00766	8.0 / 7.6		
V_{max} (mg/hr)	1.15 / 1.58	9.7 / 5.8	67.4 / 50.9	8.4 / 6.4
K_{DES} (1/hr)	0.0000783 / 0.000208	33.3 / 16.2	145.9 / 115.8	20.8 / 12.4
K_m (µg/mL)	2.56 / 1.92	16.0 / 16.8		
Ka (1/h)	0.0117 / 0.0132	5.8 / 4.7	36.1 / 40.0	12.4 / 6.8
ADD ERR (%CV)	34.8 / 22.6	0.3 / 0.6		

Abbreviations: ALB=serum albumin concentration; ADD ERR=additive error term on the log-scale; CL=linear clearance; CV=coefficient of variation; IIV=interindividual variability; K_m=Michaelis-Menten constant; Ka=first-order absorption; K_{DES}=first-order rate for decrease of V_{max}; Q=intercompartmental clearance; RSE=relative standard error; Sex=gender (female versus male); TPMM=type of myeloma (IgG versus non-IgG); 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; WT=body weight

Note: Condition number=42.8 and 34.28 for run121 and run122, respectively. Condition number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate.

For IIV, RSE% is given in %CV and is an approximate value.

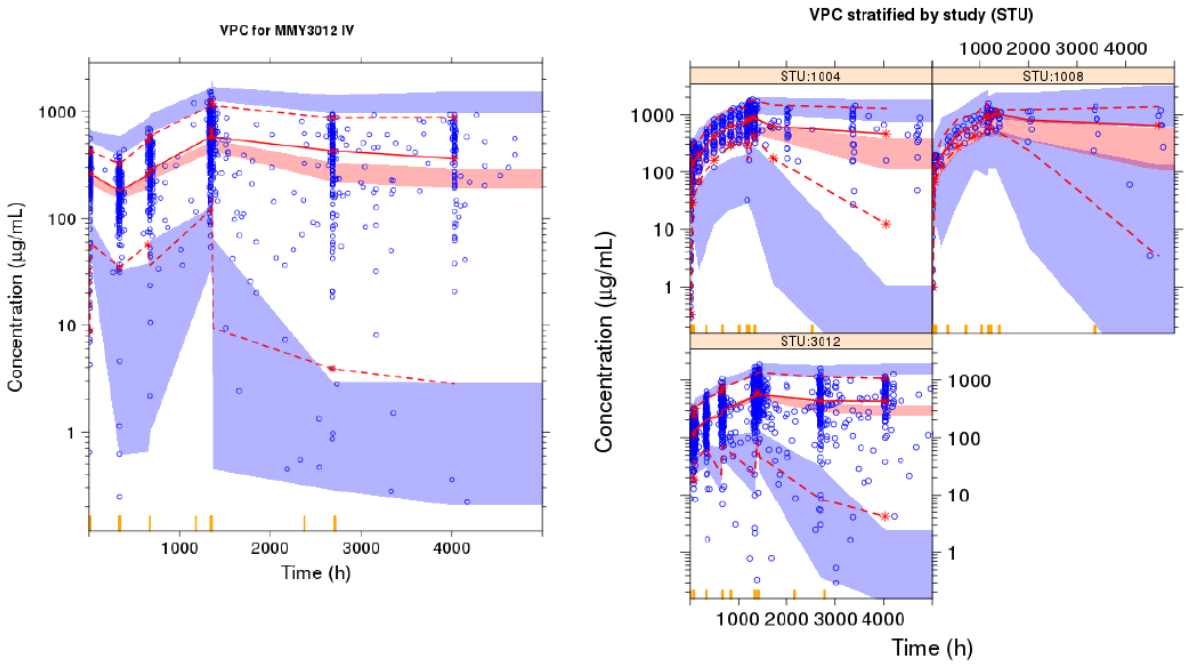
Comparison of Individual Predicted Daratumumab Concentration Based on Data With or Without Outliers



Key: blue open circle: individual predicted serum daratumumab concentration; red line: unity line.

Attachment 4: Visual Predictive Check for the Final PPK Model Stratified by Study With Daratumumab IV or SC for Monotherapy

A) Daratumumab IV **B) Daratumumab SC**



Abbreviations: IV=intravenous; PPK=population pharmacokinetics; SC=subcutaneous; STU=study; VPC=visual predictive check.
Key: Blue circle represents observation. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.
The x-axis was cut-off at 5000 hours to show the majority of the data.

Immunogenicity was not evaluated as a covariate in the Pop PK analysis. Exposure profiles did not seem to be affected in the ADA positive subjects (N=2 and N=20 for ADA against daratumumab and rHuPH20, respectively).

The rate of absorption was estimated to 0.012 h^{-1} based on Pop PK. No formal bioavailability study was performed. The bioavailability after SC injection was estimated to 68.9% by Pop PK. All clinical daratumumab SC data included in the Pop PK population used the commercial SC formulation. No bioequivalence studies were conducted. Food effect was not investigated. The mean volume of distribution was estimated to 5,25 L (V1) and 3.78 L (V2) by Pop PK analysis. The Pop PK estimated linear clearance is 4.96 mL/h and the associated mean half-life 20.4 days. After combination therapy, the half-life ranged from 23-27 days. In studies, steady-state was reached after 5 months at the proposed dose schedule for daratumumab SC monotherapy. Dose proportionality was evaluated between doses 1200 mg SC (n=4) and 1800 mg SC in study MMY1004, using the explorative formulation Dara-MD. The commercial formulation Dara-CF gave about 30% higher exposure than the Dara-MD formulation following 1800 mg SC for 8 weeks.

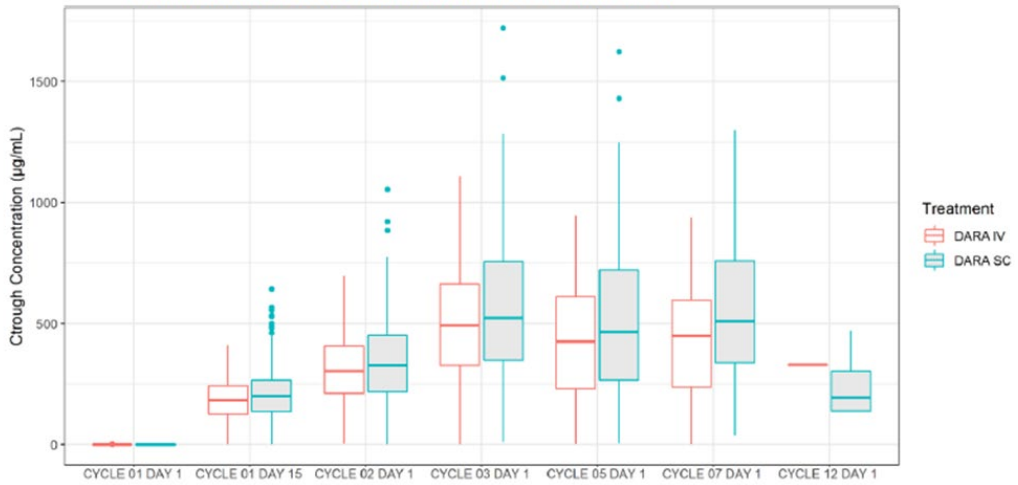
Table 4 **Pharmacokinetic Results of Daratumumab After Subcutaneous Administration of Daratumumab Mixed With rHuPH20 (Dara-MD) at 1200 mg (Cohort 1) and 1800 mg (Cohort 2, 3B, 3C, 3D), and Co-formulated Daratumumab and rHuPH20 Preparation (Dara-CF) at 1800 mg (Cohort 4) to Subjects With Relapsed or Refractory Multiple Myeloma**
(Study 54767414MMY1004: Pharmacokinetics Data Analysis Set)

Pharmacokinetics of Daratumumab (mean [SD], t_{max}: median [range])	Dara-MD 1200 mg	Dara-MD 1800 mg	Dara-CF 1800 mg
Cycle 1 – Dose 1			
n	5	42[a]	24
C_{max} (µg/mL)	81.3 (42.1)	161 (72.9)	209 (77.3)
t_{max} (hours)	72.55 (69.20-144.92)	71.84 (45.83-170.77)	71.70 (46.07-189.88)
AUC_{7days} (µg.h/mL)	10098 (5774)	21636 (10581)	29016 (11806)
Cycle 2 – Dose 4 (Last Weekly Dose)			
n	4	33[b]	18[c]
C_{trough} (µg/mL)[d]	520 (237)	710 (351)	838 (375)
C_{max} (µg/mL)	633 (366)	883 (431)	1011 (382)
t_{max} (hours)	69.95 (46.53-168.00)	69.30 (21.83-72.95)	69.18 (18.45-167.75)
AUC_{7days} (µg.h/mL)	96722 (52805)	133040 (67593)	156669 (61193)
Cycle 3 – Dose 1			
n	4	36	22
C_{trough} (µg/mL)[d]	599 (239)	778 (392)	932 (394)

Note: all descriptive statistics for the PK parameters, except for C_{trough}, Cycle 3 – Dose 1 are of the PK Data Analysis Set. Descriptive statistics of C_{trough} Cycle 3 – Dose 1 are of the PK Evaluable Subjects Analysis Set.
[a] n=41 for AUC_{7days}.
[b] n=41 for C_{trough}.
[c] n=23 for C_{trough}.
[d] C_{trough} reported is the predose concentration, just prior to administration of the indicated dose.
Cross reference: Attachment TABPK08 and Attachment TABPK10.

Daratumumab elimination showed both dose- and time-dependent clearance. Clearance decreased with increasing doses and with multiple dosing due to target depletion. Daratumumab SC accumulated over time with an accumulation ratio of 4.8 and 5.4, after eight weekly doses at 1800 mg SC, for Cmax and AUC0-7, respectively. The intra-individual variability determined by Pop PK is moderate (34.8%), while the inter-individual variability is moderate to high for PK parameters (36.9% for V1, 58.7% for CL, 67.4 for Vmax, 145.9% Kdes and 36.1% for Ka). The inter-individual variability for exposure parameters ranged from 37.8% to 50.8% in Study MMY1004 with rich PK sampling.

Figure 2: Box Plot of Daratumumab Serum Trough Concentration (µg/mL) Over Time – Pharmacokinetics Analysis Set (Study 54767414MMY3012)



Key: IQR=interquartile range
Standard boxplot visualization metrics were used. The box represents the 25th, 50th, and 75th percentile and the whiskers (line) represent the furthest value from the median that did not exceed 1.5*IQR. Data above or below the respective whisker ends were considered outliers.

Observed mean exposure (Ctrough at Cycle 3 Day 1) was comparable after SC and IV administration in Study MMY3012. This exposure level was also comparable to the simulated Cycle 3 Day 1 Ctrough by Pop PK analyses. AUC0-7d was simulated in Cycle 1 after 1st weekly dose to 720 and 1187 µg/mL×day and prior to Cycle 3 Day 1 to 4017 and 4019 µg/mL×day for daratumumab SC and IV respectively. AUC0-28d after Q4W dosing (representing steady-state) was simulated to 5887 and 5206 µg/mL×day for SC and IV respectively. The simulated exposure at steady-state was 13% higher after SC dosing than after IV. Non-inferiority between SC and IV administration was evaluated by means of Ctrough after sparse sampling and not AUC.

Attachment 10: Daratumumab Exposure Following Administration of Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Monotherapy

Parameter	Cycle	Median (5th-95th Percentiles)	
		Daratumumab SC	Daratumumab IV
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	123 (36-220)	112 (43-168)
	Cycle 3 Day 1 C_{trough} (Cycle 2, last weekly dose)	563 (177-1063)	472 (144-809)
	steady state	138 (0.3-676)	97 (0.6-517)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	132 (54-228)	256 (173-327)
	Prior to Cycle 3 Day 1 (Cycle 2, last weekly dose)	592 (234-1114)	688 (369-1061)
	steady state	276 (93- 900)	366 (216- 845)
AUC_{0-7d} (µg/mL•day)	Cycle 1, 1st weekly dose	720 (293-1274)	1187 (773-1619)
	Prior to Cycle 3 Day 1 (Cycle 2, last weekly dose)	4017 (1515-7564)	4019 (1740-6370)
	steady state*	5887 (930-22182)	5206 (1354-17668)

AUC_{0-7d}=area under the plasma concentration-time curve from time 0 to Cycle 1 Day 8 predose for Cycle 1, 1st weekly dose, and from Cycle 2 day 22 to Cycle 3 Day 1 predose for Cycle 2, last weekly dose. *AUC at steady state is AUC_{0-28d} during Q4W schedule;
C_{max}=maximum plasma concentration; C_{trough}=predicted trough concentration; IV=intravenous; SC=subcutaneous.

In Study MMY1004 and MMY1008 mean Ctrough values seemed notable higher than observed in Study MMY3012 after a similar dosing schedule and formulation. This could be attributed to differences in study characteristics.

Table 5

Across-study Summary of PK of Daratumumab After SC and IV Administration of Daratumumab After the Eighth Dose Administration (Cycle 3 Day 1) as Monotherapy (MMY1004, MMY1008, MMY3012)

Parameter	Mean (SD)			
	MMY1004 1800 mg Daratumumab SC	MMY1008 1800 mg Daratumumab SC	MMY3012 1800 mg Daratumumab SC	MMY3012 16 mg/kg Daratumumab IV
N	22	6	149	146
C_{trough}, µg/mL	932 (394)	879 (247)	593 (306)	522 (226)

C_{trough}=observed serum concentrations immediately prior to the next drug administration; IV=intravenous; N=maximum number of subjects with data; PK=pharmacokinetics; SC=subcutaneous; SD=standard deviation.
Source: Mod5.3.5.2/MMY1004 primary analysis CSR/Tab7; Mod5.3.5.2/MMY1008/Sec5.1.1; Mod5.3.5.1/MMY3012/Tab13

Variations in drug metabolising enzymes are not expected to affect the elimination of daratumumab as daratumumab is biotransformed as other endogenous IgG's. However, glomerular filtration and subsequent renal metabolism may contribute to the elimination. Forest plots of sub-group analysis showed a minor increase in predicted exposure in patients with moderate renal function compared to a typical subject. Patients with severe renal function were represented in the population (N=28) and

showed no effect on exposure based on mean Ctrough. The effect of impaired hepatic function is not evaluated for daratumumab SC as only patients with mild hepatic impairment was representative in the SC dataset.

Absorption

The rate of absorption for daratumumab after SC administration was approximately 0.012 hour-1 based on population pharmacokinetics evaluation.

- **Bioavailability**

No formal relative bioavailability study was performed.

The absolute bioavailability of 1800 mg daratumumab SC estimated using pooled population pharmacokinetics analysis was approximately 68.9% (RSE 2.7%) which is consistent with other monoclonal antibodies subcutaneously co-administered with rHuPH20.

In Study MMY3012, the mean peak serum concentration for daratumumab IV administration (16 mg/kg) was 767 (278) µg/mL and occurred at the end of infusion on Cycle 3 Day 1. For daratumumab SC (1800 mg), the mean peak serum concentration of 721 (373) µg/mL occurred on Day 4 of Cycle 3, as would be expected for subcutaneous administration of a monoclonal antibody.

Bioequivalence

No biopharmaceutic studies were conducted in support of daratumumab SC. The dose selection was based on Study MMY1004. The clinical Studies MMY1004 Part 2, MMY1008, SC arm of MMY3012, and MMY2040 used the same daratumumab SC formulation, identical to the proposed commercial formulation. Part 1 of MMY1004 used a mixed-and-deliver experimental daratumumab formulation for SC administration.

Distribution

The mean estimated volume of distribution for the central compartment (V1) was 5.25 L (36.9% CV) and for the peripheral compartment (V2) 3.78 L, suggesting that daratumumab primarily localised within the vascular system with limited extravascular tissue distribution. Both were related to body weight as expected for monoclonal antibodies.

Elimination

Excretion

The clearance of daratumumab is not expected to change as a result of change in formulation or route of administration. Daratumumab is cleared by parallel linear and nonlinear saturable, target-mediated clearance. The target-mediated clearance of daratumumab decreases with multiple dosing, as the target depletes. The Pop PK estimated mean linear clearance is 4.96 mL/h (58.7% CV), which is close to the clearance of nonspecific endogenous IgG in the literature. Body weight, baseline albumin concentration, and type of myeloma (IgG versus non-IgG) were identified as statistically significant covariates that affect linear clearance.

The model-derived geometric mean half-life associated with linear elimination was 20.4 (22.4% CV) days for monotherapy and 23-27 days for combination therapies, based on post hoc PK estimates. Similar to previous daratumumab IV monotherapy studies, steady state appears to be reached approximately 5 months into every 4 weeks dosing at the proposed dose schedule of 1800 mg daratumumab SC.

Metabolism

As an IgG1κ mAb, daratumumab is presumably biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and undergoes a similar elimination.

Dose proportionality and time dependencies

Dose proportionality

The dose proportionality was assessed in MMY1004. Following a 1.5-fold increase in dose (from 1200 mg to 1800 mg), the first dose Cmax increased 2-fold, and eighth dose Cmax increased approximately 1.4-fold and the AUC0-7d increased approximately 2-fold for first dose and 1.4-fold for the eighth weekly dose (**Table 11**).

Time dependency

The single- and multiple-dose PK of daratumumab SC were evaluated in Studies MMY1004 Part 2 and MMY1008 (**Table 12**). Daratumumab exhibited both concentration- and time-dependent PK with parallel linear and nonlinear (saturable) elimination, characteristic of target-mediated clearance.

Table 6 **Single- and Multiple-dose PK of Daratumumab After Daratumumab SC 1800 mg Administration (MMY1004, MMY1008)**

Parameter	Mean (SD); t_{max}: Median (Range)				
	MMY1004 Part 2			MMY1008	
	Cycle 1 Dose 1	Cycle 2 (Last Weekly Dose)	Cycle 3 Dose 1 (Cycle 3 Day 1)	Cycle 1 Day 1 After the First Administration	Cycle 2 Day 22 After the Eighth Administration
N	24	18[a]	22	6	6
C_{max}, µg/mL	209 (77.3)	1011 (382)	-	177 (27.8)	1092 (318)
t_{max}, h	71.7 (46.1-190)	69.2 (18.5-168)	-	71.8 (70.3-168)[b]	21.7 (20.3-74.4)[b]
AUC_{7d} µg.h/mL	29016 (11806)	156669 (61193)	-	23760 (3480)[c]	168360 (45480)[d]
C_{trough}, µg/mL[e]	-	838 (375)	932 (394)	-	-

C_{max}=maximum serum concentration; C_{trough}=predose concentrations; N=maximum number of subjects with data; PK=pharmacokinetics; SC=subcutaneous; SD=standard deviation; t_{max}=time to reach the maximum serum concentration.

[a] n=23 for C_{trough}.

[b] Source data report t_{max} Cycle 1 Day 1, 2.99 (2.93-7.00) days; Cycle 2 Day 22, 0.903 (0.847-3.10) days, converted to hours.

[c] Source data report AUC_{7d}=area under the concentration-time curve from time 0 to Cycle 1 Day 8 predose: 990 (145) day*µg/mL, converted to µg.h/mL.

[d] Source data report AUC_{7d}=area under the concentration-time curve from time Cycle 2 Day 22 predose to Cycle 3 Day 1 predose: 7015 (1895) day*µg/mL, converted to µg.h/mL.

[e] C_{trough} reported is the predose concentration, just prior to administration of the indicated dose.

Note: All descriptive statistics for the PK parameters, except for C_{trough}, Cycle 3 Dose 1 are of the PK analysis set. Descriptive statistics of C_{trough} Cycle 3 Dose 1 are of the PK-evaluable analysis set.

Source: Mod5.3.5.2/MMY1004 primary analysis CSR/Tab7; Mod5.3.5.2/MMY1004 primary analysis CSR/AttTABPK08; Mod5.3.5.2/MMY1008/Tab8; Mod5.3.5.2/MMY1008/Tab9

Intra- and inter-individual variability

In Study MMY1004, the inter-subject variability for 1800 mg Dara-CF and Dara-MD, expressed as %CV for Ctrough, Cmax and AUC7days of Cycle 2 Dose 4, was moderate and similar between formulations, ranging from 37.8% to 50.8%.

Pharmacokinetics in target population

Table 7 **Across-study Summary of PK of Daratumumab After SC and IV Administration of Daratumumab After the Eighth Dose Administration (Cycle 3 Day 1) as Monotherapy (MMY1004, MMY1008, MMY3012)**

Parameter	Mean (SD)			
	MMY1004 1800 mg Daratumumab SC	MMY1008 1800 mg Daratumumab SC	MMY3012 1800 mg Daratumumab SC	MMY3012 16 mg/kg Daratumumab IV
N	22	6	149	146
C_{trough}, µg/mL	932 (394)	879 (247)	593 (306)	522 (226)

C_{trough}=observed serum concentrations immediately prior to the next drug administration; IV=intravenous; N=maximum number of subjects with data; PK=pharmacokinetics; SC=subcutaneous; SD=standard deviation.
Source: Mod5.3.5.2/MMY1004 primary analysis CSR/Tab7; Mod5.3.5.2/MMY1008/Sec5.1.1; Mod5.3.5.1/MMY3012/Tab13

PK results across all clinical studies within the daratumumab SC program are tabulated in Appendix 3.

Appendix 3: Bioavailability PK Parameters of Daratumumab Across Clinical Studies

Study ID (Subject Population)	Dose (mg) /Formulation	N	Mean (SD); t_{max}: Median (Range)				
			t_{max} (h)	C_{trough} (µg/mL)	C_{max} (µg/mL)	AUC_{0-7d} (µg.h/mL)	$t_{1/2}$ (h)
MMY1004							
Cycle 1 Dose 1	Dara-MD 1200 mg/SC	5	72.55 (69.20-144.92)	-	81.3 (42.1)	10098 (5774)	-
	Dara-MD 1800 mg/SC	42[b]	71.84 (45.83-170.77)	-	161 (72.9)	21636 (10581)	-
	Dara-CF 1200 mg/SC	24	71.70 (46.07-189.88)	-	209 (77.3)	29016 (11806)	-
Cycle 2 Dose 4 (last weekly dose)	Dara-MD 1200 mg/SC	4	69.95 (46.53-168.00)	520 (237)[a]	633 (366)	96722 (52805)	-
	Dara-MD 1800 mg/SC	33[c]	69.30 (21.83-72.95)	710 (351)[a]	883 (431)	133040 (67593)	-
	Dara-CF 1200 mg/SC	18[d]	69.18 (18.45-167.75)	838 (375)[a]	1011 (382)	156669 (61193)	-
Cycle 3 Dose 1 (Cycle 3 Day 1)	Dara-MD 1200 mg/SC	4	-	599 (239)[a]	-	-	-
	Dara-MD 1800 mg/SC	36	-	778 (392)[a]	-	-	-
	Dara-CF 1200 mg/SC	22	-	932 (394)[a]	-	-	-
MMY1008							
Cycle 1 Day 1	Dara-SC 1800 mg/SC	6	2.99 (2.93-7.00)		177 (27.8)	990 (145)[e]	-
Cycle 2 Day 22	Dara-SC 1800 mg/SC	6	0.903 (0.847-3.10)		1092 (318)	7015 (1895)[f]	-
MMY3012							
Cycle 3 Day 1 predose	Dara 1800 mg/SC	149	-	593 (306)	-	-	-
Cycle 3 Day 1 predose	Dara 16 mg/kg IV	146	-	522 (226)	-	-	-
MMY2040							
D-VMP							
Cycle 1 Day 1	Dara 1800 mg/SC	66	-	-	98.6 (51.6)	-	-
Cycle 2 Day 4	Dara 1800 mg/SC	55	-	-	612 (256)	-	-
Cycle 2 Day 1 predose	Dara 1800 mg/SC	65	-	482 (217)	-	-	-
Cycle 3 Day 1 predose	Dara 1800 mg/SC	60	-	392 (187)	-	-	-
D-Rd							
Cycle 1 Day 4	Dara 1800 mg/SC	56	-	-	108 (49.9)	-	-
Cycle 3 Day 4	Dara 1800 mg/SC	50	-	-	648 (238)	-	-
Cycle 3 Day 1 predose	Dara 1800 mg/SC	56	-	526 (226)	-	-	-
Cycle 6 Day 1 predose	Dara 1800 mg/SC	19	-	495 (148)	-	-	-
D-VRd							

Exposure simulations

Individual Pop PK parameters for subjects from study MMY3012 were estimated using a maximum a posteriori Bayesian approach and point estimates of exposure metrics were predicted.

Attachment 10: Daratumumab Exposure Following Administration of Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Monotherapy

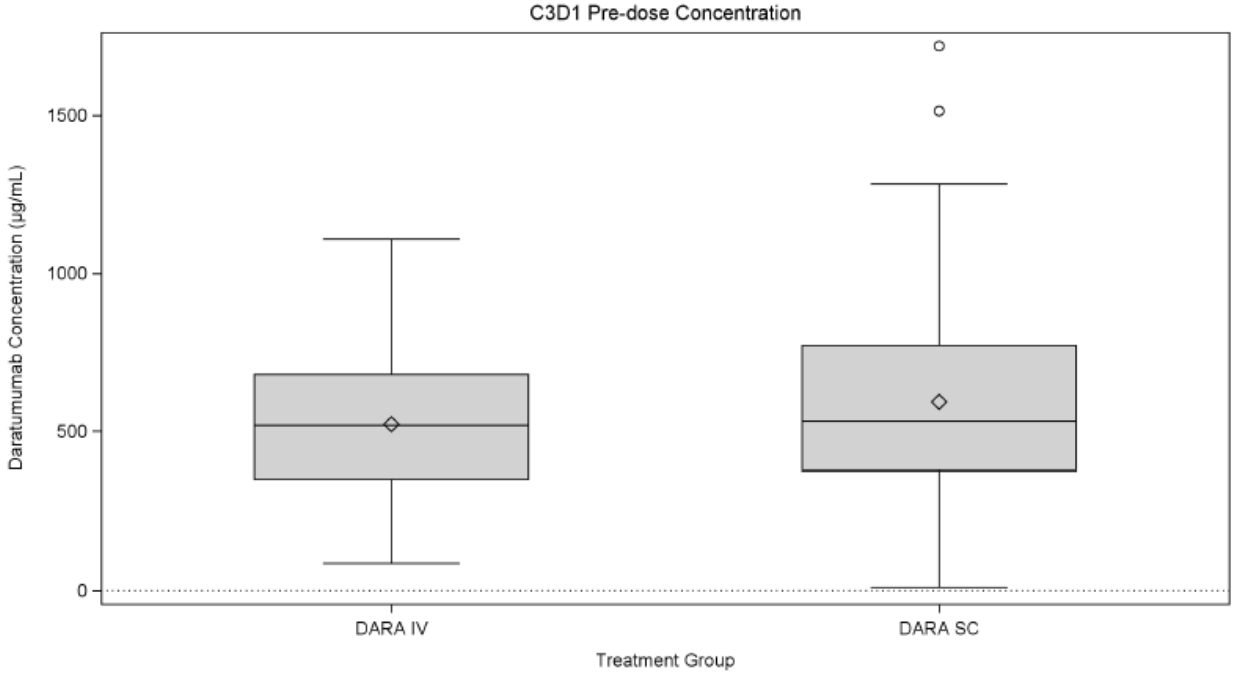
Parameter	Cycle	Median (5th-95th Percentiles)	
		Daratumumab SC	Daratumumab IV
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	123 (36-220)	112 (43-168)
	Cycle 3 Day 1 C_{trough} (Cycle 2, last weekly dose)	563 (177-1063)	472 (144-809)
	steady state	138 (0.3-676)	97 (0.6-517)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	132 (54-228)	256 (173-327)
	Prior to Cycle 3 Day 1 (Cycle 2, last weekly dose)	592 (234-1114)	688 (369-1061)
	steady state	276 (93- 900)	366 (216- 845)
AUC_{0-7d} (µg/mL•day)	Cycle 1, 1st weekly dose	720 (293-1274)	1187 (773-1619)
	Prior to Cycle 3 Day 1 (Cycle 2, last weekly dose)	4017 (1515-7564)	4019 (1740-6370)
	steady state*	5887 (930-22182)	5206 (1354-17668)

AUC_{0-7d}=area under the plasma concentration-time curve from time 0 to Cycle 1 Day 8 predose for Cycle 1, 1st weekly dose, and from Cycle 2 day 22 to Cycle 3 Day 1 predose for Cycle 2, last weekly dose. *AUC at steady state is AUC_{0-28d} during Q4W schedule;
C_{max}=maximum plasma concentration; C_{trough}=predicted trough concentration; IV=intravenous; SC=subcutaneous.

Study MMY3012: Analysis of maximum Ctrough (Cycle 3 Day 1)

A total of 295 subjects were included in the PK-evaluable analysis set, with daratumumab SC and daratumumab IV groups being generally similar in sample size. The average (SD) maximum Ctrough (Cycle 3 Day 1 predose) were 593 (306) and 522 (226) µg/mL, respectively, for the daratumumab SC and daratumumab IV groups.

GPKCONC01: Box Plot of Maximum C_{trough} Concentration (µg/mL); Pharmacokinetic-evaluable Analysis Set (Study 54767414MMY3012)



The geometric means ratio for Ctrough was 107.93% (90% CI: 95.74%, 121.67%) for daratumumab SC versus daratumumab IV. Since the lower limit of the 90% CI exceeded 80%, daratumumab SC was demonstrated to be non-inferior to daratumumab IV in terms of pharmacokinetics.

Table 8 **Summary of Maximum C_{trough} Concentration (Cycle 3 Day 1 Predose) – Pharmacokinetic-evaluable Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC
Analysis set: pharmacokinetic-evaluable	146	149
Maximum C_{trough} Concentration (µg/mL, predose on Cycle 3 Day 1)		
N	146	149
Mean (SD)	522 (226)	593 (306)
Geometric mean[a]	463	499
Ratio (Dara SC/Dara IV)		107.93%
90% CI		(95.74% - 121.67%)
Coefficient of variation	43.2%	51.6%
Median	519	532
Range	(86.1; 1109)	(9.97; 1720)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: CI=confidence interval; N=total number; SD=standard deviation
[a] Maximum C_{trough} concentration data were natural log (ln) transformed prior to the calculation of geometric mean, the ratio of geometric mean and its 90% confidence interval, and then transformed back to the linear scale.
[TPKCONC01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TPKCONC01.SAS] 05MAR2019, 16:34

Special populations

Impaired renal function

The effect of renal impairment was assessed for both monotherapy (both IV and SC) and combination therapy (SC only) treatment regimens. In the daratumumab IV monotherapy group, the geometric mean values for Cycle 3 Day 1 Ctrough by renal function were: normal (472 µg/mL, N=70), mild (380 µg/mL, N=81), moderate (452 µg/mL, N=80), and severe (362 µg/mL, N=19). In the daratumumab SC monotherapy group, the geometric mean values for Cycle 3 Day 1 Ctrough by renal function were: normal (405 µg/mL, N=80), mild (504 µg/mL, N=112), and moderate (598 µg/mL, N=87).

In the pooled population PK analyses of daratumumab SC in subjects with multiple myeloma renal impairment was not identified to significantly influence the PK of daratumumab

Of all patients included in the PK studies, 56% were ≥65 years. A total of 276 patients were aged 65.74 years and 156 patients were aged 75-84 years.

Impaired hepatic function

In the PoP PK analysis, hepatic impairment was not identified to significantly influence the PK of daratumumab in mild hepatic impairment.

Gender

The geometric mean values for Cycle 3 Day 1 Ctrough for males versus females were 433 µg/mL (N=146) and 407 µg/mL (N=108) in the daratumumab IV monotherapy group, and 476 µg/mL (N=150) and 539 µg/mL (N=138) in the daratumumab SC monotherapy group, respectively

In combination therapy, the geometric mean values for Ctrough after 6 weekly doses for males versus females were 441 µg/mL (N=124) and 542 µg/mL (N=75), respectively. The overall exposures did not overlap between the 2 groups in combination therapy.

Race

Race did not have clinically relevant effects on daratumumab exposure. **Table 15** describes the distribution of race within each study included in the Pop PK population.

Table 9

Descriptive Statistics of Baseline Categorical Covariates

Parameter	Study MMY1004 N=25	Study MMY1008 N=6	Study MMY2040 N=199	Study MMY3012 N=512	Combined N=742
Sex					
Men	56% (14)	33% (2)	62% (124)	55% (281)	57% (421)
Women	44% (11)	67% (4)	38% (75)	45% (231)	43% (321)
Race					
White, not Hispanic, or Latino	76% (19)	0	61% (121)	75% (386)	71% (526)
Black, of African heritage, or African American	8% (2)	0	4% (8)	3% (14)	3% (24)
White, Hispanic, or Latino	4% (1)	0	4% (8)	4% (18)	4% (27)
Asian	0	100% (6)	3% (5)	13% (68)	11% (79)
Native Hawaiian or Other Pacific Islander	0	0	0	0% (1)	0% (1)
Other	12% (3)	0	29% (57)	5% (25)	11% (85)

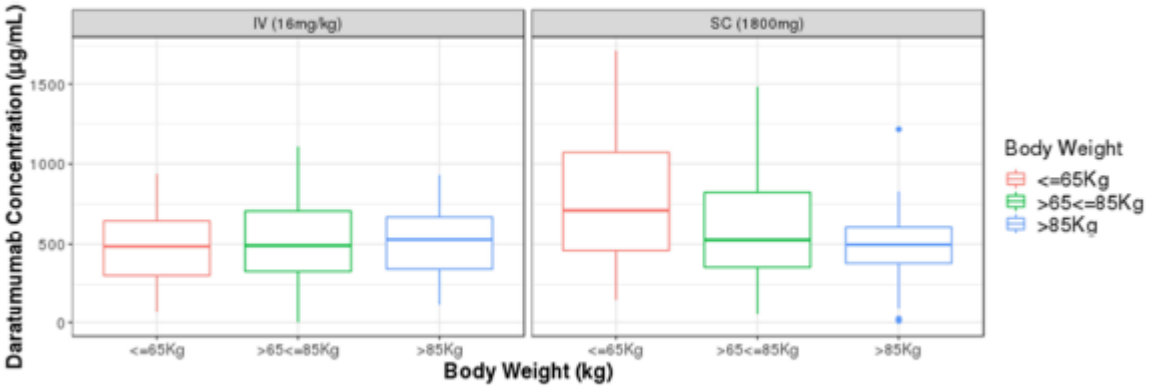
Study MMY1008 investigated the PK of daratumuma SC in 6 Japanese patients which was comparable to the across-study exposure (Table 20 Section 2.1.8). In addition, race was not a significant covariate in the Pop PK analysis. The Forest plot showed an increased Ctrough (about 30%) in non-white compared to white race. This effect was not observed after IV (16 mg/kg) administration.

Weight

The flat-dose administration of daratumumab SC achieved adequate exposure for all body weight subgroups, as the maximum Ctrough (Cycle 3 Day 1 predose) exceeded the 236 µg/mL threshold previously established in daratumumab IV studies as necessary for 99% target saturation.

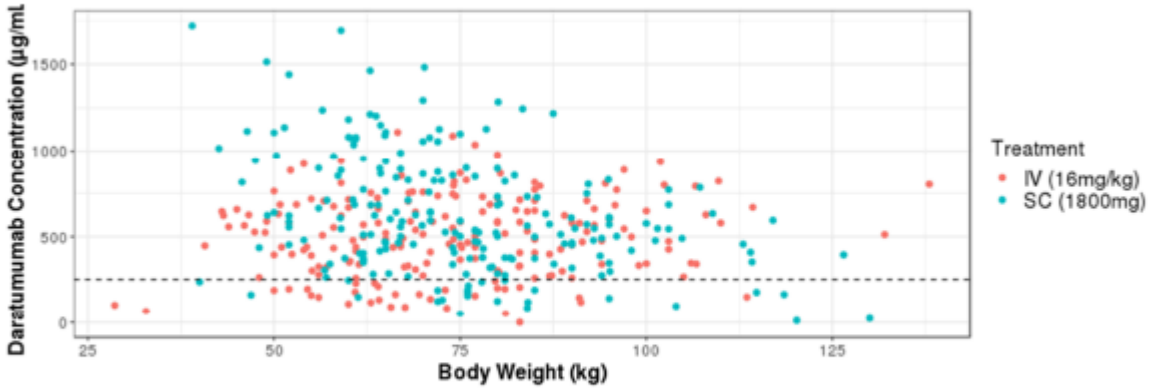
The mean observed concentrations of daratumumab for the lower body weight subgroup (≤65 kg) were approximately 60% higher in the daratumumab SC group than the daratumumab IV group based on arithmetic mean ratios. The higher exposure in this subgroup was maintained in later cycles and at steady state. The mean concentration of daratumumab in the higher body weight subgroup (>85 kg) was approximately 12% lower at Cycle 3 Day 1 predose, in the daratumumab SC group than the daratumumab IV group. At later cycles, the concentrations were comparable.

Figure 3 **Box Plot of Observed Daratumumab Trough Concentrations After 8 Weekly Doses in Weight Groups After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration for Monotherapy**



IV=intravenous; SC=subcutaneous.
Source: Mod5.3.3.5/PPK/Fig5

Figure 4 **Observed Daratumumab Trough Concentrations After 8 Weekly Doses Across the Range of Studied Body Weights After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration for Monotherapy**



IV=intravenous; SC=subcutaneous.
Note: Black dashed line represents the concentration of daratumumab at which the 99% (EC99TAR) target saturation is achieved.
Source: Mod5.3.3.5/PPK/Fig6

Weight was a significant covariate in the Pop PK analysis. Mean observed C_{trough} was about 60% higher in the lower bodyweight sub-group (≤65 kg) in the SC group as compared to the IV group in Study MMY3012. In the >85 kg sub-group, exposure was 12% lower at Cycle 3 Day 1 after SC but similar to IV at later cycles. This is further discussed in other parts of this report.

Elderly

In the daratumumab SC monotherapy group, the geometric mean values for Cycle 3 Day 1 Ctrough for age subgroups were: <65 years of age (468 µg/mL, N=127), ≥65 to <75 years (534 µg/mL, N=106), and ≥75 years (542 µg/mL, N=55). In the combination therapy dataset, the geometric mean values for Ctrough after 6 weekly doses were <65 years of age (458 µg/mL, N=76), ≥65 to <75 years (482 µg/mL, N=74), and ≥75 years (497 µg/mL, N=49).

Table 10 Age Distribution for Daratumumab SC Monotherapy & Combination Trials Included in Population PK Analysis; PK Analysis Set (Studies MMY1004, MMY1008, MMY3012, MMY2040)

	Total	Age 65-74	Age 75-84	Age 85+
PK Trials				
Pooled monotherapy	288	106 (36.8%)	54 (18.8%)	1 (0.3%)
MMY1004 (Part 2 SC)	25	12 (48.0%)	5 (20.0%)	1 (4.0%)
MMY1008	6	1 (16.7%)	3 (50.0%)	0
MMY3012 (Dara SC)	257	93 (36.2%)	46 (17.9%)	0
MMY2040 (Combination)	199	74 (37.2%)	48 (24.1%)	1 (0.5%)

Of all patients included in the PK studies, 56% were ≥65 years. A total of 276 patients were aged 65-74 years and 156 patients were aged 75-84 years. Only 3 patients included in the PK studies were ≥85 years thus no conclusion can be made separately for this age-group. However, a sufficient number of elderlies was included in the study, and therefore no dose adjustment is necessary on the basis of age.

Children

Daratumumab SC is intended for treatment of multiple myeloma that develops in adults (predominately elderly). No children were included in the daratumumab SC program.

Pharmacokinetic interaction studies

No interaction studies were conducted with daratumumab SC.

2.4.3. Pharmacodynamics

Mechanism of action

Multiple mechanisms of action have been observed for daratumumab 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 tumor-bound monoclonal antibodies (Overdijk 2016).

No mechanism of action studies were included in the current submission.

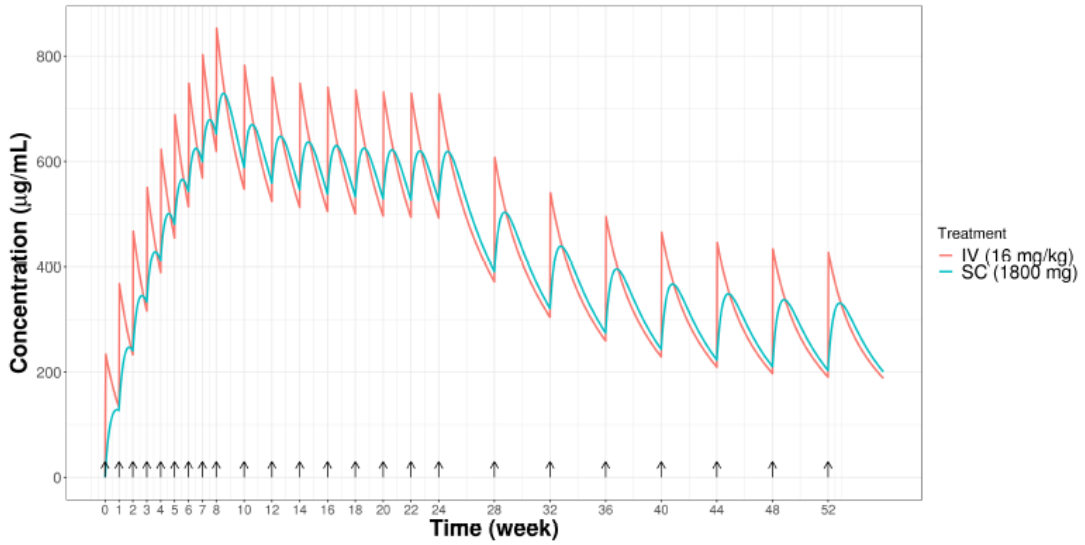
2.4.3.1. Primary and Secondary pharmacology

Primary pharmacology

Rationale for dose selection:

The simulated typical PK profiles for daratumumab SC 1800 mg and daratumumab IV 16 mg/kg administered according to the approved monotherapy dose schedule (every week for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter) are presented in Figure 7.

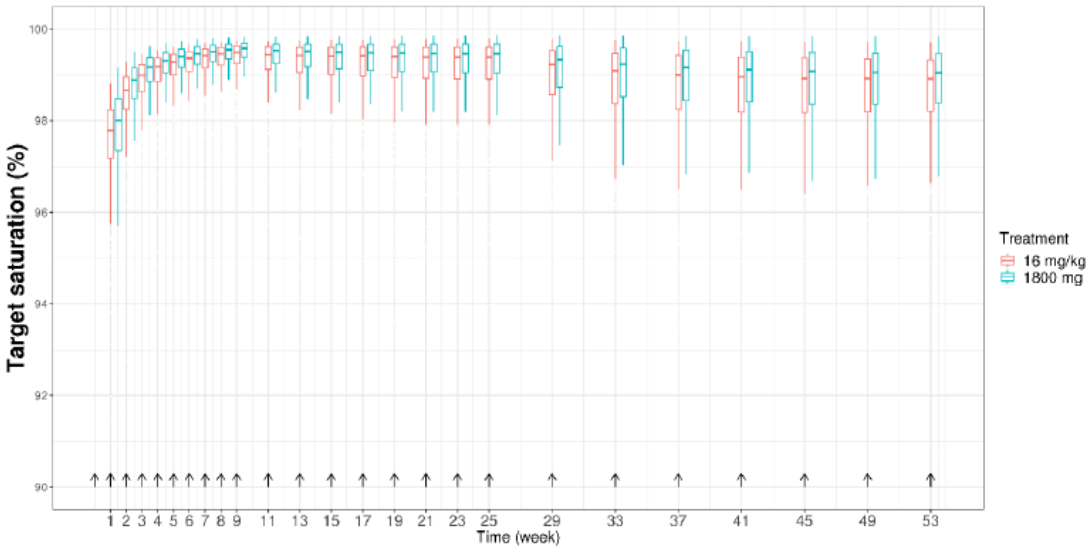
Figure 5 **Typical Pharmacokinetics Profile of Daratumumab After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration as per the Approved Dose Schedule**



Abbreviations: IV=intravenous; SC=subcutaneous.
Key: Black arrows represent dose events.
Note: Approved dose schedule consisted of weekly administration for 8 weeks (8 doses), every 2 weeks for 16 weeks (8 doses), and every 4 weeks thereafter (eg, 8 doses).

The simulated target saturation over time after daratumumab SC 1800 mg and daratumumab IV 16 mg/kg is shown in Figure 8. The target saturation with the daratumumab SC dose was similar to that with the daratumumab IV dose, which remained >96% over time. This shows that once the initial once weekly dose schedule rapidly established efficacious concentrations, dosing frequencies of every 2 weeks and every 4 weeks produced serum concentrations that maintained target saturation (Figure 8).

Figure 6 **Box Plot for the Simulated Target Saturation Over Time After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Monotherapy**



Abbreviations: IV=intravenous; SC=subcutaneous.

None of the investigated intrinsic factors (ie, age, sex, race, renal impairment, hepatic impairment, and ECOG status) had clinically relevant effects on the exposure to daratumumab. Consistent with the findings from previous IV studies, although subjects with IgG myeloma or subjects with lower baseline albumin concentrations appeared to have lower exposure, clinical analyses demonstrated that the lower daratumumab concentrations in subjects with IgG myeloma and subjects with lower baseline albumin

values had no clinically relevant effect on efficacy. Therefore, no dose adjustment is recommended based on any of these factors. Similar patterns for the effect of IgG and albumin concentrations have been observed in the previous studies for daratumumab IV monotherapy.

The population PK and E-R analyses provided the following scientific and quantitative justification for the selected flat-dose daratumumab SC 1800 mg dose:

- At the recommended dose of daratumumab SC 1800 mg, and the same dosing schedule as daratumumab IV 16 mg/kg, the predicted target saturation at the maximal trough concentrations was highly consistent (ie, >97.5%) across different body-weight subgroups although there may be some difference in the predicted maximal trough concentrations among the subgroups.
- Across body-weight range, the maximum Ctrough (Cycle 3 Day 1 predose) was higher than the concentration at 99% effect of 253 µg/mL for the majority of subjects.
- The clinical primary analysis demonstrated that daratumumab 1800 mg was well tolerated: the E-R analyses of AEs showed that there were flat E-R relationships for IRRs and neutropenia.

Immunogenicity: The incidence of treatment-emergent anti-daratumumab antibodies for daratumumab SC treatment was low, with 1 of 426 subjects (0.2%) being positive for anti-drug antibodies (ADAs). The 1 subject in monotherapy who was positive for anti-daratumumab also had transient neutralizing antibodies. There were no treatment-emergent anti-daratumumab positive subjects in the combination therapy study (MMY2040). Daratumumab exposure was comparable in subjects that were antibody negative and those with anti-daratumumab antibodies or NAbs. See Table 17.

Table 11 **Anti-daratumumab Antibody Status; Daratumumab Immunogenicity-evaluable Analysis Set (MMY1004 Part 2, MMY1008, MMY3012, MMY2040)**

	Daratumumab IV	Daratumumab SC		
	MMY3012	Pooled Monotherapy	Pooled Combination	Total
Analysis set: daratumumab immunogenicity-evaluable for subjects with appropriate samples[a]	204	236	190	426
Subjects positive for anti-daratumumab antibodies[b,c]	1 (0.5%)	1 (0.4%)	0	1 (0.2%)
Peak titer				
1:20	1	1	0	1
Subjects positive for neutralizing antibodies[d]	0	1	0	1
Subjects negative for anti-daratumumab antibodies[b]	203 (99.5%)	235 (99.6%)	190 (100.0%)	425 (99.8%)

IV=intravenous; SC=subcutaneous.

[a] Subjects who received at least 1 dose of daratumumab SC or daratumumab IV and had appropriate serum samples for detection of antibodies to daratumumab (at least 1 sample after the start of the first dose of daratumumab).

[b] Percentages are calculated with the number of subjects with appropriate sample as the denominators.

[c] Includes all subjects who had at least 1 positive sample at any time after start of treatment, including those who did not have a baseline sample. Baseline positive subjects were included only if post-treatment sample titers increased by at least 2-fold compared with baseline.

[d] Only samples positive for anti-daratumumab antibodies from anti-daratumumab positive subjects were assayed for neutralizing antibodies.

Note: The pooled monotherapy column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008; the pooled combination column includes subjects from all 3 cohorts in MMY2040.

Source: Mod5.3.5.3/ISS/AttLPKIR01

- A total of 18 of 420 (4.3%) subjects were positive for anti-rHuPH20 antibodies at baseline prior to administration of daratumumab SC. The incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 6.4% (27/420), with 6.9% (16/233) in the monotherapy

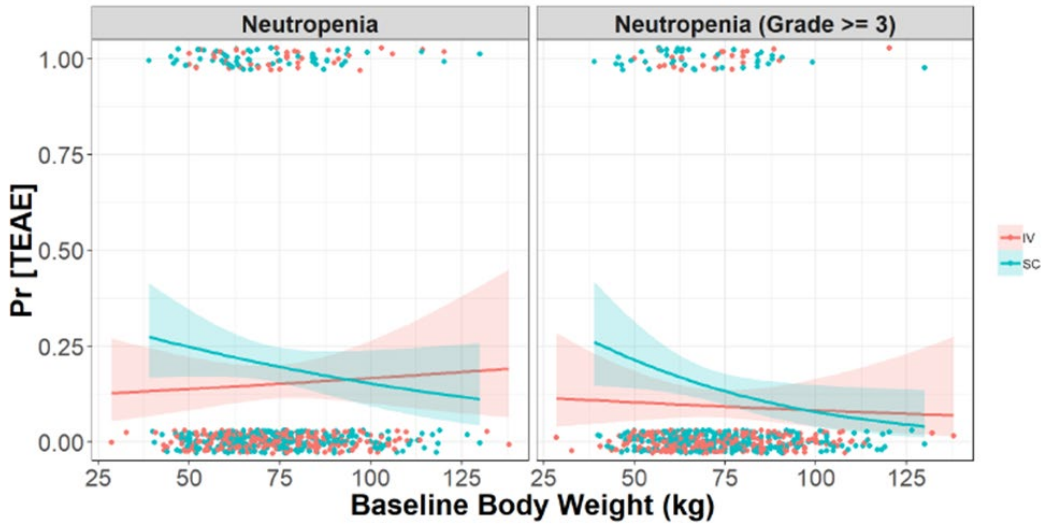
daratumumab SC groups, and 5.9% (11/187) in the pooled combination daratumumab SC groups.

2.4.3.2. Secondary pharmacology

Neutropenia

In monotherapy studies, the event rate of neutropenia (any grade and Grade 3 or higher) was higher in subjects with lower body weights following daratumumab SC compared with subjects with lower body weights following daratumumab IV (Figure 9).

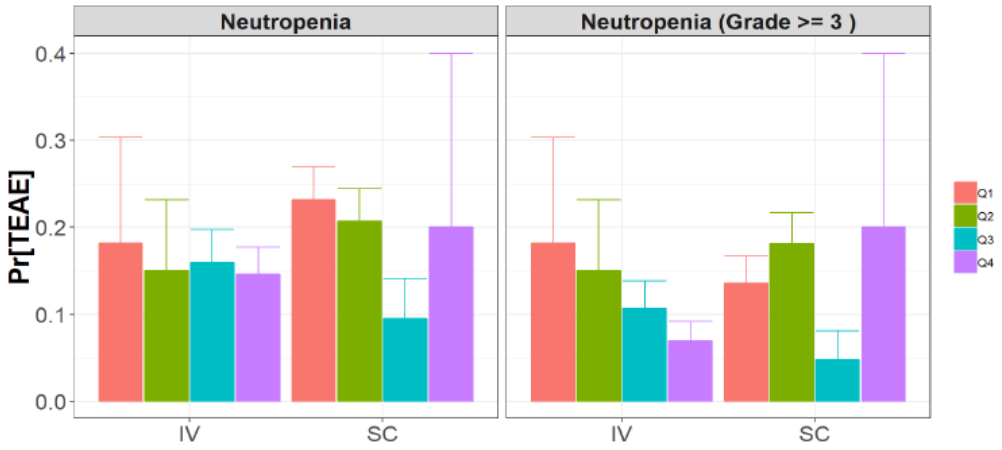
Figure 7 **Incidence Rate of Neutropenia (Any Grades and Grade 3 or Higher) in Relation to Baseline Body Weight After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy**



Abbreviations: IV=intravenous; Pr=probability; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Key: The lines represent the predicted mean curves and the shaded regions are the 95% confidence intervals. Dots represent the observed rate of TEAE.

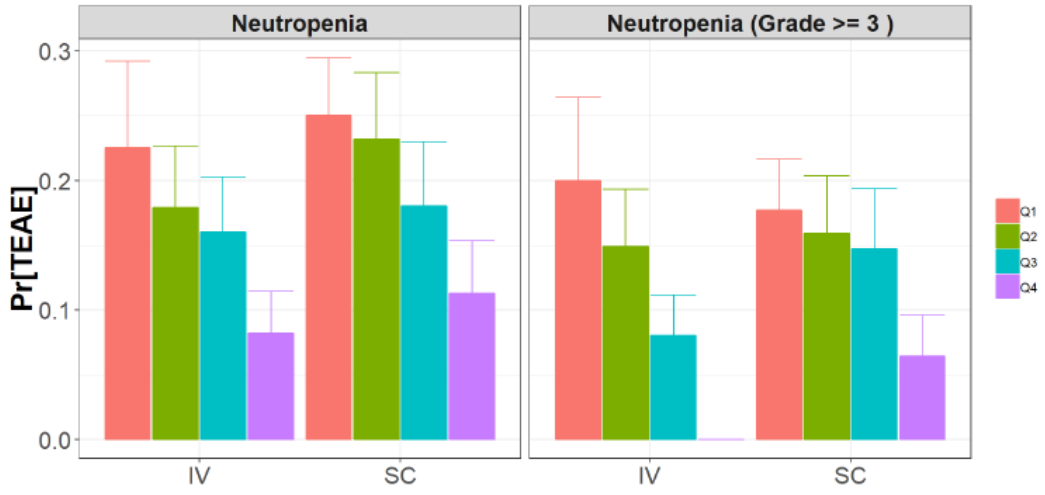
Given lower body weight subjects have higher exposure, the probability of neutropenia with increasing exposure was evaluated. The E-R analysis using the exposure metrics of Cmax after first dose (not confounded by dose interruption or dose delay) demonstrated that there was no apparent relationship between incidence of neutropenia and daratumumab exposure after daratumumab SC 1800 mg monotherapy (Figure 10, Figure 11).

Figure 8 **Rate of Neutropenia (Any Grades and Grade 3 or Higher) in Relation to Daratumumab Peak Concentrations After First Dose (by Quartiles) After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy**



Abbreviations: IV=intravenous; Pr=probability; Q=quartile; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Key: The quartiles for peak concentrations after first dose are: Q1 (8.68 to 124 µg/mL), Q2 (124 to 194 µg/mL), Q3 (194 to 254 µg/mL), and Q4 (254 to 807 µg/mL).

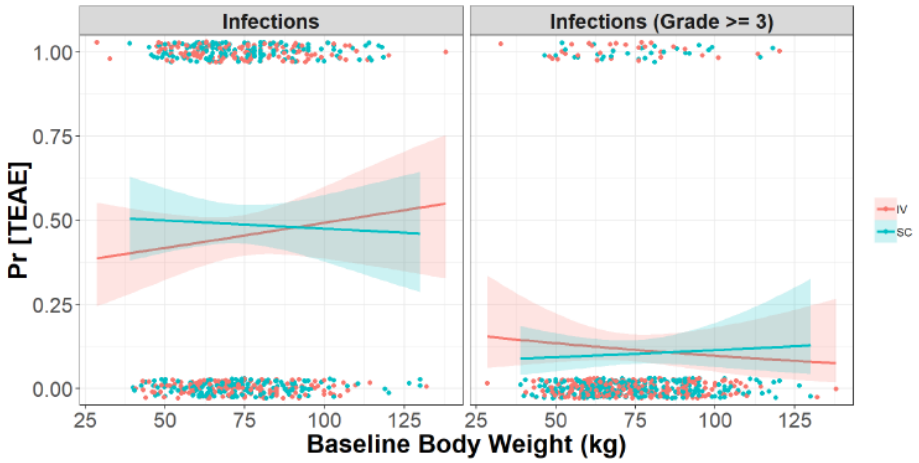
Figure 9 **Rate of Neutropenia (Any Grades and Grade 3 or Higher) in Relation to Overall Daratumumab Peak Concentrations (by Quartiles) After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy**



Abbreviations: IV=intravenous; Pr=probability; Q=quartile; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Key: The quartiles for overall peak concentrations are: Q1 (≤440 µg/mL), Q2 (440 to 641 µg/mL), Q3 (641 to 860 µg/mL), and Q4 (860 to 1,980 µg/mL).

Although slightly higher neutropenia rates were observed at lower body weights following the daratumumab SC 1800 mg administration a flat relationship was observed with body weight for both infections (any grade) and infections (Grade 3 or higher) (Figure 12).

Figure 10 **Incidence Rate of Infections (Any Grades and Grade 3 or Higher) in Relation to Baseline Body Weight After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy**



Abbreviations: IV=intravenous; Pr=probability; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Key: The lines represent the predicted mean curves and the shaded regions are the 95% confidence intervals. Dots represent the observed rate of TEAE.

The incidence rate of neutropenia (any grade and Grade 3 or higher) was increasing with lower body weights following daratumumab SC. The mean rate of neutropenia (any grade and grade 3 or higher) was similar across exposure quartiles for IV and SC, however the confidence interval for the highest exposure subgroup expressed as Cmax after the first dose (<254 ng/mL) was markedly increased following SC administration. This was effect was not present after multiple dosing. There was no relation between incidence of infections and body weight following daratumumab IV or SC.

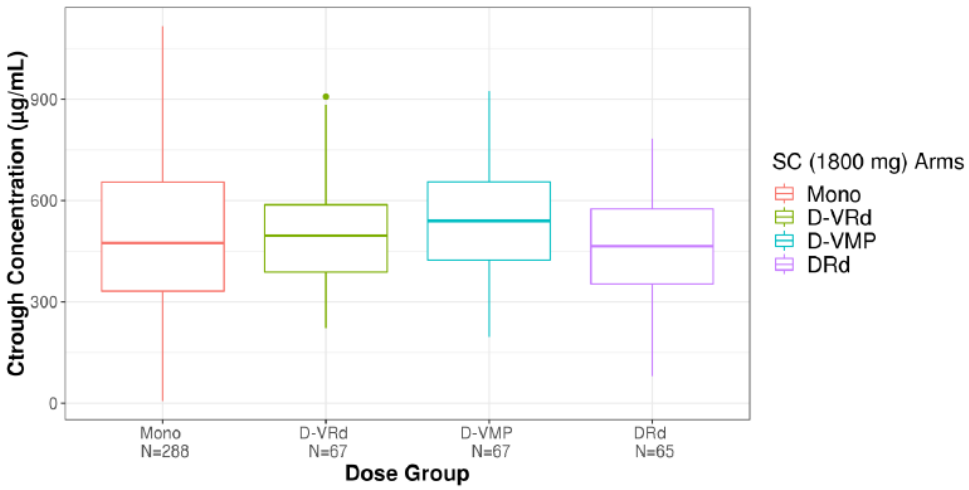
2.4.4. Pharmacodynamic interactions with other medicinal products or substances

Combination therapy with daratumumab SC 1800 mg and common small molecule treatment for multiple myeloma was studied in Study 2040 (N=122) in three study cohorts:

- D-VRd (multiple myeloma transplant eligible): bortezomib, lenalidomide, and low dose dexamethasone, dosing once weekly for Cycles 1-3 and a single dose on Day 1 of Cycle 4 (21-day cycles).
- D-VMP (multiple myeloma ineligible for transplant): bortezomib, melphalan, and prednisone, daratumumab dosing once weekly for Cycle 1 followed by every 3 weeks for Cycles 2-9, then every 4 weeks thereafter (42-day cycles for Cycles 1-9 and 28-day cycles thereafter).
- D-Rd (relapsed or refractory multiple myeloma): lenalidomide, and low dose dexamethasone, daratumumab dosing once weekly for Cycles 1 and 2 followed by every 2 weeks for Cycles 3-6, then every 4 weeks thereafter (28-day cycles).

PK results across studies (mono- and combination therapy) are tabulated in Section 2.1.8 Table "Amendment 3". The simulated trough concentrations following six weekly doses of daratumumab SC 1800 mg for combination therapies were compared with that for monotherapy in Figure 13.

Figure 11 **Simulated Daratumumab Serum Trough Concentrations After 6 Weekly Doses of Daratumumab SC 1800 mg Administration for Monotherapy or Combination Therapies**



Abbreviations: C_{trough}=predicted trough concentration; DRd=daratumumab SC, lenalidomide, and dexamethasone; D-VMP=daratumumab SC, bortezomib, melphalan, and prednisone; D-VRd=daratumumab SC, bortezomib, lenalidomide, and dexamethasone; Mono=monotherapy; N=maximum number of subjects with data; SC=subcutaneous.

Daratumumab SC in combination with common small molecule treatment of multiple myeloma was studied in study MMY2040. The mean Ctrough at Cycle 3 Day 1 was comparable between treatment cohorts D-VMP, D-Rd and D-VRd (392, 526 and 450 µg/mL respectively) and slightly lower than mean Ctrough after monotherapy, 593 µg/mL (Study MMY3012). This effect on PK was not considered clinical relevant, which is supported.

No data on the effect of concomitant treatment with antivirals, antibacterials, analgesics and other medicinal products commonly used in patients with multiple myeloma were submitted.

2.4.5. Relationship between plasma concentration and effect

The purpose of the exposure-response analysis was to supplement the evidence of efficacy and safety of daratumumab in the subjects after SC injection of daratumumab co-formulated with rHuPH20 and to confirm the selected SC dose of 1800 mg.

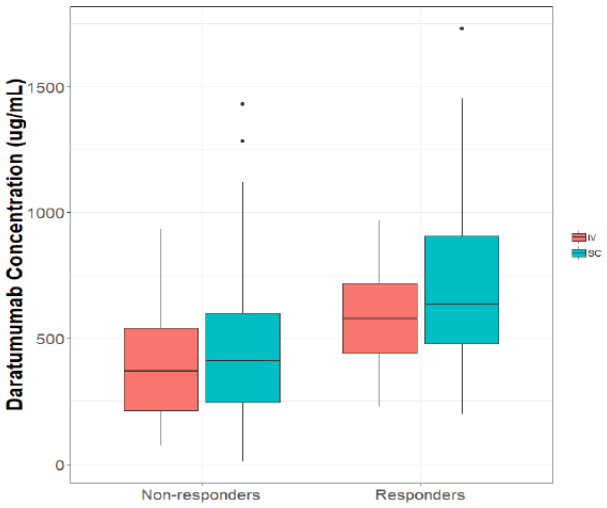
The E-R analysis for daratumumab monotherapy was based on data from studies MMY1004 Part 2, MMY1008 and MMY3012; the E-R analysis for combination therapies was based on data from study MMY2040.

Efficacy

Examination of the relationship between ORR and maximum trough concentrations suggested a similar exposure-efficacy relationship between daratumumab SC and daratumumab IV. See "Box Plot". Cross-study comparisons with data from Studies MMY3003 (in which subjects received DRd) and MMY3007 (in which subjects received D-VMP) indicated a similar E-R relationship for efficacy between daratumumab SC and daratumumab IV for both DRd and D-VMP combinations.

Figure 12

Box Plot for Daratumumab Maximum Trough Concentrations for Nonresponders and Responders After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy



Abbreviations: IV=intravenous; SC=subcutaneous.

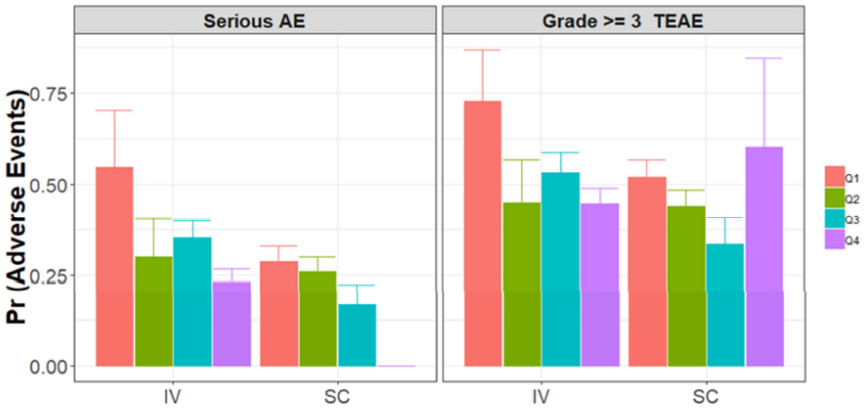
Daratumumab SC produced higher trough concentrations in both responders and nonresponders, and slightly higher ORRs compared with the approved daratumumab IV (Figure 15).

For combination therapy, a high ORR was observed across the studied concentration range, indicating that maximum efficacy in terms of ORR were attained for daratumumab SC 1800 mg. Cross-study comparisons for DRd group with Study MMY3003 (daratumumab IV, lenalidomide, and dexamethasone) and for D-VMP with Study MMY3007 (daratumumab IV, bortezomib, melphalan, and prednisone) indicated a similar E-R relationship for efficacy for daratumumab SC as for daratumumab IV, for both DRd and D-VMP combinations.

Safety

The E-R relationship for safety was explored for selected AEs, including overall SAEs, overall Grade 3 or higher TEAEs, and neutropenia. Both the peak daratumumab concentrations after the first dose, and the overall peak concentrations were investigated for their potential relationship with the other AEs. To mitigate the effect from dose interruption, modification or discontinuation, peak concentrations (Cmax) after first dose was used as an exposure metric. See Figure "Rate of SAE..". No relationship was observed between exposure and safety endpoints (SAEs and Grade 3 or higher TEAEs) using the peak concentrations after the first dose. For combination of daratumumab SC with bortezomib, lenalidomide, and dexamethasone (VRd), VMP, and lenalidomide-dexamethasone (Rd), no E-R relationship for safety was observed.

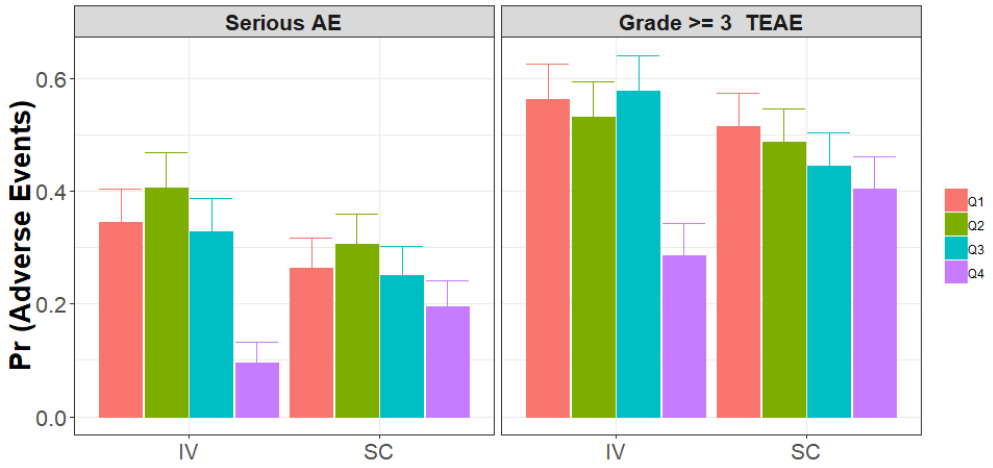
Rate of SAE and Grade 3 or Higher TEAE in Relation to Daratumumab Peak Concentrations (by Quartiles) After the First Dose of Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy



Abbreviations: AE=adverse event; IV=intravenous; Pr=probability; Q=quartile; SAE=serious adverse event; SC=subcutaneous; TEAE=treatment-emergent adverse event.
Key: The quartiles for overall peak concentrations are: Q1 (≤440 µg/mL), Q2 (440 to 641 µg/mL), Q3 (641 to 860 µg/mL), and Q4 (860 to 1,980 µg/mL).

To mitigate the impact of route of administration on daratumumab exposures, the MAH performed additional exposure-safety analyses to assess the probability of serious AEs and Grade 3 or higher TEAEs in relation to predicted peak concentration after first dose, based on exposure quartiles defined for daratumumab IV and SC administration separately.

Probability of Serious AEs and Grade 3 or Higher TEAEs in Relation to Predicted Peak Concentration After First Dose by Quartiles Based on a Dataset from IV and SC Subjects Separately for Monotherapy*



AE=adverse event; IV=intravenous; Pr=probability; Q=quartile; SC=subcutaneous; TEAE=treatment-emergent adverse events
*Data from Studies MMY3012, MMY1004, and MMY1008.

Overall, there appeared to be no apparent trend of increase in the probability of Grade 3 or higher TEAEs with increase daratumumab SC exposure when the totality of data was evaluated (from Q1 to Q4).

2.4.6. Discussion on clinical pharmacology

A validated electrochemiluminescence-based immunoassay was used for quantitation of daratumumab in serum samples. Carry-over was not investigated. Bioanalysis of daratumumab SC in studies MMY1004, MMY1008, MMY2040 and MMY3012 was performed at Frontage Satellite Laboratory in Exton, PA or in-house at Janssen. The method was cross-validated between sites. The in-study performance of the daratumumab assay was overall considered acceptable for daratumumab SC. For the SC program, the Applicant has agreed to re-assess immunogenicity of daratumumab by re-analysis of ADA samples taken in studies MMY1004, MMY1008, MMY3012 and MMY2040 using the new PandA screening assay. The tissue permeability enhancer rHuPH20 was not measurable in serum according to the Applicant and no bioanalysis of rHuPH20 was performed. rHuPH20 immunogenicity was assessed by use of validated assay.

Standard software and methods were used for pharmacokinetic data analysis. The Pop PK population consisted of data from 742 patients or 5305 data points. BLQ data (less than 3% of the data set) was excluded by the M1 method for parameter estimation but included in the final dataset. The exponents for weight on clearance and volume are 1.24 and 0.91; which is different to those expected for allometry (0.75 and 1, respectively). The intra-individual variability is moderate, 34.8%. The inter-individual variability is high (>36%) for all PK parameters. GoF plots showed a number of data points <1000 hrs with CWRES outside the ±5 limits. The Applicant did an additional sensitivity analysis, excluding 22 outliers with CWRES ≥5 in the final population PK model. The exclusion did change the estimates of the parameters slightly and did improve precision of the model. The effect was largest at the highest concentrations (Cmax). However, as there were outlier concentrations from both IV and SC administrations, it is considered acceptable that they are included in the final model as they would not impact the non-inferiority evaluation.

VPCs showed the model underpredicted long term exposure (after 1500 hrs) with wide confidence intervals. Similar trends were shown for both IV and SC data thus the model predicted daratumumab SC concentrations with similar precision as daratumumab IV. Therefore, the final Pop PK model is considered acceptable for predicting daratumumab SC exposure metrics. Immunogenicity was not evaluated as a covariate in the Pop PK analysis. However, exposure profiles did not seem to be affected in the ADA positive subjects (n=2 and 20 for ADA against daratumumab and rHuPH20, respectively).

Sex, IgG myeloma, baseline albumin and weight were identified as significant covariates for daratumumab SC exposure. No dose modifications were recommended. This is agreed except for weight. It was agreed that data available for patients above 120 are limited to make any dose recommendation. This is reflected in the SmPC of the product and the company has committed to submit efficacy data from ongoing studies in the subgroup of patients.

The rate of absorption was estimated to 0.012 h^{-1} based on Pop PK. No formal bioavailability study was performed. The bioavailability after SC injection was estimated to 68.9% by Pop PK. All clinical daratumumab SC data included in the Pop PK population used the commercial SC formulation. No bioequivalence studies were conducted. Food effect was not investigated. The mean volume of distribution was estimated to 5,25 L (V1) and 3.78 L (V2) by Pop PK analysis. The Pop PK estimated linear clearance is 4.96 mL/h and the associated mean half-life 20.4 days. After combination therapy, the half-life ranged from 23-27 days. In studies, steady-state was reached after 5 months at the proposed dose schedule for daratumumab SC monotherapy. Daratumumab is biotransformed as other endogenous IgG's. Variations in drug metabolising enzymes are not expected to affect the elimination of daratumumab. Dose proportionality was evaluated between doses 1200 mg SC (n=4) and 1800 mg SC in study MMY1004, using the explorative formulation Dara-MD. The commercial formulation Dara-CF gave about 30% higher exposure than the Dara-MD formulation following 1800 mg SC for 8 weeks.

For daratumumab IV formulation, dose proportionality has been shown for doses ≥1 mg/kg. The MAH argues that the PK profiles for Dara-CF and Dara-MD SC are similar to daratumumab IV, and that the time- and concentration-dependent PK are similar. It was agreed that this supports dose proportionality between 1200 mg SC and 1800 mg SC.

Daratumumab elimination showed both dose- and time-dependent clearance. Clearance decreased with increasing doses and with multiple dosing due to target depletion. Daratumumab SC accumulated over time with an accumulation ratio of 4.8 and 5.4, after eight weekly doses at 1800 mg SC, for Cmax and AUC0-7, respectively. The intra-individual variability determined by PopPK is moderate (34.8%), while the inter-individual variability is moderate to high for PK parameters (36.9% for V1, 58.7% for CL, 67.4 for Vmax, 145.9% Kdes and 36.1% for Ka). The inter-individual variability for exposure parameters ranged from 37.8% to 50.8% in Study MMY1004 with rich PK sampling. All clinical studies in the daratumumab SC program were conducted in patients with multiple myeloma.

Observed mean exposure (Ctrough at Cycle 3 Day 1) was comparable after SC and IV administration in Study MMY3012. This exposure level was also comparable to the simulated Cycle 3 Day 1 Ctrough by Pop PK analyses. AUC0-7d was simulated in Cycle 1 after 1st weekly dose to 720 and 1187 µg/mL×day and prior to Cycle 3 Day 1 to 4017 and 4019 µg/mL×day for daratumumab SC and IV respectively. AUC0-28d after Q4W dosing (representing steady-state) was simulated to 5887 and 5206 µg/mL×day for SC and IV respectively. The simulated increase in AUC at steady-state after SC dosing corresponds to 13%. Further safety implications are not expected since the higher steady-state exposure following 1800 mg SC administration are within exposures observed in daratumumab IV clinical studies.

Non-inferiority between SC and IV administration was evaluated by means of C_{trough} after sparse sampling and not AUC. The simulated concentration-time profiles and observed C_{trough} values for SC and IV were comparable.

In Study MMY1004 and MMY1008 mean Ctrough values seemed notable higher than observed in Study MMY3012 after a similar dosing schedule and formulation. The Applicant argued that differences in study characteristics could explain the higher mean Ctrough observed in studies MMY1004 and MMY1008 compared to MMY3012. There was a notable smaller sample size in studies MMY1004 (n=25) and of MMY1008 (n=6) compared to MMY3012 (n=257). This explanation was accepted.

In the combination therapy dataset, the geometric mean values for Ctrough after 6 weekly doses were: normal (441 µg/mL, N=69), mild (480 µg/mL, N=77), and moderate or severe (522 µg/mL, N=53). Generally, the moderate renal impairment group had slightly higher Ctrough, but the difference is not considered to be significant or clinically meaningful.

Very few subjects with moderate or severe hepatic impairment were represented in the daratumumab SC program in both the monotherapy (N=0) and combination therapy (N=1) dataset to make meaningful conclusions for daratumumab SC dosing for these hepatic subgroups. This is also reflected in the SmPC of the product.

In the pooled population PK analyses of daratumumab SC in subjects with multiple myeloma, gender had a statistically significant effect on V1. However, it did not have a significant overall effect on exposure and is not considered to have clinical relevance.

No interaction studies were conducted with daratumumab SC. Daratumumab is biotransformed like other endogenous IgGs. No interactions with concomitant medications are expected.

Exposure-response relationships were investigated by means of exploratory regression models. Simulations showed a similar target saturation with the daratumumab SC 1800 mg dosing schedule as observed for the approved daratumumab IV dosing schedule for multiple myeloma.

The baseline and treatment-emergent immunogenicity incidence for anti-rHuPH20 antibodies were consistent with literature reports (Rosengren 2015) and as seen for Rituxan Hycela and Herceptin Hylecta Daratumumab exposure was comparable between antibody negative subjects and those with anti-rHuPH20 antibodies.

The incidence rate of neutropenia (any grade and Grade 3 or higher) was increasing with lower body weights following daratumumab SC. The mean rate of neutropenia (any grade and grade 3 or higher) was similar across exposure quartiles for IV and SC, however the confidence interval for the highest exposure subgroup expressed as Cmax after the first dose (<254 ng/mL) was markedly increased following SC administration. This was effect was not present after multiple dosing. There was no relation between incidence of infections and body weight following daratumumab IV or SC.

Daratumumab SC in combination with common small molecule treatment of multiple myeloma was studied in study MMY2040. The mean Ctrough at Cycle 3 Day 1 was comparable between treatment cohorts D-VMP, D-Rd and D-VRd (392, 526 and 450 µg/mL respectively) and slightly lower than mean Ctrough after monotherapy, 593 µg/mL (Study MMY3012). This effect on PK was not considered clinical relevant, which is supported. No studies on the effect of concomitant treatment with antivirals, antibacterials, analgesics and other medicinal products commonly used in patients with multiple myeloma were submitted. Daratumumab acts through multiple MoA's and are eliminated independent of CYPs, hence genetic differences are not expected to result in different PD responses.

Responders (ORR) had slightly higher exposure compared to non-responders with no difference for SC or IV. According to the Applicant, no relation was established between safety end points and daratumumab exposure. This is not agreed. The probability for adverse events was slightly lower for SC compared to IV across concentration quartiles, with a trend of less events with increasing exposure. Patients after SC treatment in the high exposure quartile Q4 had a lower probability for Serious AEs but notable higher probability of Grade 3 or higher TEAE's as compared to IV. Overall, there appeared to be no apparent trend of increase in the probability of Grade 3 or higher TEAEs with increase daratumumab SC exposure when the totality of data was evaluated (from Q1 to Q4)

The clinical pharmacology was adequately addressed.

2.4.7. Conclusions on clinical pharmacology

The clinical pharmacology for daratumumab SC was described in 4 clinical studies in patients with multiple myeloma: MMY1004, MMY1008, MMY2040 and MMY3012. The bioanalysis and PK evaluation was overall acceptable. Evaluation of immunogenicity status of daratumumab SC was not considered acceptable and should be re-assessed using a newly developed analytical method.

Non-inferiority between SC and IV administration was evaluated by means of C_{trough} after sparse sampling and not AUC. The simulated concentration-time profiles and observed C_{trough} values for SC and IV were comparable. Non-inferiority was established between the approved daratumumab IV dose regimen (16 mg/kg) and daratumumab SC (1800 mg) based on sparse sampling Ctrough as exposure metric and not AUC. Similar significant covariates were identified for daratumumab SC as for IV with no recommendations for dose modification. Concomitant daratumumab SC with common small molecule treatment for multiple myeloma was evaluated in Study 2040. The proposed dosing schedules resulted in similar daratumumab exposure levels. It was agreed that data available for patients above 120 kg body weight are too limited to make any dose recommendation. This is reflected in the SmPC of the product and the company has committed to submit efficacy data from ongoing studies in the subgroup of patients.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- to re-assess immunogenicity of daratumumab by re-analysis of ADA samples taken in studies MMY1004, MMY1008, MMY3012 and MMY2040 using the new PandA screening assay.
- concerning patients above 120 kg are limited to make any dose recommendation.

2.5. Clinical efficacy

The clinical studies which provide the basis for evaluation of the efficacy of subcutaneous (SC) daratumumab in Multiple Myeloma (MM), consists of the pivotal phase 3 study MMY3012 of monotherapy daratumumab, and the phase 2 study MMY2040, where daratumumab is combined with standard background therapies in MM. Further two supportive studies have been submitted.

Tabular overview of clinical studies

Table 12 **Overview of Clinical Studies Included in This Submission**

Study ID	Study Title	Primary Objectives	Number of Subjects
Monotherapy in Relapsed/Refractory Multiple Myeloma			
MMY3012	A Phase 3 Randomized, Multicenter Study of Subcutaneous versus Intravenous Administration of Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma	To show that SC administration of daratumumab co-formulated with rHuPH20 (ie, daratumumab SC) is non-inferior to IV administration of daratumumab (ie, daratumumab IV) in terms of the ORR To show that daratumumab SC is non-inferior to daratumumab IV in terms of maximum C_{trough} (Cycle 3 Day 1 predose)	N=522 daratumumab SC: 263 daratumumab IV: 259
MMY1004	An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab with the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma	Part 1: To evaluate the PK and safety of the SC delivery of daratumumab Part 2:[a] To evaluate the PK and safety of the SC delivery of daratumumab	N=78 Part 1: 1200 mg daratumumab SC[a]: 8 1800 mg daratumumab SC[a]: 45 Part 2: 1800 mg daratumumab SC[a]: 25
MMY1008	A Phase 1 Study of Subcutaneous Delivery of JNJ-54767414 (Daratumumab) in Japanese Subjects With Relapsed or Refractory Multiple Myeloma	To evaluate the tolerability and safety of SC delivery of daratumumab SC in Japanese subjects with relapsed or refractory multiple myeloma	N=6
Combination Therapy in Newly Diagnosed or Relapsed/Refractory Multiple Myeloma			
MMY2040	A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens	To evaluate the clinical benefit of daratumumab SC in combination with standard multiple myeloma regimens in subjects with multiple myeloma as measured by ORR or VGPR or better rate	N=199 D-VMP: 67 D-Rd: 65 D-VRd: 67

C_{trough}=trough concentration; D-Rd=daratumumab SC, lenalidomide, and dexamethasone; D-VMP=daratumumab SC, bortezomib, melphalan, and prednisone; D-VRd=daratumumab SC, bortezomib, lenalidomide, and dexamethasone; IV=intravenous; ORR=overall response rate; PK=pharmacokinetics; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; VGPR=very good partial response

[a] Part 2 of the study evaluated the final, co-formulated preparation of daratumumab 1800 mg and rHuPH20 for SC administration (ie, daratumumab SC, same investigational product examined in Study 3012). Therefore, only data from Part 2 will be included in the submission as supportive data.

2.5.1. Dose response study(ies)

The Phase 1b study MMY1004, is an open-label, nonrandomized, multicenter, dose escalation study (Part 1) to evaluate the pharmacokinetics, safety and anti-tumor activity of SC daratumumab with rHuPH20 to subjects with relapsed or refractory multiple myeloma. Two doses of daratumumab (1200 and 1800 mg) in an intermediate SC formulation were evaluated. Eligible patients had to be ≥18 years of age with documented MM and had undergone prior treatment with ≥2 lines of anti-myeloma therapy. Prior lines of therapy must have included a PI and an IMiD.

A total of 53 patients were included in the Part 1 using a mix- and deliver preparation, 8 subjects in the 1200 mg group and 45 subjects in the 1800 mg group. The 1800 mg dose level provided similar or higher exposure to IV 16 mg/kg daratumumab and was therefore selected for further investigation. Part 2 (dose confirmation) of Study MMY1004 tested a final, co-formulated preparation of a flat dose of daratumumab and rHuPH20, 1800 mg of the same investigational product examined in Study MMY3012. The schedule was identical to that used for all daratumumab SC studies, including Study MMY3012. The peak plasma concentrations of daratumumab SC occurred approximately 72 hours after injection, whereas peak plasma concentration with IV administration occurred at or near the end of the infusion. Assessments of tumor response and disease progression were conducted in accordance with the IMWG response criteria. A validated computerized algorithm based on IMWG criteria was used to determine response and disease progression for each subject. No formal statistical hypothesis testing was conducted.

Response rates and the safety profile (including immunogenicity) for daratumumab SC in Study MMY1004 appeared similar to the approved IV formulation of daratumumab. The incidence of IRRs was 16%. These results indicated that flat dosing of daratumumab (1800 mg) via SC administration is a feasible approach and could bring benefits in terms of reduced administration time and IRRs compared with daratumumab IV. Based on data from studies MMY1004 and MMY1008, daratumumab SC 1800 mg was selected for further evaluation in Phase 2 and 3 studies.

The dose-response study MMY1004 was performed using an experimental, not the commercial daratumumab-MD formulation, at the dose levels 1200 mg and 1800 mg. Only four patients received the 1200 mg dose of daratumumab-MD.

2.5.2. Main study(ies)

Monotherapy MMY3012

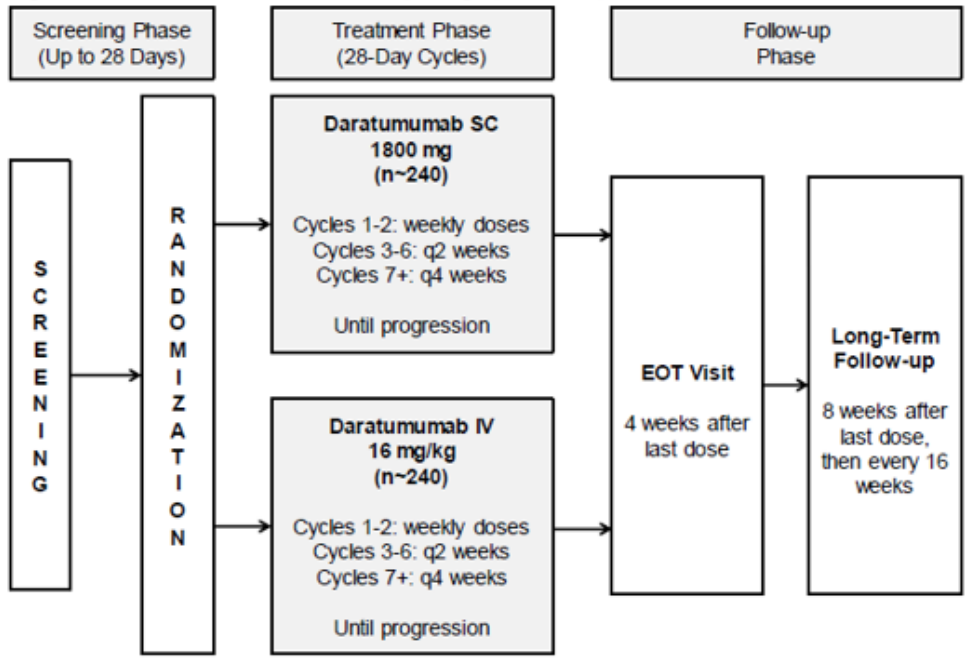
The Study MMY3012 is a Phase 3, randomized, open-label, active-controlled, multicenter study comparing monotherapy of the SC formulation of daratumumab to the IV formulation in subjects with Multiple myeloma who had received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease was double refractory to both a PI and an IMiD. The planned total sample size was approximately 480 subjects, randomly assigned to the Dara-SC group or the Dara-IV group in a 1:1 ratio.

The randomization will be stratified by body weight at baseline ≤ 65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤ 4 prior lines versus >4 prior lines) and type of myeloma (IgG versus non-IgG). The data cutoff for the primary analysis occurred on 08 January 2019, approximately 6 months after the last subject was randomized.

The aim of the study was to demonstrate non-inferiority of SC daratumumab to IV daratumumab with comparable efficacy between both formulations and no clinically meaningful difference in safety except from a lower rate of IRRs for daratumumab SC.

A schematic overview of the study design is provided in Figure 15.

Figure 13 **Schematic Overview of Study Design (MMY3012)**



EOT=End-of-Treatment; q2=every 2; q4=every 4.

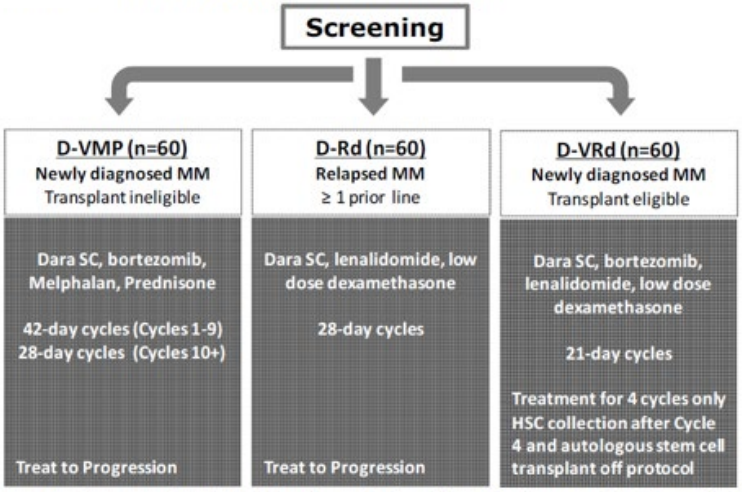
The study consists of 3 phases: a Screening Phase up to 28 days before randomization, a Treatment Phase, and a Follow-up Phase. The Treatment Phase will extend from randomization until discontinuation of study treatment due to disease progression, unacceptable toxicity, or other reasons. The Follow-up Phase begins following the End-of-Treatment Visit, and will continue until death, loss to follow up, withdrawal of consent for study participation, or end of study, whichever occurs first. Treatment cycles are 28 days in length. The dosing schedule for both groups will be weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter. Subjects who are assigned to the Dara-SC group will receive a fixed dose of Dara-SC 1800 mg (daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL). Dara-SC will be delivered by SC injection in the abdominal SC tissue in left/right locations, alternating between individual doses. All subjects in the Dara-SC group will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive injections. Subjects who are assigned to the Dara-IV group will receive Dara-IV 16 mg/kg by IV infusion pump.

Combination Therapy MMY2040

MMY2040 is an open-label, multicenter, Phase 2 study of daratumumab SC in combination with standard MM regimens containing PIs and IMiDs. Patients had newly diagnosed (eligible or ineligible for ASCT), relapsed or refractory MM.

The study design, treatment schedules and backbone therapies are all acceptable, and provided in Fig. 2 and Tables 1-3. The dosing schedules for daratumumab SC were consistent with the approved dosing schedules for daratumumab IV.

Figure 14 **Schematic Overview of Study Design (MMY2040)**



Dara SC=daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated; D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; D-VMP=Dara SC, bortezomib, melphalan, and prednisone; Dara-Rd=Dara SC, lenalidomide, and dexamethasone; HSC=hematopoietic stem cell; MM=multiple myeloma.

Methods

Study Participants

Main Inclusion Criteria

Subjects had to meet all of the following criteria to be enrolled in the study:

Study MMY 3012 and MMY 2040

1. At least 18 years of age.

2. Documented multiple myeloma as defined by the criteria below:

- Multiple myeloma diagnosis according to the IMWG diagnostic criteria.
- Measurable disease at Screening as defined by any of the following:
  - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
  - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

3. ECOG Performance Status score of 0, 1, or 2.

4. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

- hemoglobin ≥7.5 g/dL (≥5 mmol/L) (without prior red blood cells [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
- absolute neutrophil count ≥1.0 × 109/L (prior growth factor support is permitted);
- platelet count ≥50 × 109/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count);
- aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN);
- alanine aminotransferase (ALT) ≤2.5 × ULN;

Study MMY 3012 only

6. Evidence of a response (PR or better based on investigator's determination of response by IMWG criteria) to at least 1 prior treatment regimen.

7. Relapsed or refractory disease as defined below:

- Relapsed disease is defined as an initial response to previous treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.
- Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤ 60 days after cessation of treatment.

8. Received at least 3 prior lines of therapy including a PI (≥2 cycles or 2 months of treatment) and an IMiD (≥2 cycles or 2 months of treatment) in any order during the course of treatment (except for subjects who discontinued either of these treatments due to a severe allergic reaction within the first 2 cycles/months).

or

Refractory to both a PI and an IMiD. For subjects who have received more than 1 type of PI, their disease must be refractory to the most recent one. Similarly, for those who have received more than 1 type of IMiD, their disease must be refractory to the most recent one.

9. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

- total bilirubin ≤2.0 × ULN
- estimated creatinine clearance ≥20 mL/min per 1.73m2.
- albumin-corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

Study MMY2040 only

10. Meets one of the sets of the following criteria:

- For inclusion into the D-VRd cohort for newly diagnosed disease:
- Newly diagnosed MM by IMWG criteria and eligible/planned for high dose therapy and autologous stem cell transplant (ASCT)
- For inclusion into the D-VMP cohort:
- Newly diagnosed and previously untreated MM by IMWG criteria and not considered a candidate for high-dose chemotherapy with ASCT due to:
- Being age ≥65 years, or in subjects <65 years: ineligible to ASCT due to comorbid condition(s)
- For inclusion into the D-Rd cohort:
- Relapsed disease, defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment
- Or refractory disease, defined as either PD by IMWG criteria during previous treatment or ≤ 60 days after cessation of treatment
- Subject must have received at least 1 prior line of therapy for MM
- Subjects must have progressed from or be refractory to their last line of treatment
- Subject must have achieved a response (PR or better based on investigator's evaluation of response by the IMWG criteria) to at least 1 prior treatment regimen

11. Pretreatment clinical laboratory values during the Screening Phase:

- For subjects in whom <50% of bone marrow nucleated cells are plasma cells, platelet count for D-Rd and D-VRd cohorts: >75 × 109/L, for D-VMP cohort: ≥70 x 109/L. Otherwise platelet count ≥50 × 109/L.
- For the D-Rd cohort: total bilirubin ≤2.0 × ULN; for the D-VMP, and D-VRd cohorts: total bilirubin ≤1.5 × ULN.
- Estimated creatinine clearance ≥40mL/min (D-VMP cohort) or ≥30 mL/min (for D-VRd and D-Rd cohorts).
- Corrected serum calcium ≤13.5 mg/dL (≤3.4 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

Main Exclusion Criteria

Study MMY 3012 and MMY 2040

Subjects could not have had any of the following to be eligible for the study:

1. Received daratumumab or other anti-CD38 therapies previously.

2. Received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization.

MMY 2040 only: Refractory to or intolerant to lenalidomide for the lenalidomide-containing cohorts.

3. Prior ASCT within 12 weeks before the date of randomization, or prior allogeneic stem cell transplant (regardless of timing).

4. History of other malignancy unless all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease. Further exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, considered cured with minimal risk of recurrence within 3 years.

5. Clinical signs of meningeal involvement of multiple myeloma.

6. Chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted normal/moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently uncontrolled asthma of any classification.

7. Seropositive for HIV, positive test for HBsAg. Subjects positive to antiHBc and/or positive to antiHBs must be screened using real-time PCR measurement of HBV DNA levels. Those who are PCR positive will be excluded unless with serologic findings suggestive of HBV vaccination (antiHBs positive) AND a known history of prior HBV vaccination.

8. Seropositive for hepatitis C.

9. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, including clinically significant cardiac disease.

10. Known allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, mAbs, human proteins, or their excipients, or known sensitivity to mammalian-derived products.

11. Plasma cell leukemia (>2.0 × 109/L circulating plasma cells), POEMS syndrome, Waldenström's macroglobulinemia or amyloidosis.

13. *MMY 2040*: For D-VMP cohort: Neuropathy or neuropathic pain ≥ Grade 2, as defined by (NCI CTCAE) Version 4.03.

Treatments

Dara-SC will be provided as a fixed-dose of 1800 mg (combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL)), the volume being 15 ml administered by manual push over 3-5 minutes in the abdominal SC tissue in left/right locations, alternating between individual doses. Dara-IV will be provided as in previous studies and according to the SmPC.

The dose and schedule of daratumumab, bortezomib, lenalidomide, melphalan, prednisone and dexamethasone are in line with clinical practice and acceptable. The guidelines for prevention and management of infusion-related reactions due to daratumumab are in line with clinical practice and the SmPC, (see the AR for details).

Study MMY 3012

Each treatment cycle is 28 days. Study drug will be administered once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and then every 4 weeks thereafter. Tight visit windows (±1 day) are required for Day 1 in the first 3 treatment cycles because of the co-primary endpoint assessments at those visits. Changes to within-cycle dosing should not affect Day 1 of the next cycle.

Table 13 **Study Drug (Dara-SC or Dara-IV) Administration Schedule**

Cycle	Schedule	Day 1	Day 8	Day 15	Day 22
Cycles 1-2	Weekly	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)
Cycle 3	Every 2 weeks	Day 1 (±1d)	–	Day 15 (±3d)	–
Cycles 4-6	Every 2 weeks	Day 1 (±3d)	–	Day 15 (±3d)	–
Cycles 7+	Every 4 weeks	Day 1 (±3d)	–	–	–

For dose delays and modification, see protocol for details.

Study MMY 2040

D-VMP Cohort: The Treatment Phase consist of 9 cycles of the VMP regimen (1 Cycle = 6 weeks) with daratumumab. Thereafter, subjects will receive daratumumab monotherapy in 28-day cycles and continue to receive study drugs until disease progression, unacceptable toxicity, or other reasons.

Table 14 **Treatment Schedule and Dosing (D-VMP Cohort)**

Drug, Route of Administration	Dose, Cycle 1 (42-day cycles)	Dose, Cycles 2-9 (42-day cycles)	Dose, Cycles 10+ (28-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15, 22, 29, 36	1800 mg on Days 1, 22	1800 mg on Day 1
Bortezomib, SC	1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29, 32	1.3 mg/m^2 on Days 1, 8, 22, 29	
Melphalan, PO	9 mg/m^2 on Days 1-4	9 mg/m^2 on Days 1-4	
Prednisone, PO	60 mg/ m^2 on Days 1-4	60 mg/ m^2 on Days 1-4	

D-VMP=Dara SC, bortezomib, melphalan, and prednisone; PO=orally; SC=subcutaneous

Prednisone will not be given on days that dexamethasone is given as pre-medication. Instead, dexamethasone will serve as the treatment dose of corticosteroid for Day 1 of Cycles 1 through 9

D-Rd Cohort: Each treatment cycles is approximately 28 days and subjects will continue to receive study drugs until disease progression, unacceptable toxicity, or other reasons.

Table 15 **Treatment Schedule and Dosing (D-Rd Cohort)**

Drug, Route of administration	Cycles 1 & 2 (28-day cycles)	Cycles 3-6 (28-day cycles)	Cycles 7+ (28-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15, 22	1800 mg on Days 1 and 15	1800 mg on Day 1
Lenalidomide, PO	25 mg on Days 1 to 21	25 mg on Days 1 to 21	25 mg on Days 1 to 21
Dexamethasone, IV or PO	40 mg on weekly*	40 mg on Days 1*, 8, 15*, 22	40 mg on Days 1*, 8, 15, 22

D-Rd=Dara SC, lenalidomide, and dexamethasone; PO=orally, IV=intravenous, SC=subcutaneous

* During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose will be given on the day of administration (20 mg) and half the dose will be given via PO administration the day after the administration (20 mg). Subjects older than 75 years or underweight who may be taking the 20-mg dose should receive the entire 20 mg prior to daratumumab administration only.

During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose will be given on the day of administration via IV or PO administration before the administration and half the dose will be given via PO administration the day after the administration. This is applicable only for subjects taking the full 40-mg dose. Subjects on the 20-mg dose should receive the entire 20 mg prior to daratumumab administration. During weeks when no daratumumab administration is administered, dexamethasone will be administered at a dose of 40 mg/week PO (or 20 mg/week PO for subjects ≥75 years or BMI <18.5).

D-VRd Cohort : The Treatment Phase consist of 4 cycles of approximately 21 days. Subjects in the D-VRd cohort will continue to receive the study drugs for a maximum of 4 cycles (see Table 22), if disease progression, unacceptable toxicity, or other reasons, the subject will discontinue treatment before the 4 cycles are completed.

Table 16 **Treatment Schedule and Dosing (D-VRd Cohort)**

Drug, Route of administration	Dose, Cycles 1-3 (21-day cycles)	Dose, Cycle 4 (21-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15	1800 mg on Day 1
Bortezomib, SC	1.3 mg/m^2 on Days 1, 4, 8, 11	1.3 mg/m^2 on Days 1, 4, 8, 11
Lenalidomide, PO	25 mg on Days 1-14	25 mg on Days 1-14
Dexamethasone, IV or PO	20 mg on Days 1, 2, 8, 9, 15, 16	20 mg on Days 1, 2, 8, 9, 15, 16

D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; PO=orally, IV=intravenous, SC=subcutaneous

For subjects with creatinine clearance between 30 and 60 mL/min, the dose of Lenalidomide is 10 mg every 24 hours.

Bortezomib must be administered after the daratumumab administration and may be up to 48 hours, however subsequent doses must be adjusted to account for the delay.

Dexamethasone will be administered at 20 mg weekly for subjects ≥75 years of age or underweight (body mass index [BMI] <18.5). If dexamethasone is given on the daratumumab dosing day, then this will serve as the premedication and no additional dexamethasone administration will be needed.

Objectives and Endpoints

Study MMY 3012

Primary Objectives

To show that SC administration of daratumumab co-formulated with rHuPH20 (ie, daratumumab SC) is non-inferior to IV administration of daratumumab (ie, daratumumab IV) in terms of the ORR and in terms of maximum Ctrough.

Secondary Objectives

- To assess the pharmacokinetics and immunogenicity of daratumumab SC and daratumumab IV
- To evaluate the safety of daratumumab SC and daratumumab IV
- To evaluate the clinical benefit of daratumumab SC and daratumumab IV

- To evaluate the immunogenicity of rHuPH20 following daratumumab SC administration
- To evaluate patient-reported satisfaction with daratumumab SC and daratumumab IV

Primary Endpoints

- ORR, objective response rate, defined as the proportion of subjects who achieve partial response (PR) or better, PR including VGPR, complete response (including stringent complete response [sCR]), during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy
- Ctrough, defined as the concentration at pre-dose on Cycle 3 Day 1

Key Secondary Endpoints

- Rate of Infusion-related Reactions (IRRs) (relevant to both the IV and SC formulation)
- Progression free survival (PFS), defined as the duration from the date of randomization to either progressive disease, or death due to any cause, whichever occurs first
- Response rate of VGPR or better, defined as the proportion of subjects with a response of VGPR or better (VGPR, CR or sCR), during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy
- Response rate of CR or Better, defined as the proportion of subjects with a response of CR or better (CR or sCR), during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy
- Overall survival (OS), defined as the time from the date of randomization to the date of the subject's death due to any cause. Death after end of study will also be considered as an OS event

Study MMY2040

Primary Objectives

To evaluate the clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM as measured by ORR or VGPR or better rate.

Secondary Objectives

- To evaluate safety and pharmacokinetics (PK) of SC administration of daratumumab in combination with standard MM regimens
- To evaluate additional clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM
- To characterize the immunogenicity of daratumumab and rHuPH20 following SC administration
- To evaluate minimal residual disease (MRD) negativity rate in the D-VMP and D-Rd (daratumumab in in combination with lenalidomide and dexamethasone) cohorts.

Primary Endpoints

- ORR, defined as the proportion of subjects with a partial response or better as defined by the IMWG response criteria (D-VMP and D-Rd cohorts)
- VGPR or better rate, defined as the proportion of subjects with a VGPR or better rate as defined by the IMWG response criteria (D-VRd cohort)

Key Secondary Endpoints

- VGPR or better rate, (D-VMP and D-Rd cohort)
- ORR (D-VRd cohort)
- Duration of response (DOR)
- MRD Negative Rate

All responses are according to the International Myeloma Working Group (IMWG) response criteria.

The primary endpoint ORR is fully acceptable in the monotherapy study of daratumumab comparing the SC and the IV formulation, as well as for the combination studies D-VMP and D-Rd cohorts. However, for the D-VRd group, the primary endpoint is VGPR or better. The MAH has justified, that historical data showed, that the ORR for patients treated with VRd and eligible for autologous stem cell transplant (ASCT) was 97% or higher. In order to allow assessment of a clinical benefit of adding daratumumab to the VRd backbone regimen, the MAH therefore decided to use VGPR or better as primary endpoint. This is acceptable.

The MAH has formulated several clinically relevant secondary endpoints in both studies. The MAH has planned to evaluate MRD negativity rate in subjects who received D-VMP and D-Rd. The MAH has clarified, that due to the shortness of the study of D-VRd in transplant eligible patients, only 3 months of treatment, they considered it not appropriate to require patients to undergo a bone marrow procedure for MRD analysis.

Sample size

Study MMY3012

Non-inferiority of Dara SC to Dara IV was defined using a 60% retention of the lower bound (20.8%) of the 95% CI of ORR from Study MMY2002. In the clinical Study MMY2002, a study of 106 subjects with relapsed or refractory multiple myeloma who had received at least 3 prior therapies and who were treated with Dara IV 16 mg/kg, an ORR of 29.2% (95% CI: 20.8%, 38.9%) was observed. The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of Dara SC and a strong indication of similar efficacy from early efficacy and pharmacokinetics data. With a planned 1:1 randomization, 480 subjects (n=240 in the Dara SC group and n=240 in the Dara IV group) will be needed to demonstrate non-inferiority with a power of 80% and a one-sided alpha=0.025, assuming that the true ORR is the same for both groups. The sample size calculation is based on the methodology for the non-inferiority test for non-unity null, as described by Farrington and Manning (1990).

The study recruited 263 subjects in the Dara SC group and 259 subjects in the Dara IV group, 522 in total. The enrolment of the extra 42 Japanese subjects beyond the initially planned 480 subjects was to meet a health authority commitment request.

The study is also designed to establish comparability of maximum C_{trough} between Dara SC and Dara IV. The selection of non-inferiority margin and the choice of alpha level follow the convention for bioequivalence studies. The two formulations of daratumumab will be considered similar if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} on Cycle 3 Day 1 is at least 80% (noninferiority margin of 20%). A one-sided test is selected based on previous analyses that demonstrated a strong relationship between maximum C_{trough} and efficacy. However, there is no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest. With a planned 1:1 randomization, 480 subjects, and a one-sided alpha=0.05, the power will be >95%. This assumes a true ratio of the C_{trough} of 1, a non-inferiority margin of at least 80% of the geometric mean ratio and a coefficient of variation of 0.6.

Study MMY2040

Table 17 **Hypothesis and Power Table**

Cohort	N	H_0	H_1	Power
D-VRd	60	VGPR or better rate ≤50%	VGPR or better rate ≥70%	>93%
D-VMP	60	ORR ≤70%	ORR ≥90%	>98%
D-Rd	60	ORR ≤75%	ORR ≥90%	>90%

In the study MM2040 combination study a naïve comparison with historical trials will be performed. The MAH did not specify which method was used to calculate the confidence interval and neither whether the estimate or the lower bound of the confidence interval will be used for the comparison.

Randomisation and blinding (masking)

Randomization 1:1 in the **study MMY3012** was centralized computer-generated, block randomization was applied based on the stratification factors: body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG). **Study MMY2040** is a single arm study and therefore randomization was not applicable. Both studies are open-label, it is acceptable that they are not blinded.

Statistical methods

The method described by Farrington and Manning (1990) for the non-inferiority of non-unity null is used. In the *Study MMY3012*, the response is measured during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy. Therefore, the primary estimand is discussing the treatment effect in a scenario where patients could discontinue the daratumuab treatment but are not allowed to switch to other anticancer therapies before PD. Non-inferiority of daratumumab SC will be declared if both ORR and C_{though} are meet. The objective of the study is to assess the comparability of daratumumab SC and daratumumab IV without the influence of subsequent therapy. Two different strategies are used to handle intercurrent events. Observations that occurred after treatment discontinuation but before starting a new anticancer therapy were included in the analysis (treatment policy). Observations occurred after starting a new anti-cancer therapy were not included in the analysis (hypothetical strategy). The handling of intercurrent events is concordant with the objectives of the study. Supplementary estimands were requested during the assessment to contextualize the results.

Given that the objective of the study is to demonstrate, at least, non-inferiority of daratumumab SC relative to daratumumab IV, a hypothetical estimand considering the per-protocol population will also be evaluated during the assessment.

For the *Study MMY2040*,

the MAH clarified that the primary estimand in Study MMY2040 is the best response rate (ORR or VGPR or better) prior to any subsequent anticancer therapy for multiple myeloma but ignoring treatment discontinuation (any component of the combination treatment). The ORR or rate of VGPR or better reported in the Study MMY2040 CSR for D-VRd, D-VMP, and D-Rd cohorts were based on disease evaluations prior to start of subsequent anticancer therapy for multiple myeloma, which reflected response to the study treatment without confounding the impact of subsequent therapy.

It is acceptable, that for both studies, MMY3012 and MMY2040, the primary efficacy analysis will be based on the results of a validated computerized algorithm, based on the IMWG response criteria. Although all randomized patients analysis set (ITT) is preferred for the efficacy analyses, both the ITT and the PP-analysis sets are considered equally important for the non-inferiority analyses.

Primary endpoints

The co-primary efficacy endpoint of **the study MMY 3012** is overall response rate (ORR). Subjects with overall responses achieved after the start of subsequent anticancer therapy will not be considered as responders. For each response categories, two-sided 95% Clopper-Pearson exact confidence interval (CI) will be presented by treatment group. Farrington-Manning (FM) test will be used to test the overall response rate. The FM estimate of relative risk with its 2-sided 95% confidence interval and p-value will be reported. If the lower bound of the 95% CI is ≥ 60%, the non-inferiority of Dara SC relative to Dara IV will be concluded. If non-inferiority in ORR is established and the lower limit of the 95% CI of the relative risk is ≥100%, the superiority of Dara SC relative to Dara IV will be concluded. No data imputation will be applied for missing response data.

A sensitivity analysis of ORR based on the per-protocol and response-evaluable analysis sets will be performed in a similar manner as described in the primary analysis.

A sensitivity analysis of ORR, in which disease response is based on investigator assessment according to the IMWG response criteria, will also be performed in a similar manner as in the primary analysis.

A supplementary analysis of ORR based on the first 480 randomized subjects in intent-to-treat analysis set will also be performed in a similar manner as in the primary analysis.

Subjects who switched to another treatment without experiencing PD were censored in the PFS analysis at their last observation before starting the new treatment. Many of the subjects who discontinued did so based on unconfirmed PD and clinical suspicion of progression. In several cases, investigators call PD based on imaging or hypercalcemia, that the algorithm did not agree with. In the ITT population, 12 (4.6 %) and 17 (6.5 %) patients switched to other treatment before PD in the Dara IV and Dara SC arms, respectively. In the answer to OC 32 the MAH presented sensitivity analysis for PFS where these patients are considered events. The results are consistent with those presented in the primary analysis. There are 14 and 9 patients who were considered non-evaluable in the Dara IV and Dara SC arm, respectively. The MAH explained that 4 subjects never received treatment, 14 subjects discontinued before the first post-dose disease assessment and 5 subjects had a first dose closed to the data cut-off date and therefore their assessments were not included in the primary analysis.

The superiority of Dara SC to Dara IV was not demonstrated since the relative risk did not exceed 1, therefore only non-inferiority is assessed in this report.

For **the Study MMY2040**, the ORR is the primary efficacy endpoint for the D-VMP and D-Rd cohorts, and the VGPR or better response rate is the primary efficacy endpoint for the D-VRd cohort. The implementation of Clopper-Pearson exact 90 % CI is agreed for each response rate. A sensitivity analysis based on the investigator assessment was planned. According to the CSR (page 31/1897) the discontinuation rate is 5 (D-VMP), 2 (D-VRd) and 5 (D-Rd). The MAH clarified that according to the protocol subjects who discontinue study treatment before disease progression will continue have disease evaluation every 4 weeks until 8 weeks after the final dose of study drug at which point the subject will be considered as completed in the study. Patients who discontinued treatment were included in the analysis of response rate with their best response. Observations made after the patients started a new anti-cancer therapy were ignored.

There are 1 (D-VRd), 2 (D-VMP) and 2 (D-Rd) patients which are classified as non-evaluable. The MAH explained that 2 subjects who are listed as non-evaluable died before the first post-baseline assessment. Three patients were hospitalized with very poor condition that did not allowed a full evaluation.

Key secondary endpoints for MMY3012 and MMY2040

The key secondary endpoints related to IRRs, VGPR or better, ORR and CR or better, were analyzed in the same way as the primary endpoint. Stratified CMH test will be used, and the CMH estimate of odds ratio and its 2-sided 95% confidence interval and p-value will be reported.

Analysis of PFS and OS will be performed on the ITT analysis set. The Kaplan-Meier method will be used to estimate the distribution of overall PFS and OS for each treatment group. The median PFS and OS with 95% CI will be provided, and the distributions between the 2 treatment groups will be compared using the stratified log-rank test. 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.

Sensitivity analysis were based on investigator assessment according to the IMWG response criteria and will be performed in a similar manner as described above.

Censoring rules for PFS

Table 18 **PFS Event and Censoring Method**

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

The censoring rules are not totally agreed, censoring of patients who did not receive study product and without any post-baseline data is accepted since those patients are very few (Dara IV = 1, Dara SC= 1). However, censoring patients who switched to other anti-cancer therapies (Dara IV = 12, Dara SC= 17) or withdrew consent (Dara IV = 4, Dara SC= 3) or were lost to follow-up (Dara IV = 0, Dara SC= 1) before a PFS event is not endorsed. The reason is that treatment discontinuation/switch could be related to the study treatment. The MAH presented the following sensitivity analyses:

1. Patients who discontinued daratumumab due to any reason before experiencing a PFS event are imputed as PFS events.

2. Patients who discontinued daratumumab and started a new anticancer therapy before experiencing a PFS event are imputed as PFS events. Patients who were lost to follow-up or withdrew consent are censored.

The results of the requested sensitivity analysis to assess the impact of the censoring rules of PFS were concordant with those presented in the primary analysis.

For both analyses, patients still ongoing in the trial should be censored (administrative censoring) as well as patients who did not receive any investigational product and did not have any post-baseline data. According to table TEFPFS03 (CSR page 802) there are no patients censored due to discontinuation due to AE and therefore censoring rules are not defined for those patients. The MAH explained that subjects who discontinue study treatment due to an AE but develop confirmed disease progression or who died prior to the start of other anticancer therapy are considered PD or death. A total of 39 subjects discontinued study treatment due to an AE; 23 of 39 subjects developed confirmed disease progression

or died, 16 subjects were censored due to receiving other anticancer therapy (9 subjects), withdrawal consent to study (1 subject), lost to follow-up (1 subject) or study cut-off (5 subjects).

Duration of response and the MRD negativity rate for the Study MMY2040, was planned in the SAP but not presented in the submission. The MAH clarified that among responders, the median duration of response could not be estimated for either cohort because most responders were alive and progression-free at the time of the primary analysis. In addition, the initial IV studies for these combinations have extensive long-term follow-up. The MAH presented MRD results during the responses D150. The MRD results for patients who had a suspected complete response showed 16.4% and 15.4% MRD negativity by the threshold of 10^{-5} for the D-VMP and D-Rd groups respectively, this is reassuring in a relapse/refractory setting of MM.

Multiplicity control for the primary and secondary endpoints

Non-inferiority of Dara SC relative to Dara IV will be claimed if both endpoints of ORR and maximum Ctrough meet their criteria. Therefore, the overall type I error will be strictly controlled at level of alpha=0.025 (one-sided). In order to control for multiplicity for several secondary endpoints, the MAH used a hierarchical approach. The strategy applied controls the false positive rate at 5 %. For Study MMY2040, no type I error control strategy was defined, neither in the SAP nor in the protocol. The study has only one primary endpoint, and several major secondary endpoints. The p-value of the secondary endpoints is not interpretable since the MAH has not planned for a strategy to prevent multiplicity issues.

The original version of the SAP for study MMY 3012 was dated Feb 6 2018. The SAP was amended in Feb 12 2019, and the section regarding the statistical hypotheses was changed. However, the changes were not described initially by the MAH. The MAH explained that the only clarification changes were in the Amendment 1 of the SAP. The MAH also presented the requested document with track-changes.
The first version of the SAP for study MMY2040 was dated 20 March 2019, and was not amended. It is noted that the SAP was finalized posterior to the data cutoff date (4 March 2019). DoR was not calculated; however this was not reflected in the SAP. The MAH clarified that the SAP was finalized after the data cut-off date and before the database lock. The MAH also wrote in the SAP that DOR may not be mature at the time of the primary analysis.

Table 19 **Summary of Subject Treatment Disposition – Safety Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Analysis set: safety	258	260	518
Subjects who are still on treatment	111 (43.0%)	111 (42.7%)	222 (42.9%)
Subjects who discontinued treatment	147 (57.0%)	149 (57.3%)	296 (57.1%)
Reason for discontinuation			
Adverse event	21 (8.1%)	18 (6.9%)	39 (7.5%)
Death	3 (1.2%)	2 (0.8%)	5 (1.0%)
Physician decision	4 (1.6%)	9 (3.5%)	13 (2.5%)
Progressive disease	114 (44.2%)	112 (43.1%)	226 (43.6%)
Withdrawal by subject	5 (1.9%)	7 (2.7%)	12 (2.3%)
Other	0	1 (0.4%)	1 (0.2%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: Percentages are calculated with the number of subjects in each treatment group as the denominators.
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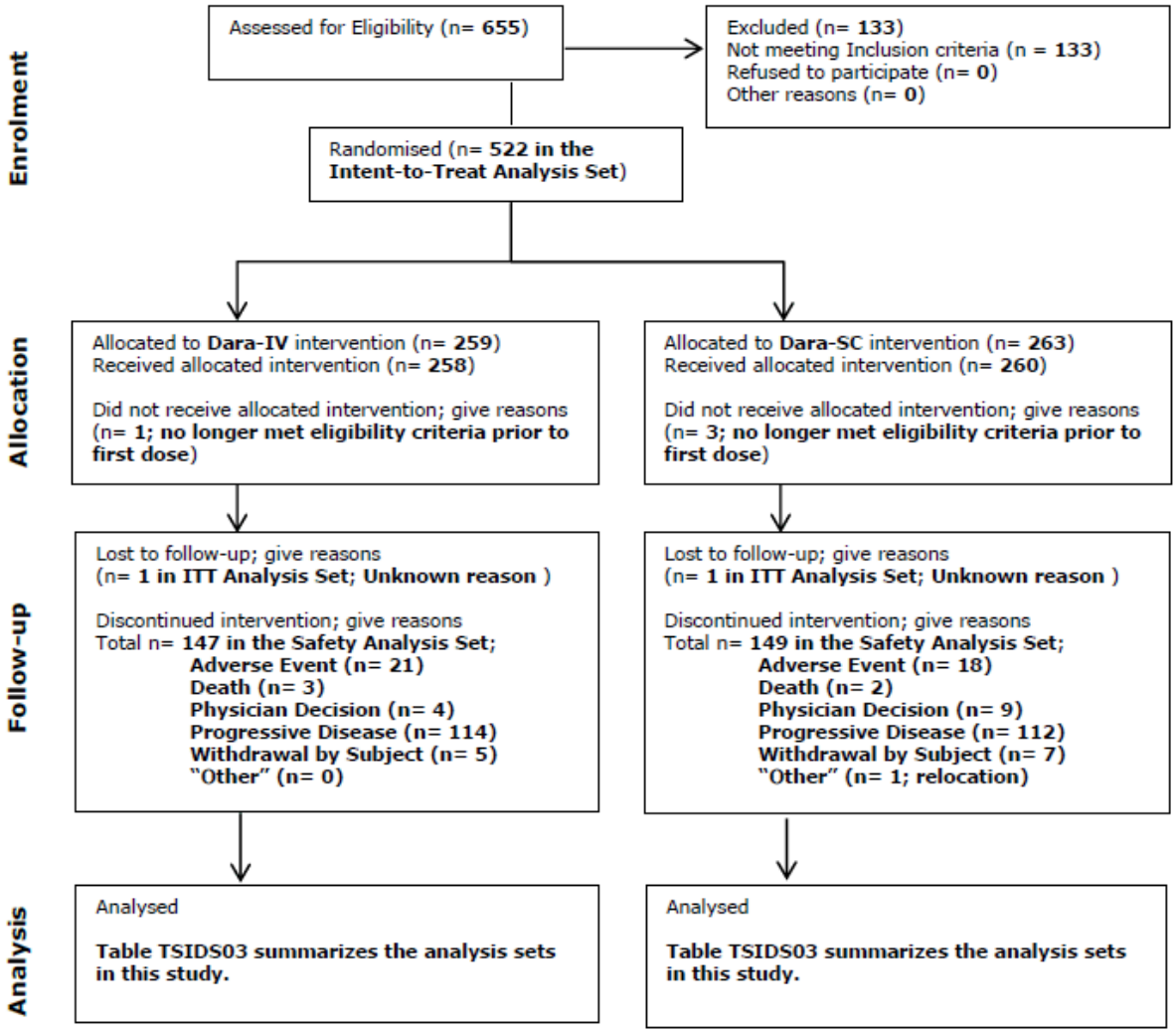
The discontinuation rate was approximately 57% for both Dara IV and Dara SC. The main reason for discontinuation was progressive disease (PD), similar for the Dara SC and the Dara IV arm,43.1% and 44.2% respectively. A high discontinuation rate due to PD is expected in a study with relapsed/refractory MM on monotherapy daratumumab. Adverse events comprised 7.5%, with more AEs in the Dara IV arm. The reported "discontinuation due to physician decision" was higher in the Dara SC arm, as compared with the Dara IV arm. The main reasons were decline in clinical condition, lack of response or suspicion of PD, reasons that are comprehensible in a relapse/refractory setting. No correlation to dosing route or treating Principal Investigator was identified.

It is clear from the figure how many patients that were assesses for eligibility, enrolled, received treatment etc. Table 23 is included in the AR.

Figure 15: ***Participant Flow Diagram (Study MMY3012)***



Dara-IV=daratumumab IV; Dara-SC=daratumumab SC; ITT=intent-to-treat; IV=intravenous
Note: Table TSIDS03 is presented as Table 23 below.

Table 20: ***Summary of Subjects per Analysis Set; All Subjects (Study 54767414MMY3012)***

	Dara IV	Dara SC	Total
Subjects screened			655
Intent-to-treat[a] (ITT)	259 (100.0%)	263 (100.0%)	522 (100.0%)
Safety[b]	258 (99.6%)	260 (98.9%)	518 (99.2%)
Per-protocol[c] (PP)	257 (99.2%)	257 (97.7%)	514 (98.5%)
Response-evaluable[d]	245 (94.6%)	254 (96.6%)	499 (95.6%)
Pharmacokinetics[e]	255 (98.5%)	257 (97.7%)	512 (98.1%)
Pharmacokinetic-evaluable[f]	146 (56.4%)	149 (56.7%)	295 (56.5%)
Immunogenicity-evaluable			
daratumumab[g]	204 (78.8%)	205 (77.9%)	409 (78.4%)
rHuPH20[h]		202 (76.8%)	202 (76.8%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[a] Includes all subjects randomized.
[b] Includes all randomized subjects who received at least 1 dose of study drug.
[c] Includes all treated subjects who had measurable disease at baseline and had no major protocol deviations with respect to eligibility.
[d] Includes subjects who had a confirmed diagnosis of multiple myeloma and measurable disease and must have received at least 1 administration of study drug and had at least 1 post-baseline disease assessment.
[e] Includes subjects who received at least 1 administration of study drug and had at least 1 pharmacokinetics sample concentration value after the first dose administration.
[f] Includes subjects who received all 8 weekly full doses of Dara IV or Dara SC in Cycle 1 and Cycle 2 within the dosing time window and provided a pre-dose pharmacokinetic sample on Cycle 3 Day 1 within the sampling window of 8 hours prior to the start of dose administration
[g] Includes subjects who received at least 1 dose of Dara SC or Dara IV and had at least 1 sample after the start of dose administration.
[h] Includes subjects who received at least 1 dose of Dara SC and had at least 1 sample after the start of dose administration.
Note: Percentages are calculated with the number of subjects in ITT analysis set as the denominators.

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Baseline data

Table 21 **Summary of Demographics – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Analysis set: intent-to-treat	259	263	522
Age (years)			
N	259	263	522
Category, n (%)			
18 -<65	100 (38.6%)	121 (46.0%)	221 (42.3%)
65 -<75	100 (38.6%)	95 (36.1%)	195 (37.4%)
≥ 75	59 (22.8%)	47 (17.9%)	106 (20.3%)
Mean (SD)	66.8 (10.16)	65.3 (9.11)	66.1 (9.66)
Median	68.0	65.0	67.0
Range	(33; 92)	(42; 84)	(33; 92)
Sex, n (%)			
N	259	263	522
Male	149 (57.5%)	136 (51.7%)	285 (54.6%)
Female	110 (42.5%)	127 (48.3%)	237 (45.4%)
Race, n (%)			
N	259	263	522
White	201 (77.6%)	207 (78.7%)	408 (78.2%)
Black or African American	5 (1.9%)	9 (3.4%)	14 (2.7%)
Asian	40 (15.4%)	32 (12.2%)	72 (13.8%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.2%)

Table 22 **Summary of Demographics – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Native Hawaiian or other Pacific Islander	1 (0.4%)	0	1 (0.2%)
Not Reported	12 (4.6%)	14 (5.3%)	26 (5.0%)
Ethnicity, n (%)			
N	259	263	522
Hispanic or Latino	9 (3.5%)	14 (5.3%)	23 (4.4%)
Not Hispanic or Latino	227 (87.6%)	225 (85.6%)	452 (86.6%)
Not Reported	23 (8.9%)	24 (9.1%)	47 (9.0%)
Weight (kg)			
N	258	262	520
Category, n (%)			
≤65	92 (35.7%)	94 (35.9%)	186 (35.8%)
>65 - 85	105 (40.7%)	102 (38.9%)	207 (39.8%)
>85	61 (23.6%)	66 (25.2%)	127 (24.4%)
Mean (SD)	73.72 (17.864)	74.55 (18.240)	74.14 (18.042)
Median	73.00	72.40	72.60
Range	(28.6; 138.0)	(39.0; 130.0)	(28.6; 138.0)
Height (cm)			
N	259	263	522
Mean (SD)	164.49 (11.173)	164.27 (10.813)	164.38 (10.983)
Median	165.00	165.00	165.00
Range	(125.4; 190.0)	(140.0; 194.0)	(125.4; 194.0)
Baseline ECOG score, n (%)			
N	259	263	522
0	88 (34.0%)	64 (24.3%)	152 (29.1%)
1	132 (51.0%)	152 (57.8%)	284 (54.4%)
2	38 (14.7%)	47 (17.9%)	85 (16.3%)
>2[a]	1 (0.4%)	0	1 (0.2%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: ECOG=Eastern Cooperative Oncology Group; N=total number; n=number; SD=standard deviation
Note: Subject baseline body weight could not be collected for 1 subject in each treatment group, both of which were randomized and not treated.
[a] 1 subject who met the eligibility criteria with ECOG score of 1 at screening was assessed with ECOG performance score of 3 at Cycle 1 Day 1 as the baseline.

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In general the baseline demographics characteristics are well balanced between the two treatment groups. The median age in the total population was 67.0 years with approximately 20% being ≥75 of age. More patients were in the range 18 -< 65 years of age in the Dara SC group compared with the Dara IV group, 46% versus 38.6%. A majority of the patients were male (54.6%) and most subjects were white (78.2%), and ECOG 0-1. The median weight was 73 kg (range 29-138). A range from 28.6 - 39 kg is an extremely low weight, The MAH has explained, that a total of 11 patients had a body weight below 45 kg, 5 patients in the SC group and 6 patients in the IV group, the MAH has provided narratives for all these patients. The protocol did not specify any body weight-based exclusions. It is of concern, that 2 patients had hepatitis C and chronic hepatitis B respectively and some had cardio-vascular diseases, thus comorbidity combined with older age and low body weight makes these patients highly fragile from a clinical point of view. It could be questioned whether some of these patients should have been excluded. However discontinuation due to AE and death was similar in both treatment arms, and although small numbers, no safety concerns were raised. The fact that these fragile patients actually tolerated several cycles of treatment is reassuring.

Table 23 **Summary of Baseline Disease Characteristics – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Analysis set: intent-to-treat	259	263	522
Type of myeloma by immunofixation or serum FLC assay, n (%)			
N	259	263	522
IgG	144 (55.6%)	156 (59.3%)	300 (57.5%)
IgA	45 (17.4%)	45 (17.1%)	90 (17.2%)
IgM	0	2 (0.8%)	2 (0.4%)
IgD	2 (0.8%)	4 (1.5%)	6 (1.1%)
IgE	0	0	0
Light chain	62 (23.9%)	53 (20.2%)	115 (22.0%)
Kappa	45 (17.4%)	27 (10.3%)	72 (13.8%)
Lambda	15 (5.8%)	23 (8.7%)	38 (7.3%)
FLC-Kappa[a]	1 (0.4%)	2 (0.8%)	3 (0.6%)
FLC-Lambda[b]	1 (0.4%)	1 (0.4%)	2 (0.4%)
Biclonal	6 (2.3%)	3 (1.1%)	9 (1.7%)
Type of measurable disease[c], n (%)			
N	259	263	522
Serum only	137 (52.9%)	144 (54.8%)	281 (53.8%)
IgG	109 (42.1%)	109 (41.4%)	218 (41.8%)
IgA	25 (9.7%)	31 (11.8%)	56 (10.7%)
Other[d]	3 (1.2%)	4 (1.5%)	7 (1.3%)
Serum and urine	45 (17.4%)	47 (17.9%)	92 (17.6%)
Urine only	45 (17.4%)	44 (16.7%)	89 (17.0%)
Serum FLC only	32 (12.4%)	28 (10.6%)	60 (11.5%)
ISS Staging[e], n (%)			
N	259	262	521
I	94 (36.3%)	82 (31.3%)	176 (33.8%)
II	89 (34.4%)	101 (38.5%)	190 (36.5%)
III	76 (29.3%)	79 (30.2%)	155 (29.8%)
Cytogenetic Risk[f]			
N	202	198	400
Standard risk	167 (82.7%)	146 (73.7%)	313 (78.3%)
High risk	35 (17.3%)	52 (26.3%)	87 (21.8%)
Del(17p)	22 (10.9%)	32 (16.2%)	54 (13.5%)
t(4; 14)	15 (7.4%)	22 (11.1%)	37 (9.3%)
t(14; 16)	4 (2.0%)	7 (3.5%)	11 (2.8%)
Number of lines of prior therapy, n (%)			
N	259	263	522
≤4 Lines	175 (67.6%)	174 (66.2%)	349 (66.9%)
>4 Lines	84 (32.4%)	89 (33.8%)	173 (33.1%)
Mean (SD)	4.3 (1.78)	4.3 (1.72)	4.3 (1.75)
Median	4.0	4.0	4.0
Range	(1; 15)	(2; 12)	(1; 15)
Time since initial diagnosis to randomization (years)			
N	259	263	522
Mean (SD)	6.14 (4.112)	6.64 (3.823)	6.39 (3.973)
Median	5.36	6.01	5.57
Range	(0.6; 39.0)	(0.8; 21.1)	(0.6; 39.0)

Table 24 **Summary of Baseline Disease Characteristics – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Number of lytic bone lesions, n (%)			
N	259	263	522
None	58 (22.4%)	49 (18.6%)	107 (20.5%)
1-3	27 (10.4%)	29 (11.0%)	56 (10.7%)
4-10	48 (18.5%)	34 (12.9%)	82 (15.7%)
More than 10	126 (48.6%)	151 (57.4%)	277 (53.1%)
Presence of diffuse myeloma-related osteopenia, n (%)			
N	259	263	522
Yes	118 (45.6%)	126 (47.9%)	244 (46.7%)
No	141 (54.4%)	137 (52.1%)	278 (53.3%)
Presence of extramedullary plasmacytomas, n (%)			
N	259	263	522
Yes	18 (6.9%)	17 (6.5%)	35 (6.7%)
No	241 (93.1%)	246 (93.5%)	487 (93.3%)
Bone marrow % plasma cells, n (%)			
N	255	255	510
<10	64 (25.1%)	53 (20.8%)	117 (22.9%)
10-30	112 (43.9%)	107 (42.0%)	219 (42.9%)
>30	79 (31.0%)	95 (37.3%)	174 (34.1%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: FLC=free light chain; Ig=immunoglobulin; ISS=International Staging System; N=total number; n=number; SD=standard deviation
Note: Percentages are calculated with the number of subjects in each group with available data as denominator.
[a] Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing.
[b] Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing.
[c] Includes subjects without measurable disease in serum and urine.
[d] Includes IgD, IgM, IgE and biclonal.
[e] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[f] Cytogenetic risk is based on FISH or karyotyping.
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The majority of patients had IgG myeloma and had measurable disease in serum only (53.8%) or urine only (17%). Patients were evenly distributed across ISS stages, 70.7% and 69.8% had stage I and II in the dara IV group compared with the dara SC group. Dara SC group. Most patients had standard risk disease, and the baseline disease characteristics are well balanced, except from a higher proportion of patients with high risk cytogenetics in the dara SC group, 26.3% vs. 17.3% in the dara IV group. Median time since diagnosis was 5.6 years, and patients had received a median of 4 prior lines of therapy. Approximately 1/3 of the patients had received > 4 lines of therapy, while 2/3 had received ≤ 4 lines. One of the inclusion criteria was that patients should have received at least 3 prior lines of chemotherapy including a PI and an IMiD. The MAH has clarified that a total of 496 of 522 subjects (95%) had before study entry, received at least 3 prior lines of chemotherapy, including a PI or an IMID. The remaining 26 (5%) were refractory to both a PI and an IMID.

Patients included had received multiple prior regimens, all patients had previously received PI(s) and IMiD(s), and 84.9% had received prior bortezomib and lenalidomide. The use of prior therapies was overall similar between the two treatment groups, except from the use of ASCT. In the dara SC group, 54.8% were treated with ASCT compared with 46.7% in the dara IV group. This may be related to the slightly higher proportion of patients at age 18-<65 years in the dara SC group compared with the dara IV group. Approximately 30% were refractory to PI+IMiD+Alky, and a total of 49.4% were refractory to both a PI and an IMiD, this is adequately reflected in the SmPC.

Numbers analysed

Table 25 **Summary of Subjects per Analysis Set – All Subjects (Study 54767414MMY3012)**

	Dara IV	Dara SC	Total
Subjects screened			655
Intent-to-treat[a] (ITT)	259 (100.0%)	263 (100.0%)	522 (100.0%)
Safety[b]	258 (99.6%)	260 (98.9%)	518 (99.2%)
Per-protocol[c] (PP)	257 (99.2%)	257 (97.7%)	514 (98.5%)
Response-evaluable[d]	245 (94.6%)	254 (96.6%)	499 (95.6%)
Pharmacokinetics[e]	255 (98.5%)	257 (97.7%)	512 (98.1%)
Pharmacokinetic-evaluable[f]	146 (56.4%)	149 (56.7%)	295 (56.5%)
Immunogenicity-evaluable			
daratumumab[g]	204 (78.8%)	205 (77.9%)	409 (78.4%)
rHuPH20[h]		202 (76.8%)	202 (76.8%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[a] Includes all subjects randomized.
[b] Includes all randomized subjects who received at least 1 dose of study drug.
[c] Includes all treated subjects who had measurable disease at baseline and had no major protocol deviations with respect to eligibility.
[d] Includes subjects who had a confirmed diagnosis of multiple myeloma and measurable disease and must have received at least 1 administration of study drug and had at least 1 post baseline disease assessment.
[e] Includes subjects who received at least 1 administration of study drug and had at least 1 pharmacokinetics sample concentration value after the first dose administration.
[f] Includes subjects who received all 8 weekly full doses of Dara IV or Dara SC in Cycle 1 and Cycle 2 within the dosing time window and provided a pre-dose pharmacokinetic sample on Cycle 3 Day 1 within the sampling window of 8 hours prior to the start of dose administration.
[g] Includes subjects who received at least 1 dose of Dara SC or Dara IV and had at least 1 sample after the start of dose administration.
[h] Includes subjects who received at least 1 dose of Dara SC and had at least 1 sample after the start of dose administration.
Note: Percentages are calculated with the number of subjects in ITT analysis set as the denominators.
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Outcomes and estimation

Co-Primary endpoint: ORR

Table 26 **Summary of Best Overall Response Based on Computerized Algorithm – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV		Dara SC			
	n (%)	95% CI for %[a]	n (%)	95% CI for %[a]	Relative Risk[b] (95% CI)	P-value[c]
Analysis set: intent-to-treat	259		263			
Best overall response						
Stringent complete response (sCR)	2 (0.8%)	(0.1%, 2.8%)	2 (0.8%)	(0.1%, 2.7%)		
Complete response (CR)	5 (1.9%)	(0.6%, 4.4%)	3 (1.1%)	(0.2%, 3.3%)		
Very good partial response (VGPR)	37 (14.3%)	(10.3%, 19.1%)	45 (17.1%)	(12.8%, 22.2%)		
Partial response (PR)	52 (20.1%)	(15.4%, 25.5%)	58 (22.1%)	(17.2%, 27.6%)		
Minimal response (MR)	28 (10.8%)	(7.3%, 15.2%)	25 (9.5%)	(6.2%, 13.7%)		
Stable disease (SD)	94 (36.3%)	(30.4%, 42.5%)	102 (38.8%)	(32.9%, 45.0%)		
Progressive disease (PD)	27 (10.4%)	(7.0%, 14.8%)	19 (7.2%)	(4.4%, 11.1%)		
Not evaluable (NE)	14 (5.4%)	(3.0%, 8.9%)	9 (3.4%)	(1.6%, 6.4%)		
Overall response (sCR+CR+VGPR+PR)	96 (37.1%)	(31.2%, 43.3%)	108 (41.1%)	(35.1%, 47.3%)	1.11 (0.89, 1.37)	<0.0001
CR or better (sCR+CR)	7 (2.7%)	(1.1%, 5.5%)	5 (1.9%)	(0.6%, 4.4%)		
VGPR or better (sCR+CR+VGPR)	44 (17.0%)	(12.6%, 22.1%)	50 (19.0%)	(14.5%, 24.3%)		

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: CI=confidence interval; n=number
[a] Clopper-Pearson exact confidence intervals are provided.
[b] Farrington-Manning estimates of the relative risk of Dara SC over Dara IV and associated CI are provided.
[c] P-value is from Farrington-Manning test for the non-inferiority hypothesis that Dara SC retains at least 60% of ORR in Dara IV.
Note: Percentages are calculated with the number of subjects in each group as denominators.
[TEFORR01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TEFORR01.SAS] 05MAR2019, 16:31

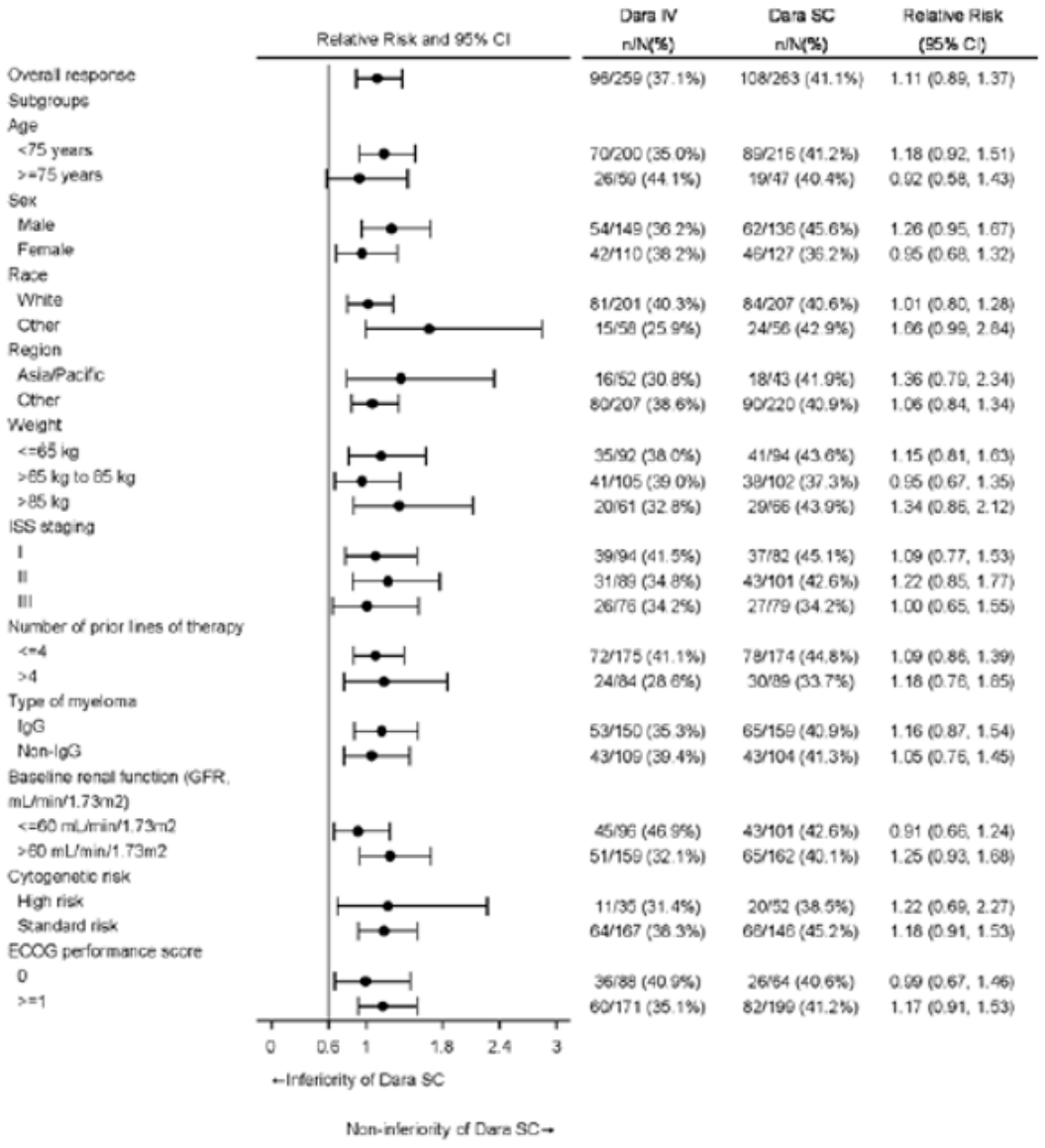
The ORR was 41.1% for Dara SC and 37.1% for Dara IV. The relative risk of Dara SC over Dara IV

and 95% CI was 1.11 (0.89, 1.37), p value < 0.0001. This indicated 89% retention of ORR with 97.5% confidence, thus the study met its co-primary endpoint, showing dara SC is non-inferior to dara IV.

The primary results were consistent across multiple sensitivity analyses, incl. PP analysis and response-evaluable analysis set.

Subgroup Analyses of Overall Response Rate

Figure 16 **Forest Plot of Subgroup Analyses on Overall Response Rate Based on Computerized Algorithm – Intent-to-treat Analysis Set (Study 54767414MMY3012)**



Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; GFR=glomerular filtration rate; Ig=immunoglobulin; ISS= International Staging System; N=total number; n=number
For type of myeloma: Type of myeloma by immunofixation is used.
For cytogenetic risk, the subjects with cytogenetic risk of "Not determined" are not included.
Farrington-Manning estimates of the relative risk of Dara SC over Dara IV and associated CI are provided.
[GEFORR01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\GEFORR01.SAS] 05MAR2019, 16:30

Overall, analyses on ORR showed consistent results across the different subgroups. There seem to be no difference pertained to type of myeloma (IgG or non-IgG) or to number of prior lines of therapy (≤ 4 or > 4 lines), except from ORR seemed better for patients who received ≤ 4 prior lines, however this subgroup was small and the 95% CI wide. Body weight analyses of ORR showed consistent efficacy,

except from the ≤ 65 kg and > 85 kg subgroups. Although small subgroups and a wide 95% CI, there seem to be a trend to a better ORR in the Dara SC group. The effect of weight on ORR is discussed in the pharmacological section.

Secondary Endpoints

The incidence of IRRs

Table 27 **Summary of Rate of Treatment-emergent Infusion-related Reactions – Safety Analysis Set (Study 54767414MMY3012)**

	Dara IV		Dara SC			
	n (%)	95% CI for %[a]	n (%)	95% CI for %[a]	Odds Ratio[b] (95% CI)	P-value[c]
Analysis set: safety	258		260			
Subjects who had treatment-emergent IRRs	89 (34.5%)	(28.7%, 40.6%)	33 (12.7%)	(8.9%, 17.4%)	0.28 (0.18, 0.44)	<0.0001

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: CI=confidence interval; Ig=immunoglobulin; IRR=infusion-related reaction; n=number
[a] Clopper-Pearson exact confidence intervals are provided.
[b] Stratified Cochran-Mantel-Haenszel estimate of the common odds ratio of Dara SC over Dara IV is used. The stratification factors include body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).
[c] P-value is from Cochran-Mantel-Haenszel Chi-Squared test.
Note: Percentages are calculated with the number of subjects in each group as denominators.
[TSFAEIRR01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TSFAEIRR01.SAS] 05MAR2019, 16:39

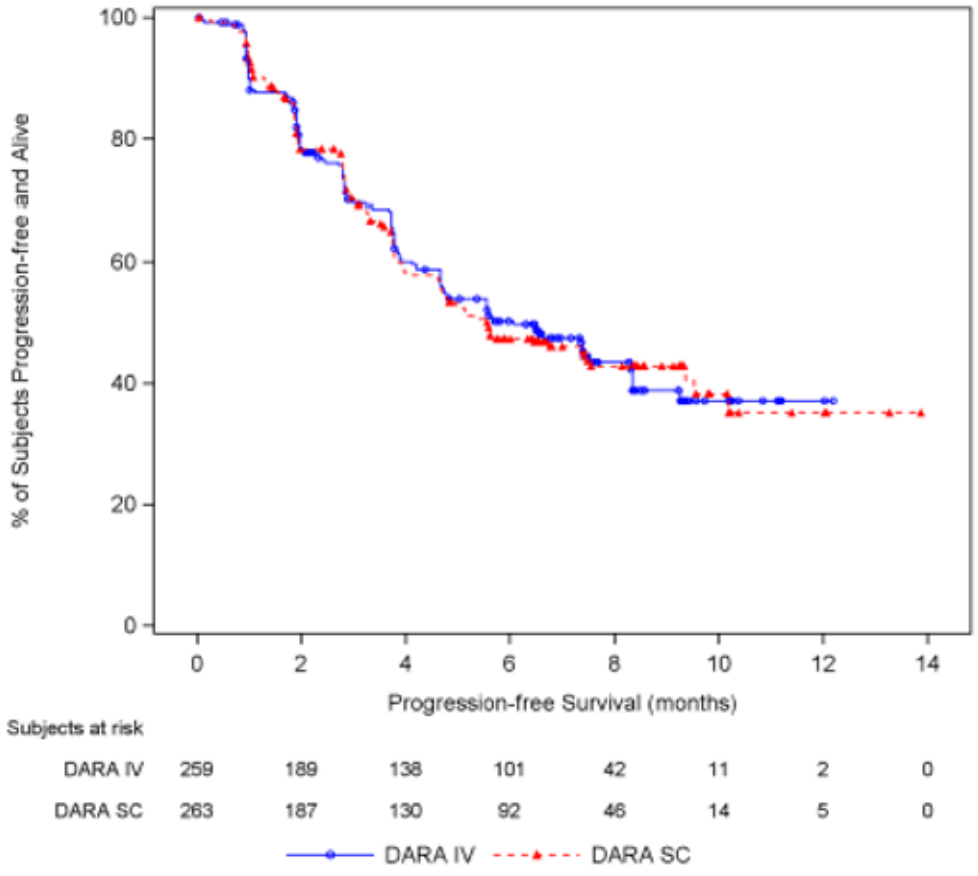
Progression-free Survival (PFS)

Table 28 **Summary of Progression-free Survival Based on Computerized Algorithm – Intent-to-treat Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC
Analysis set: intent-to-treat	259	263
Progression-free survival (PFS)		
Number of events (%)	133 (51.4%)	133 (50.6%)
Number of censored (%)	126 (48.6%)	130 (49.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	2.79 (1.97, 2.96)	2.79 (1.94, 3.06)
Median (95% CI)	6.08 (4.67, 8.31)	5.59 (4.67, 7.56)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.9258
Hazard ratio (95% CI)[b]		0.99 (0.78, 1.26)
6-month PFS rate % (95% CI)	50.3 (43.7, 56.5)	47.3 (40.8, 53.6)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: CI=confidence interval; Ig=immunoglobulin; NE=not evaluable
[a] P-value is based on the log-rank test stratified with body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).
A hazard ratio<1 indicates an advantage for Dara SC.
[TEFPFS01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TEFPFS01.SAS] 05MAR2019, 16:32
Source: Modified from Attachment TEFPFS01.

Figure 17 **Kaplan-Meier Plot for Progression-free Survival Based on Computerized Algorithm – Intent-to-treat Analysis Set (Study 54767414MMY3012)**



Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).

[GEFPFS01.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\GEFPFS01.SAS] 05MAR2019, 16:31

No clinical significant difference was shown between the Dara SC and Dara IV pertaining to the secondary endpoints PFS, rate of CR or better, time to next therapy or time to response, PR or better or VGPR or better. The median duration of response was not reached, and PFS on next line of therapy data were not yet mature as of time of data cutoff.

Study MMY2040

Table 29 **Summary of Subject Treatment Disposition; All Treated Analysis Set (Study 54767414MMY2040)**

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Subjects who completed treatment	65 (97.0%)	NA	NA
Subjects who are still on treatment	0	55 (82.1%)	48 (73.8%)
Subjects who discontinued treatment	2 (3.0%)	12 (17.9%)	17 (26.2%)
Reason for discontinuation	1 (1.5%)	3 (4.5%)	6 (9.2%)
Death	0	1 (1.5%)	1 (1.5%)
Progressive disease	1 (1.5%)	7 (10.4%)	10 (15.4%)
Withdrawal by subject	0	1 (1.5%)	0

Key: Dara-SC = daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd
= Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.

[TSIDS02.RTF] [JNJ-54767414\MMY2040\DBR_ASH_2019_10\RE_ASH_2019_10\PROD\TSIDS02.SAS] 18NOV2019, 11:32

Numbers of patients in the MMY2040 are few, but the MAH has updated the results, **,** two patients did not meet the eligibility criteria in the D-Rd arm and were considered major protocol deviations, 5 patients discontinued, 4 due to AEs and 1 due to PD. The update of the results with a data cut-off of 11 November 2019 added 7.4 months of follow-up. The median duration of treatment in the D-VMP and D-Rd cohorts was 14.3 and 14.9 months, respectively. In the D-VRd cohort, the median treatment duration was
unchanged from the initial SC submission (2.6 months). The ORR was 89.6% for the D-VMP cohort (initial SC submission: 88.1%) and 93.8% for D-Rd cohort (initial SC submission: 90.8%). The ORR for VRd was unchanged at 97% as all subjects had completed or discontinued the study at the time of the initial SC submission. The depth of response improved with a CR/sCR rate of 47.8% (initial SC submission: 17.9%) in the D-VMP cohort and CR/sCR rate of 38.5% (initial SC submission: 18.5%) in the D-Rd cohort.
The MMY2040 protocol was amended a few times, but the amendments were not considered controversial to the study. However the table: "Summary of Protocol Amendments" listed on p. 24 in the csr-body-54767414mmy2040 and in the AR says: MMY3012. The MAH confirms that the information in the Summary of Protocol Amendments table in Section 3.1.2 of the Study MMY2040 clinical study report (CSR) is correct and relevant to Study MMY2040. An erratum has been prepared.

Baseline data

Demographics

The median age was 59 years in the D-VRd group, and 69 and 75 years in the D-Rd and D-VMP group respectively. Approximately 21.5% of the patients in the D-Rd group were ≥75 years of age. Most patients are white (56.7%, 68.7% and 69.2% in the D-VRd, D-VMP and D-Rd groups) and the majority of patients are male, 71.6% and 69.2% (D-VRd and D-Rd). The median weight for the 3 treatment groups was 66-80.6 kg with a wide range: 43- 147.6 kg. Patients were ECOG 0-2 (D-VRd and D-VMP) and ECOG 0-1 (D-Rd). In general, the baseline demographics characteristics are well balanced between the treatment groups.

Table 30 Summary of Demographics and Baseline Characteristics; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Age, [years]			
N	67	67	65
Mean (SD)	57.3 (9.47)	74.9 (4.54)	66.8 (9.58)
Median	59.0	75.0	69.0
Range	(33; 76)	(66; 86)	(33; 82)
18 - <65	54 (80.6%)	0	22 (33.8%)
65 - <75	12 (17.9%)	33 (49.3%)	29 (44.6%)
≥75	1 (1.5%)	34 (50.7%)	14 (21.5%)
Sex			
N	67	67	65
Female	19 (28.4%)	36 (53.7%)	20 (30.8%)
Male	48 (71.6%)	31 (46.3%)	45 (69.2%)
Race			
N	67	67	65
Asian	0	5 (7.5%)	0
Black or African American	5 (7.5%)	1 (1.5%)	2 (3.1%)
White	38 (56.7%)	46 (68.7%)	45 (69.2%)
Not reported	24 (35.8%)	15 (22.4%)	18 (27.7%)
Ethnicity			
N	67	67	65
Hispanic or Latino	3 (4.5%)	6 (9.0%)	0
Not Hispanic or Latino	34 (50.7%)	39 (58.2%)	45 (69.2%)
Not reported	30 (44.8%)	22 (32.8%)	20 (30.8%)
Weight, kg			
N	67	67	65
≤65	13 (19.4%)	32 (47.8%)	9 (13.8%)
>65 - 85	32 (47.8%)	25 (37.3%)	33 (50.8%)
>85	22 (32.8%)	10 (14.9%)	23 (35.4%)
Mean (SD)	79.77 (20.112)	68.69 (14.827)	82.16 (17.662)
Median	77.00	66.00	80.60
Range	(43.0; 147.6)	(45.0; 100.0)	(53.6; 142.9)
Height, cm			
N	67	67	65
Mean (SD)	172.60 (9.310)	162.31 (9.675)	168.91 (10.075)
Median	174.00	160.00	170.00

Table 8: Summary of Demographics and Baseline Characteristics; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Range	(152.0; 193.0)	(145.0; 185.4)	(148.0; 192.0)
ECOG			
N	67	67	65
0	40 (59.7%)	25 (37.3%)	36 (55.4%)
1	26 (38.8%)	38 (56.7%)	29 (44.6%)
2	1 (1.5%)	4 (6.0%)	0

Key: Dara-SC = daratumumab and recombinant human hyaluronidase PH20 for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
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Baseline disease characteristics

The majority of patients had IgG myeloma (61.2%, 50.8% and 53.7%), had measurable disease in serum only (56.7%, 53.8% and 49.3%), (D-VMP, D-Rd and D-VRd) and had ISS stages I-II. In the D-VMP and D-VRd group with newly diagnosed patients, median time from initial diagnosis was 1.18 months, compared with 35.02 months for relapsed/refractory patients in the D-Rd group. Of the patients who had baseline cytogenetic data reported, the majority in all 3 treatment groups had standard risk disease, 75.5%, 80.5% and 64.5% in the D-VRd, D-VMP and the D-Rd groups. Cytogenetic data were all based on local laboratories.

Baseline Laboratory values

Median hematology values for hemoglobin, neutrophils, and platelet count, and median selected biochemistry laboratory values at baseline were similar between all 3 cohorts. A summary of baseline

laboratory values by grade is also provided in detail in the CSR, few Grade 3 abnormal values were reported

Table 31 Summary of Baseline Disease Characteristics; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Type of myeloma by immunofixation or serum FLC assay, n (%)			
N	67	67	65
IgG	36 (53.7%)	41 (61.2%)	33 (50.8%)
IgA	12 (17.9%)	16 (23.9%)	17 (26.2%)
IgM	0	0	0
IgD	0	0	0
IgE	0	0	0
Light chain	17 (25.4%)	6 (9.0%)	14 (21.5%)
Kappa	12 (17.9%)	2 (3.0%)	8 (12.3%)
Lambda	3 (4.5%)	4 (6.0%)	4 (6.2%)
FLC-Kappa[a]	2 (3.0%)	0	1 (1.5%)
FLC-Lambda[b]	0	0	1 (1.5%)
Biclonal	2 (3.0%)	4 (6.0%)	1 (1.5%)
Negative immunofixation	0	0	0
Type of measurable disease[c], n (%)			
N	67	67	65
Serum only	33 (49.3%)	38 (56.7%)	35 (53.8%)
IgG	26 (38.8%)	28 (41.8%)	25 (38.5%)
IgA	7 (10.4%)	9 (13.4%)	9 (13.8%)
Other[d]	0	1 (1.5%)	1 (1.5%)
Serum and urine	12 (17.9%)	17 (25.4%)	9 (13.8%)
Urine only	14 (20.9%)	6 (9.0%)	4 (6.2%)
Serum FLC only	8 (11.9%)	6 (9.0%)	17 (26.2%)
ISS Staging[e], n (%)			
N	67	67	64
I	30 (44.8%)	22 (32.8%)	27 (42.2%)
II	23 (34.3%)	30 (44.8%)	19 (29.7%)
III	14 (20.9%)	15 (22.4%)	18 (28.1%)
Cytogenetic risk[f]			
N	53	41	31
Standard risk	40 (75.5%)	33 (80.5%)	20 (64.5%)
High risk	13 (24.5%)	8 (19.5%)	11 (35.5%)
del(17p)	5 (9.4%)	4 (9.8%)	4 (12.9%)
t(4; 14)	9 (17.0%)	2 (4.9%)	6 (19.4%)
t(14; 16)	1 (1.9%)	2 (4.9%)	3 (9.7%)

Table 32 Summary of Baseline Disease Characteristics; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Time since initial diagnosis (months)			
N	67	67	65
Mean (SD)	1.90 (2.285)	1.55 (1.133)	55.12 (54.419)
Median	1.18	1.18	35.02
Range	(0.3; 14.5)	(0.5; 5.3)	(3.6; 384.5)
Number of lytic bone lesions, n (%)			
N	66	67	64
None	19 (28.8%)	11 (16.4%)	16 (25.0%)
1 - 3	18 (27.3%)	25 (37.3%)	14 (21.9%)
4 - 10	15 (22.7%)	10 (14.9%)	14 (21.9%)
More than 10	14 (21.2%)	21 (31.3%)	20 (31.3%)
Presence of diffuse myeloma-related osteopenia, n (%)			
N	66	67	64
Yes	17 (25.8%)	25 (37.3%)	18 (28.1%)
No	49 (74.2%)	42 (62.7%)	46 (71.9%)
Presence of extramedullary plasmacytomas, n (%)			
N	67	67	65
Yes	0	4 (6.0%)	2 (3.1%)
No	67 (100.0%)	63 (94.0%)	63 (96.9%)
Bone marrow % plasma cells, n (%)			
N	67	67	65
<10	0	3 (4.5%)	15 (23.1%)
10 - 30	29 (43.3%)	31 (46.3%)	28 (43.1%)
>30	38 (56.7%)	33 (49.3%)	22 (33.8%)

Key: Dara-SC = daratumumab and recombinant human hyaluronidase PH20 for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
[a] Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing.
[b] Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing.
[c] Includes subjects without measurable disease in serum and urine.
[d] Includes IgD, IgM, IgE and biclonal.
[e] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[f] Cytogenetic risk is based on FISH or karyotyping.
Note: Percentages are calculated with the number of subjects in each group with available data as denominators.
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Numbers analysed

The median duration of follow-up for subjects in the D-VMP, D-Rd and D-VRd cohorts was 6.90, 7.13 and 3.94 months, respectively. The median duration of daratumumab SC injection was 5 minutes for all 3 cohorts. The median treatment duration was 6.5 months for the D-VMP cohort, 7.0 months for the D-Rd cohort, and 2.6 months for the D-VRd cohort. The primary analysis population was the All Treated Analysis Set.

Outcomes and estimation

Primary endpoint: ORR

VGPR and PR contributed the most to the ORR in all 3 treatment groups. The primary endpoint by computerized algorithm was met for all treatment groups, for D-VMP with an ORR of 88.1% (90% CI: 79.5%, 93.9%) and for D-Rd, 90.8% (90% CI: 82.6%, 95.9%). For the D-VRd group the primary endpoint was VGPR or better, the rate being 71.6% (95% CI: 61.2%, 80.6%).

*Table 33: **Summary of Best Overall Response and Overall Response Rate Based on Computerized Algorithm; All Treated Analysis Set (Study 54767414MMY2040)***

	D-VRd		D-VMP		D-Rd	
	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]
Analysis set: all treated	67		67		65	
Best overall response						
Stringent complete	6 (9.0%)	(4.0%, 16.9%)	13 (19.4%)	(11.9%, 29.1%)	12 (18.5%)	(11.0%, 28.2%)

Complete response (CR)	5 (7.5%)	(3.0%, 15.1%)	19 (28.4%)	(19.4%, 38.8%)	13 (20.0%)	(12.3%, 29.9%)
Very good partial response (VGPR)	37 (55.2%)	(44.5%, 65.6%)	20 (29.9%)	(20.7%, 40.4%)	26 (40.0%)	(29.8%, 51.0%)
Partial response (PR)	17 (25.4%)	(16.9%, 35.6%)	8 (11.9%)	(6.1%, 20.5%)	10 (15.4%)	(8.6%, 24.7%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	1 (1.5%)	(0.1%, 7.1%)
Stable disease (SD)	1 (1.5%)	(0.1%, 6.9%)	5 (7.5%)	(3.0%, 15.1%)	1 (1.5%)	(0.1%, 7.1%)
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)	0	(NE, NE)
Not evaluable (NE)	1 (1.5%)	(0.1%, 6.9%)	2 (3.0%)	(0.5%, 9.1%)	2 (3.1%)	(0.5%, 9.4%)
Overall response (sCR+CR+VGPR+PR)	65 (97.0%)	(90.9%, 99.5%)	60 (89.6%)	(81.3%, 95.0%)	61 (93.8%)	(86.5%, 97.9%)
CR or better (sCR + CR)	11 (16.4%)	(9.5%, 25.7%)	32 (47.8%)	(37.2%, 58.5%)	25 (38.5%)	(28.3%, 49.4%)
VGPR or better (sCR + CR + VGPR)	48 (71.6%)	(61.2%, 80.6%)	52 (77.6%)	(67.6%, 85.7%)	51 (78.5%)	(68.4%, 86.5%)

Key: Dara-SC = daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.

[a] Clopper-Pearson exact confidence intervals are provided.

Note: For previously untreated subjects in D-VRd and D-VMP cohorts, MR category is not assigned/not applicable.

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

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Ancillary analyses

N/A

Summary of main study(ies)

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 34. Summary of efficacy for trial MMY3012

Title: A Phase 3 Randomized, Multicenter Study of SC vs. IV Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma		
Study identifier	57467414MMY3012; EudraCT NUMBER: 2017-000206-38; ClinicalTrials.gov Identifier: NCT03277105	
Design	Phase 3, randomized, open-label, active-controlled, multicenter study to demonstrate that the efficacy and pharmacokinetics of Dara-SC are not inferior to those for Dara IV.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 1.25 years- FPI 31 Oct 17; data cut off 8 Jan 19; ongoing N/A N/A
Hypothesis	Non-inferiority	

Treatments groups	Dara IV		Dara IV 16 mg/kg IV, once weekly in C 1-2, Q 2 weeks in C 3-6, and Q 4 weeks thereafter. Cycle repeats: every 28 days.
	Dara SC		Dara SC 1800 mg fixed dose, once weekly in C 1- 2, Q 2 weeks in C 3 - 6, and Q 4 weeks thereafter. Cycle repeats: every 28 days.
Endpoints and definitions	Co-Primary endpoints	ORR	ORR: The number and proportion of subjects who achieve PR or better will be calculated for each group based on computerized algorithm according to IMWG criteria.
		Maximum Ctrough (Cycle 3 Day 1 predose)	Maximum C_{trough} (Predose on Cycle 3 Day 1): the ratio of the geometric means and the corresponding 90% CI utilizing logarithmic transformation of maximum C_{trough} values will be provided
	Secondary endpoint	IRR	The proportion of subjects who have an AE that is considered an IRR based on investigator assessment.
	Secondary endpoint	PFS	The duration from the date of randomization to either progressive disease, based on computerized algorithm according to IMWG criteria, or death, whichever occurred first.
	Secondary endpoint	VGPR or better	The proportion of subjects who have a VGPR or better based on computerized algorithm according to IMWG criteria.
	Secondary endpoint	CR or better	The proportion of subjects who have a CR or better based on computerized algorithm according to IMWG criteria.
	Secondary endpoint	Time to next therapy (TNT)	Time from randomization to the start of the first subsequent anti-cancer therapy
	Secondary endpoint	OS	Time from randomization to the date of death
Database lock	18 Feb 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Dara IV	Dara SC
	Number of subjects	259	263
	Co-Primary endpoint ORR 95% CI	37.1% (31.2%, 3.3%)	41.1% (35.1%, 47.3%)
	Co-Primary endpoint Maximum C_{trough} Geometric Mean Range	n= 146 463 86.1-1109	n= 149 499 9.97-1720

	Sec. endpoint IRR Total number of subjects (%) 95% CI	89 (34.5%) 28.7%, 40.6%	33 (12.7%) 8.9%, 17.4%
	Sec. endpoint PFS Median PFS, months 95% CI	6.08 4.67, 8.31	5.59 4.67-7.56
	Sec. endpoint VGPR or better, rate n(%) 95% CI	44 (17%) 12.6%, 22.1%	50 (19%) 14.5%, 24.3%
	Sec. endpoint CR or better rate, n (%) 95% CI	7 (2.9%) 1.2%, 5.8%	5 (2.0%) 0.6%, 4.5%
	Sec. endpoint TNT Median (months) 95% CI	8.67 7.69, 11.14	9.72 7.59, NE
	Sec. endpoint OS Median (months) 95% CI	13.08 NE. NE	NE 11.63, NE
Effect estimate per comparison	Co-Primary endpoint: ORR	Comparison groups	Dara SC v Dara IV
		Relative Risk	1.11
		95% CI	0.89, 1.37
Effect estimate per comparison	Co-Primary endpoint: Maximum Ctrough (Cycle 3 Day 1 predose)	Comparison groups	Dara SC vs Dara IV
		Geometric mean Ratio	107.93%
		90% CI	95.74%, 121.67%
	Secondary endpoint: IRR	Comparison groups	Dara SC vs Dara IV
		Odds Ratio	0.28
		95% CI	0.18, 0.44
		P-value	<0.0001
	Secondary endpoint: PFS	Comparison groups	Dara SC vs Dara IV
		Hazard ratio	0.99
		90% CI	0.78, 1.26
		P-value	0.9258
	Secondary endpoint: VGPR or better	Comparison groups	Dara SC vs Dara IV
		Odds Ratio	1.16
		95% CI	0.73, 1.85
		p-value	0.5280
	Secondary endpoint: OS	Comparison groups	Dara SC vs Dara IV
		Hazard ratio	0.90
		95% CI	0.59, 1.35
		p-value	0.6032

Table 35. Summary of efficacy for trial MMY2040

Title: A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens	
Study identifier	54767414MMY2040

Design	Phase 2, open-label, multi-center trial		
	Duration of main phase:		Study initiation date 02 May 2018, data cut off 4 March2019, ongoing.
	Duration of Run-in phase:		n/a
	Duration of Extension phase:		n/a
Hypothesis	D-VRd: the H_0 : VGPR or better is at most 50%, against the alternative hypothesis that the ORR is at least 70% D-VMP: the H_0 : ORR is at most 70%, against the alternative hypothesis that the ORR is at least 90% D-Rd: the H_0 : ORR is <= 75% against the alternative hypothesis that the ORR is >=90%		
Treatments groups	D-VRd		Dara 1800 mg SC on d. 1, 8, 15 for C 1-2, d. 1 C 4. Lenalidomide 25 mg (PO) d. 1-14. Bortezomib 1.3 mg/m^2 on d. 1, 4, 8, 11. Dexamethasone 40 mg weekly. Cycle repeats every 21 days. Subjects will continue to receive the study drugs for a maximum of 4 cycles. HSC collection after Cycle 4 and autologous stem cell transplant off protocol.
	D-VMP		Dara SC 1800 mg on d. 1, 8, 15, 22, 29, 36 of each 42- day cycle for C 1, days 1, 22 for C 2-9, day 1 for of each 28-day cycle for C 10 and beyond. Bortezomib SC 1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29, 32 for C 1; then on d. 1, 8, 22, 29 for C 2-9. Cycles repeats every 42 days. Melphalan 9 mg/m^2 PO d. 1-4 for C 1-9. Cycles repeats every 42 days. Prednisone 60 mg/m^2 PO on Days 1-4, C 1-9. Cycle repeats every 42 day
	D-Rd		Daratumumab SC 1800 mg on d. 1, 8, 15, 22 for C 1 - 2; on d. 1 and 15 for C 3-6; d. 1 for C 7 and beyond. Lenalidomide 25 mg PO on days 1- 21. Dexamethasone (oral or IV) 40 mg once a week. Cycle repeats every 28 days.
Endpoints and definitions	Primary endpoint	VGPR or better rate (D-VRd cohort)	The proportion of subjects with a VGPR or better rate as defined by the IMWG response criteria.
		ORR for D-VMP and D-RD cohorts	The proportion of subjects with a PR or better as defined by the IMWG.
	Secondary endpoint	ORR (D-VRd cohort)	The proportion of subjects who achieve a PR or better as defined by the IMWG.
		VGPR or better (D-VMP and D-Rd cohort)	The proportion of subjects with a VGPR or better rate as defined by the IMWG.

	Secondary endpoint	CR or better rate	Proportion of subjects with a response of CR or better based on computerized algorithm according to IMWG.
	Secondary endpoint	MRD-negativity rate	Proportion of subjects assessed as MRD negative, at any timepoint after the first dose date (D-VMP and D-Rd cohorts).
Database lock	29Mar2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All Treated		

Descriptive statistics and estimate variability	Treatment group	D-VRd	D-VMP	D-Rd
	Number of subjects	67	67	65
	Primary endpoint: VGPR or better rate (VRd)	71.6%		
	90% CI	(61.2%, 80.6%)		
	Primary endpoint: ORR (D-VMP, D-Rd)		88.1%	90.8%
	90% CI		(79.5%, 93.9%)	(82.6%, 95.9%)
	Secondary endpoint: ORR (D-VRd)	97%		
	90% CI	(90.9%, 99.5%)		
	Secondary endpoint: VGPR or better rate (D-VMP, D-Rd)		64.2%	64.6%
	90% CI		(53.5%, 73.9%)	(53.7%, 74.5%)
	Secondary endpoint: CR or better rate	16.4%	17.9%	18.5%
	90% CI	(9.5%, 25.7%)	(10.7%, 27.4%)	(11%, 28.2%)

Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy Results Comparison with Historic IV Studies

The results from the Study MMY 2040 were compared with historical data from previously submitted IV combination studies (MMY3007 and MMY3003), using the Safety Analysis Set to ensure consistency.

Due to the different lengths of follow-up between Study MMY2040 and previously submitted IV combination studies (MMY3007 and MMY3003), ORR data from the first dose of study treatment up to the end of Month 6 for each subject was compared across studies: D-VMP cohort (n=67) vs. MMY3007 IV group (n=346); D-Rd cohort (n=65) vs. MMY3003 IV group (n=283). To ensure consistency across studies, the Safety Analysis Set was used for side-by-side comparisons of Study MMY2040 with Studies MMY3007 and MMY3003.

Combination Therapy Study Population, Subject and Enrollment Information

Subject enrollment information for the primary analysis is summarized above for Study MMY2040 in Section 3.1.2. Subject information for previously submitted Studies MMY3007 and MMY3003 is available

Table 36 Overall Response Rate Up to Month 6: DVMP; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040)

	MMY 3007 Dara IV + VMP		MMY 2040 Dara SC + VMP	
	n (%)	90% CI for %*	n (%)	90% CI for %*
Analysis set: safety	346		67	
Best overall response				
Stringent complete response (sCR)	12 (3.5%)	(2.0%, 5.6%)	2 (3.0%)	(0.5%, 9.1%)
Complete response (CR)	14 (4.0%)	(2.5%, 6.3%)	3 (4.5%)	(1.2%, 11.2%)
Very good partial response (VGPR)	164 (47.4%)	(42.9%, 52.0%)	35 (52.2%)	(41.5%, 62.8%)
Partial response (PR)	112 (32.4%)	(28.2%, 36.8%)	17 (25.4%)	(16.9%, 35.6%)
Stable disease (SD)	36 (10.4%)	(7.8%, 13.5%)	8 (11.9%)	(6.1%, 20.5%)
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)
Not evaluable (NE)	8 (2.3%)	(1.2%, 4.1%)	2 (3.0%)	(0.5%, 9.1%)
Overall response (sCR+CR+VGPR+PR)	302 (87.3%)	(84.0%, 90.1%)	57 (85.1%)	(76.0%, 91.7%)
CR or better (sCR + CR)	26 (7.5%)	(5.3%, 10.3%)	5 (7.5%)	(3.0%, 15.1%)
VGPR or better (sCR + CR + VGPR)	190 (54.9%)	(50.3%, 59.4%)	40 (59.7%)	(48.9%, 69.8%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.
* Clopper-Pearson exact confidence intervals are provided.
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 denominators.
Note: Both initial response date and confirmation date need to be within Month 6.
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Table 37

Table 11: Overall Response Rate Up to Month 6: DRd; Safety Analysis Set (Combination Therapy Studies: MMY3003 and MMY2040)

	MMY 3003 Dara IV + Rd		MMY 2040 Dara SC + Rd	
	n (%)	90% CI for %*	n (%)	90% CI for %*
Analysis set: safety	283		65	
Best overall response				
Stringent complete response (sCR)	7 (2.5%)	(1.2%, 4.6%)	1 (1.5%)	(0.1%, 7.1%)
Complete response (CR)	27 (9.5%)	(6.8%, 12.9%)	5 (7.7%)	(3.1%, 15.5%)
Very good partial response (VGPR)	135 (47.7%)	(42.7%, 52.8%)	32 (49.2%)	(38.5%, 60.1%)
Partial response (PR)	82 (29.0%)	(24.5%, 33.7%)	21 (32.3%)	(22.8%, 43.1%)
Minimal response (MR)	9 (3.2%)	(1.7%, 5.5%)	3 (4.6%)	(1.3%, 11.5%)
Stable disease (SD)	19 (6.7%)	(4.4%, 9.7%)	1 (1.5%)	(0.1%, 7.1%)
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)
Not evaluable (NE)	4 (1.4%)	(0.5%, 3.2%)	2 (3.1%)	(0.5%, 9.4%)
Overall response (sCR+CR+VGPR+PR)	251 (88.7%)	(85.1%, 91.7%)	59 (90.8%)	(82.6%, 95.9%)
CR or better (sCR + CR)	34 (12.0%)	(9.0%, 15.7%)	6 (9.2%)	(4.1%, 17.4%)
VGPR or better (sCR + CR + VGPR)	169 (59.7%)	(54.7%, 64.6%)	38 (58.5%)	(47.5%, 68.8%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); Rd = lenalidomide/dexamethasone.
* Clopper-Pearson exact confidence intervals are provided.
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 denominators.
Note: Both initial response date and confirmation date need to be within Month 6.
[TEFORR01B1.RTF] [JNJ-54767414\Z_SCS\DBR_BLA_SUBQ_2019\RE_BLA_SUBQ_COMBI_2019\PROD\TEFORR01B1.SAS] 26APR2019, 09:56

Due to the different length of the follow-up period, the ORR data was compared across studies, from the first dose of study treatment up to the end of Month 6 for each patient: D-VMP vs. MMY3007 (dara IV + VMP) and D-Rd vs. MMY3003 (dara IV + Rd). The ORR results appear similar for dara SC in the D-VMP and D-Rd groups when compared with dara IV in the MMY3007 and MMY3003 (Table 10, 11). However, data should be interpreted with caution, the SC data are compared with historical data,patients characteristics were not quite similar. In the IV dara-VMP group, more patients had ISS stage III and ECOG 2 (41% and 26%) compared with the SC dara + VMP (22% and 6%), but number of patients with cytogenetic high-risk disease was similar. In the Dara-RD group, there were more patients with cytogenetic high-risk disease in the SC group compared with the IV group, 36% vs. 15%.

Clinical studies in special populations

None submitted

Supportive study(ies)

For the supportive studies MMY1004 and MMY1008, please see the Clinical Pharmacology and Clinical Safety sections.

2.5.3. Discussion on clinical efficacy

The current submission is supported by one Phase 3 study MMY3012 of SC vs. IV administration of Daratumumab in patients with relapsed or refractory Multiple Myeloma, and one phase 2 study to evaluate SC Daratumumab in combination with standard Multiple Myeloma treatment regimens.

Design and conduct of clinical studies

The pivotal study in the efficacy evaluation is the phase 3 study MMY3012, a randomized, active controlled multicentre study of monotherapy SC daratumumab versus IV daratumumab. The MAH has also submitted a phase 2 study of SC daratumumab in combination with 3 different standard Multiple myeloma treatment regimens: bortezomib + melphalan + prednisone (D-VMP), lenalidomide + dexamethasone (D-Rd) and bortezomib + lenalidomide + dexamethasone (D-VRd). Daratumumab SC is administered as a 1800 mg flat dose, co-formulated with rHuPH20 in both studies. No comparator is in the combination therapy study, data is compared to historical data from previously submitted IV combination studies.

The in- and exclusion criteria clearly define 4 groups of patients, above 18 years and ECOG 0-2, with Multiple Myeloma: 1) Relapsed/refractory MM who have received at least 3 prior lines of therapy for monotherapy daratumumab and whose prior therapy included a PI and an IMiD, 2) newly diagnosed MM ineligible for ASCT for the combination D-VMP, 3) newly diagnosed MM eligible for ASCT for D-VRd and 4) relapsed MM who have received at least one prior therapy (D-Rd). No trials were performed for dara in combination with bortezomib and dexamethasone and who have received at least one prior treatment. The MAH has justified the extrapolation of the indication daratumumab in combination with other standard back-bone therapies such as the combination bortezomib and dexamethasone.

In general the baseline demographics characteristics are well balanced between the two treatment groups in the MMY3012 Study, except from a higher proportion of subjects with high cytogenetic risk in the dara SC group (dara SC: 26.3%vs. dara IV: 17.3%). The study population in the two studies was overall representative to patients with Multiple Myeloma. However, the range of weight was wide with extremely low values as 28.6 - 39 kg; a total of 11 patients had a body weight below 45 kg, 5 patients in the SC group and 6 patients in the IV group, the MAH has provided narratives for the these patients, they were in general considered fragile with comorbidities, but the protocol did not specify any body weight-based exclusions. No difference in discontinuation due to AE and death was reported and no further safety concerns were raised. The fact that these fragile patients actually tolerated several cycles of treatment is reassuring.

The reported "discontinuation due to physician decision" was higher in the Dara SC arm, as compared with the Dara IV arm. The main reasons were decline in clinical condition, lack of response or suspicion of PD, reasons that are comprehensible in a relapse/refractory setting. No correlation to dosing route or treating Principal Investigator was identified.

Overall, the studies were well conducted, the study MMY2040 was still ongoing and most patients still on treatment, but the MAH has updated the study adding 7.4 months of follow-up.

The primary endpoint ORR is fully acceptable for the monotherapy study of daratumumab comparing the SC and the IV formulation, as well as for the combination studies D-VMP and D-Rd cohorts. However, for the D-VRd group, the primary endpoint is VGPR or better. The MAH has justified, that historical data have showed, that the ORR for patients treated with VRd and eligible for autologous stem cell transplant (ASCT) was 97% or higher. In order to allow assessment of a clinical benefit of adding daratumumab to the VRd backbone regimen, the MAH decided to use VGPR or better as primary endpoint.

The secondary endpoints in both studies are considered clinically relevant. However, the MRD negativity is evaluated in all patients, except from newly diagnosed patients eligible to ASCT. The MAH has clarified, that due to the shortness of the study of D-VRd in transplant eligible patients, only 3 months of treatment, they considered it not appropriate to require patients to undergo a bone marrow procedure for MRD analysis.

The studies are aiming at non-inferiority of Dara SC to Dara IV, defined by using a 60% retention of the lower bound (20.8%) of the 95% CI from a previous Study MMY2002 of Dara IV. In the MMY2002 Study in relapsed or refractory multiple myeloma, patients who had received at least 3 prior therapies, had an ORR of 29.2% (95% CI: 20.8%, 38.9%) after Dara IV 16 mg/kg.

The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of Dara SC and a strong indication of similar efficacy from early efficacy and pharmacokinetics data. Stratification factors for study MMY3012 were body weight at baseline (≤ 65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤ 4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

Efficacy data and additional analyses

The monotherapy study met its co-primary endpoint showing that Daratumumab SC was non-inferior to daratumumab IV in terms of ORR as assessed by the computerized algorithm according to IMWG criteria. The results were consistent across several sensitivity analyses and across the pre-specified subgroups. There seem to be no difference pertained to type of myeloma (IgG or non-IgG). Pertained to number of prior lines of therapy (≤ 4 or > 4 lines), the ORR seems better for patients who received ≤ 4 prior lines, however this subgroup was small and the 95% CI wide. Although small subgroups and a wide 95% CI, there seem to be a trend to a better ORR in the Dara SC group. Body weight analyses of ORR showed consistent efficacy, except from the ≤ 65 kg and > 85 kg subgroups. Thus further justification for a flat SC dose regimen should be discussed in relation to high body weight extremes with low exposure and a potential risk of lower efficacy.

The median PFS was comparable between treatment, as were the rate of VGPR or better, but the OS data were not mature

For both studies, the median duration of administration was significantly shorter, 5 min. in the SC group compared with the IV administration in the monotherapy study. This may have an impact on the secondary endpoint, IRR, which was significantly reduced in the Dara SC group compared with the Dara IV group, daratumumab SC: 12.7%; daratumumab IV: 34.5%; odds ratio=0.28 (95% CI: 0.18, 0.44; p<0.0001).

The combination therapy study MMY 2040 was updated, adding 7,4 months of follow-up.

The median duration of treatment in the D-VMP and D-Rd cohorts was 14.3 and 14.9 months, respectively. In the D-VRd cohort, the median treatment duration was unchanged from the initial SC submission (2.6 months). The ORR was 89.6% for the D-VMP cohort (initial SC submission: 88.1%) and 93.8% for D-Rd cohort (initial SC submission: 90.8%). The ORR for VRd was unchanged at 97%

as all subjects had completed or discontinued the study at the time of the initial SC submission. The depth of response improved with a CR/sCR rate of 47.8% (initial SC submission: 17.9%) in the D-VMP cohort and CR/sCR rate of 38.5% (initial SC submission: 18.5%) in the D-Rd cohort.

The MAH has compared the SC combination therapy of D-VMP and D-Rd with historical data from previously submitted IV combination. Although the baseline characteristics were not quite similar in relation to age and number of patients with cytogenetic high-risk disease, and patients on SC dara combinations had a short follow up period of approximately 7 months, the ORR for SC D-VMP was 89.6% compared with 90.9% with the similar combination treatment using dara IV. The ORR for the SC D-Rd was 93.8% compared with 92.9% for the IV formulation. The secondary endpoints were in general not mature, but overall, the SC data seem consistent with the previous historical IV data for the daratumumab combination therapy.

2.5.4. Conclusions on the clinical efficacy

The Study MMY3012 met its primary endpoint and showed statistically significant results. The observed mean exposure (C_{trough} at Cycle 3 Day 1) was comparable after SC and IV administration by Pop PK analyses: 463 (86.1-1109) vs. 499 (9.97-1720). The ORR was 41.1% for Dara SC and 37.1% for Dara IV. The relative risk of Dara SC over Dara IV and 95% CI was 1.11 (0.89, 1.37), $p < 0.0001$, thus the study met its co-primary endpoint, showing Dara SC is non-inferior to dara IV. The concern regarding lower exposure in extreme high body weight SC patients and potential loss of efficacy, has been addressed with text amendments to the SmPC sections 4.2, 4.4 and 5.2.

2.6. Clinical safety

In the 3 monotherapy studies (MMY3012, MMY1004, MMY1008) and 1 combination study (MMY2040) included in this submission, safety data for daratumumab SC reflect data derived from subjects treated with daratumumab as an 1800 mg flat dose (co formulated with rHuPH20 30,000 U) and injected SC into the abdomen.

Table 38: Overview of Daratumumab Studies Contributing Safety Data to Summary of Clinical Safety

Study ID EudraCT Number FPFV/Completion Date Study Status	Study Phase Description/Design Population Primary Objective(s)	Study Drug Formulation(s) (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Contributing Data to SCS (by Treatment Group)
Studies with Daratumumab SC as Monotherapy			
54767414MMY3012 2017-000206-38 31 Oct 2017/ 08 Jan 2019 (primary analysis cutoff) Ongoing	Phase 3 Randomized, open-label, active-controlled, parallel-group, multicenter study Subjects with relapsed or refractory multiple myeloma who had received at least at least 3 prior regimens or who were refractory to both a PI and IMiD. To show that SC administration of daratumumab co-formulated with rHuPH20 is non-inferior to IV administration of daratumumab in terms of the ORR and maximum trough concentration	Daratumumab SC group: Daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL; administered SC Daratumumab IV group: Daratumumab 16 mg/kg, administered as IV infusion In both treatment groups, all cycles were 28 days, and daratumumab was administered at following dosing schedule: Cycle 1 and 2: Once weekly Cycles 3 to 6: Once every 2 weeks Cycles 7+: Once every 4 weeks until disease progression or unacceptable toxicity	Daratumumab SC: 260 Daratumumab IV: 258
54767414MMY1004 2015-001210-94 23 Oct 2015/ 14 Dec 2018 (interim cutoff) Ongoing	Phase 1b Nonrandomized, open-label, multicenter study conducted in 2 parts: Part 1: dose escalation and Part 2 to evaluate appropriate therapeutic dose selected in Part 1 Subjects with relapsed or refractory multiple myeloma who had received at least 2 prior regimens (must have included PI and IMiD) To evaluate the pharmacokinetics and safety of the Dara-MD SC delivery of daratumumab (Part 1) and to evaluate the pharmacokinetics and safety of the Dara-CF SC delivery of daratumumab (Part 2).	Part 1: Dara-MD mix-and-deliver preparation. Daratumumab solution mixed with rHuPH20 on day of planned infusion given SC. Daratumumab doses evaluated were 1200 mg and 1800 mg. Part 2: Dara-CF solution (SC). Daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL In both study parts, cycles were 28 days and daratumumab was administered at following dosing schedule: Cycle 1 and 2: Once weekly Cycles 3 to 6: Once every 2 weeks Cycles 7+: Once every 4 weeks until disease progression or unacceptable toxicity	Daratumumab SC (Dara-CF): 25
54767414MMY1008 N/A 25 Aug 2017/ 31 Oct 2018 Ongoing	Phase 1 Nonrandomized, open-label, multicenter study Japanese subjects with relapsed or refractory multiple myeloma who had received at least 2	Daratumumab solution (SC): Daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL All cycles were 28 days. Daratumumab (16 mg/kg) was administered at following dosing schedule:	Daratumumab SC: 6

	prior regimens (must have included PI and IMiD) without further established treatment option To evaluate tolerability and safety of SC delivery of daratumumab SC in Japanese subjects with relapsed or refractory multiple myeloma	Cycles 1 and 2: Once weekly Cycles 3 to 6: Once every 2 weeks Cycles 7+: Day 1 (once every 4 weeks) until disease progression or unacceptable toxicity	
Study with Daratumumab SC in Combination Therapy			
54767414MMY2040 2017-004203-41 01 May 2018/ 01 April 2019 (primary analysis cutoff) Ongoing	Phase 2 Nonrandomized, open-label, multicenter study Subjects with newly diagnosed multiple myeloma (eligible or ineligible for transplant) or subjects with relapsed or refractory multiple myeloma To evaluate the clinical benefit of SC daratumumab administered in combination with standard multiple myeloma regimens as measured by ORR or VGPR or better rate	Daratumumab solution (SC): Daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL <u>D-VMP regimen (newly diagnosed multiple myeloma ineligible for transplant)</u>: Daratumumab administered at following dosing schedule: Cycle 1 (42-day cycle): Once weekly Cycles 2 to 9 (42-day cycle): Once every 2 weeks Cycle 10+ (28-day cycle): Once every 4 weeks VMP regimen administered for 9 cycles (42-day cycles) at following dosing schedule: Bortezomib SC 1.3 mg/m^2 twice weekly in Cycle 1 followed by once weekly in Cycles 2 to 9 Melphalan PO at 9 mg/m^2 on Day 1 to 4 of each bortezomib cycle Prednisone PO at 60 mg/m^2 on Day 1 to 4 of each bortezomib cycle <u>D-Rd regimen (relapsed or refractory multiple myeloma)</u>: Daratumumab administered at following dosing schedule (28-day cycles): Cycles 1 and 2: Once weekly Cycles 3 to 6: Once every 2 weeks Cycles 7+: Day 1 (once every 4 weeks) until disease progression or unacceptable toxicity Rd regimen administered at 28-day cycles at following dosing schedule: Lenalidomide 25 mg PO each day on Days 1 to 21 of each cycle for subjects with creatinine clearance >60 mL/min and 10 mg daily for subjects with creatinine clearance between 30 and 60 mL/min Dexamethasone 40 mg weekly. For subjects >75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose could be reduced to 20 mg weekly <u>D-VRd regimen (newly diagnosed multiple myeloma eligible for transplant)</u>: Daratumumab administered at following dosing schedule:	D-VMP: 67 D-Rd: 65 D-VRd: 67

	Cycles 1 to 3 (21-day cycle): Once weekly Cycle 4 (21-day cycle): Once every 3 weeks VRd regimen administered for 4 cycles (21-day cycles) at following dosing schedule: Bortezomib SC 1.3 mg/m^2 twice weekly in Cycles 1 to 4 (Days 1, 4, 8, and 11) Lenalidomide 25 mg PO each day on Days 1 to 14 of each bortezomib cycle for subjects with creatinine clearance >60 mL/min and 10 mg daily for subjects with creatinine clearance between 30 and 60 mL/min Dexamethasone 20 mg on Days 1, 2, 9, 15, and 16 of each bortezomib cycle	

KEY: FPFV=first patient/first visit; IMiD=immunomodulatory drug; IV=intravenous; ORR=overall response rate; PFS=progression-free survival; PI=proteasome inhibitor; PO: orally; QW=once weekly; Q2W=biweekly; Q4W=once every 4 weeks; SC=subcutaneous; SCS=Summary of Clinical Safety

For monotherapy administration, data from subjects treated with daratumumab SC 1800 mg from Study MMY3012, either alone or pooled with data from supportive Studies MMY1004 and MMY1008, are described and compared to data from subjects treated with daratumumab IV in Study MMY3012. For Study MMY1004, only data from subjects who received co-formulated daratumumab SC are included in this SCS (ie, data from Part 2).

Table 39: Treatment Disposition; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Subjects who are still on treatment	111 (43.0%)	111 (42.7%)	120 (41.2%)
Subjects who discontinued treatment	147 (57.0%)	149 (57.3%)	171 (58.8%)
Reason for discontinuation			
Progressive disease	114 (44.2%)	112 (43.1%)	132 (45.4%)
Adverse event	21 (8.1%)	18 (6.9%)	18 (6.2%)
Physician decision	4 (1.6%)	9 (3.5%)	11 (3.8%)
Withdrawal by subject	5 (1.9%)	7 (2.7%)	7 (2.4%)
Death	3 (1.2%)	2 (0.8%)	2 (0.7%)
Other	0	1 (0.4%)	1 (0.3%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Note: Percentages are calculated with the number of subjects in each treatment group as the denominators.

Mod5.3.5.3/ISS/AttTSIDS01

For combination therapies, data from subjects treated with daratumumab SC 1800 mg in combination with standard background therapies (VMP, Rd, VRd) in Study MMY2040 are described.

Table 40: Treatment Disposition; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Subjects who completed treatment	65 (97.0%)	NA	NA
Subjects who are still on treatment	0	62 (92.5%)	59 (90.8%)
Subjects who discontinued treatment	2 (3.0%)	5 (7.5%)	5 (7.7%)
Reason for discontinuation			
Adverse event	1 (1.5%)	2 (3.0%)	4 (6.2%)
Death	0	1 (1.5%)	0
Progressive disease	1 (1.5%)	2 (3.0%)	1 (1.5%)

Key: Dara-SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20). D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: One subject in D-Rd cohort discontinued treatment due to progressive disease was recorded as "completed" on eCRF treatment disposition page.

Modified from Mod5.3.5.2/MMY2040/Tab6

Patient exposure

In Study MMY3012, both the median total number of treatment cycles completed (6.0) and median duration of treatment (4.7 months) for the daratumumab SC group were similar to that for the daratumumab IV group. Subjects assigned to the daratumumab SC group received up to 15 cycles of treatment with daratumumab SC and had a duration of treatment of up to 12.9 months. This was consistent with the maximum number of cycles and maximum treatment duration for the daratumumab IV group (Table 47)

Table 41: Summary of Number of Cycles, Treatment Duration, Dose Intensity, and Relative Dose Intensity; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Number of treatment cycles			
Mean (SD)	6.2 (3.25)	6.1 (3.34)	6.7 (4.21)
Median	6.0	6.0	6.0
Range	(1; 14)	(1; 15)	(1; 21)
Duration of treatment (months)			
N	258	260	291
Mean (SD)	5.015 (2.8839)	4.910 (2.9678)	5.491 (3.7675)
Median	5.355	4.747	5.322
Range	(0.03; 12.16)	(0.03; 12.91)	(0.03; 18.50)
Total number of daratumumab infusions/injections			
N	258	260	291
Mean (SD)	14.1 (5.65)	13.9 (5.67)	14.7 (6.32)
Median	16.0	15.0	16.0
Range	(1; 24)	(1; 25)	(1; 31)
Daratumumab dose intensity (mg/cycle)[a]			
N	258	260	291
Mean (SD)	2880.64 (1021.852)	4496.89 (979.312)	4410.91 (1022.055)
Median	2721.60	4371.43	4371.43
Range	(12.2; 6848.0)	(1800.0; 7200.0)	(1800.0; 7200.0)
Relative dose intensity of daratumumab (%)[b]			
N	258	260	291
Mean (SD)	96.56 (11.341)	96.68 (9.639)	97.03 (9.167)
Median	99.92	100.00	100.00
Range	(1.3; 106.2)	(25.0; 100.0)	(25.0; 100.0)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.

[a] Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles.

[b] Relative dose intensity (%) is defined as the ratio of total dose received and total planned dose.

A subject is considered as treated in a cycle if he/she received any non-zero dose of daratumumab in that cycle.

Modified from Mod5.3.5.3/ISS/AttTSIEXP01, AttTSIEXP02

Combination therapy

The median duration of treatment in the D-VMP and D-Rd cohorts of Study MMY2040 was 6.5 and 7.0 months, respectively, with subjects in these cohorts receiving up to 9 months of study treatment prior to the primary analysis cut-off date. In the D-VRd cohort, the median treatment duration was 2.6 months (maximum, 4 months) (Table 49).

Cross-study comparisons of data for the D-VMP and D-Rd cohorts of Study MMY2040 (daratumumab SC) with corresponding combination therapy groups for daratumumab IV from Studies MMY3007 and MMY3003, respectively, were limited to data collected from the first dose of study treatment through the end of Month 6 for each subject. For this reason, the median total number of treatment cycles and median duration of study treatment was approximately 6 for each cohort/study

Table 42: Summary of Number of Cycles, Treatment Duration, and Relative Dose Intensity; All Treated Analysis (Study 54767414 MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Number of treatment cycles			
Mean (SD)	4.0 (0.37)	5.3 (1.18)	7.7 (1.72)
Median	4.0	5.0	8.0
Range	(1; 4)	(1; 7)	(1; 10)
Duration of study treatment (months)			
N	67	67	65
Mean (SD)	2.6 (0.33)	6.6 (1.69)	6.8 (1.60)
Median	2.6	6.5	7.0
Range	(0; 4)	(0; 9)	(0; 9)
Number of Dara SC injections			
N	67	67	65
Mean (SD)	9.7 (1.12)	13.4 (2.96)	16.8 (3.42)
Median	10.0	14.0	18.0
Range	(2; 10)	(2; 18)	(2; 20)
Dara SC relative dose intensity (%)			
N	67	67	65
Mean (SD)	97.13 (7.115)	94.80 (10.776)	95.78 (9.719)
Median	100.00	100.00	100.00
Range	(66.7; 100.0)	(33.3; 100.0)	(47.1; 100.0)
Bortezomib (mg/m^2) relative dose intensity (%)			
N	67	67	N/A
Mean (SD)	92.90 (12.382)	89.73 (14.538)	
Median	97.90	95.25	
Range	(41.7; 103.3)	(44.2; 102.9)	
Lenalidomide (mg) relative dose intensity (%)			
N	67	N/A	65
Mean (SD)	93.75 (12.193)		81.84 (20.024)
Median	100.00		88.58
Range	(55.0; 100.0)		(30.1; 100.0)
Dexamethasone (mg) relative dose intensity (%)			
N	67	N/A	65
Mean (SD)	98.03 (6.395)		75.25 (25.207)
Median	100.00		83.33
Range	(75.0; 126.3)		(23.3; 135.3)
Melphalan (mg/m^2) relative dose intensity (%)			
N	N/A	67	N/A
Mean (SD)		92.75 (17.000)	
Median		98.49	
Range		(26.5; 121.3)	
Prednisone equivalents (mg/m^2) relative dose intensity (%)			

Table 42: Summary of Number of Cycles, Treatment Duration, and Relative Dose Intensity; All Treated Analysis (Study 54767414 MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
N	N/A	67	N/A
Mean (SD)		96.68 (6.448)	
Median		98.35	
Range		(71.2; 108.0)	

Note: Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); D-Rd = Dara-SC, lenalidomide, and dexamethasone; D-VMP = Dara-SC, bortezomib, melphalan, and prednisone; D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone; N/A = not applicable.
Note: Relative dose intensity (%) is defined as the ratio of total dose received and total planned dose.

Adverse events

Table 43: Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Any TEAE	230 (89.1%)	228 (87.7%)	259 (89.0%)
Drug-related	149 (57.8%)	132 (50.8%)	152 (52.2%)
Any serious TEAE	76 (29.5%)	68 (26.2%)	74 (25.4%)
Drug-related	22 (8.5%)	17 (6.5%)	17 (5.8%)
Maximum toxicity grades of TEAE			
Grade 1	23 (8.9%)	19 (7.3%)	22 (7.6%)
Grade 2	81 (31.4%)	90 (34.6%)	102 (35.1%)
Grade 3	81 (31.4%)	83 (31.9%)	97 (33.3%)
Grade 4	28 (10.9%)	22 (8.5%)	24 (8.2%)
Grade 5	17 (6.6%)	14 (5.4%)	14 (4.8%)
TEAE leading to treatment discontinuation	21 (8.1%)	18 (6.9%)	18 (6.2%)
Drug-related	8 (3.1%)	2 (0.8%)	2 (0.7%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as the denominators.

Mod5.3.5.3/ISS/AttTSFAE01

Table 44: Overview of Treatment-emergent Adverse Events; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Any TEAE	67 (100.0%)	67 (100.0%)	65 (100.0%)
At least 1 related to Dara SC	46 (68.7%)	50 (74.6%)	43 (66.2%)
Serious TEAE	19 (28.4%)	25 (37.3%)	26 (40.0%)
At least 1 related to Dara SC	8 (11.9%)	10 (14.9%)	10 (15.4%)
Maximum toxicity grades of TEAE			
Grade 1	9 (13.4%)	3 (4.5%)	1 (1.5%)
Grade 2	19 (28.4%)	18 (26.9%)	13 (20.0%)
Grade 3	30 (44.8%)	29 (43.3%)	33 (50.8%)
Grade 4	8 (11.9%)	15 (22.4%)	17 (26.2%)
Grade 5	1 (1.5%)	2 (3.0%)	1 (1.5%)
TEAE leading to treatment discontinuation	1 (1.5%)	2 (3.0%)	3 (4.6%)

Table 44: Overview of Treatment-emergent Adverse Events; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
TEAE leading to treatment discontinuation of daratumumab	2 (3.0%)	3 (4.5%)	3 (4.6%)

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20). D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.

Modified from Mod5.3.5.2/MMY2040/AttTSFAE01A, AttTSFAE01B

Table 45: Overall Summary of Treatment-emergent Adverse Events: D-VMP and D-Rd; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040, MMY3003 and MMY2040)

	Primary Analysis	Through Month 6		Primary Analysis	Through Month 6	
	CSR MMY 3007 Dara IV + VMP	MMY 3007 Dara IV + VMP	MMY 2040 Dara SC + VMP	CSR MMY 3003 Dara IV + Rd	MMY 3003 Dara IV + Rd	MMY 2040 Dara SC + Rd
Analysis set: safety	346	346	67	283	283	65
Any TEAE	334 (96.5%)	324 (93.6%)	67 (100.0%)	278 (98.2%)	277 (97.9%)	65 (100.0%)
At least 1 related to Dara SC	206 (59.5%)	197 (56.9%)	49 (73.1%)	215 (76.0%)	207 (73.1%)	41 (63.1%)
Serious TEAE	144 (41.6%)	115 (33.2%)	24 (35.8%)	138 (48.8%)	99 (35.0%)	23 (35.4%)
Maximum toxicity grades of TEAE						
Grade 1	12 (3.5%)	23 (6.6%)	3 (4.5%)	5 (1.8%)	15 (5.3%)	3 (4.6%)
Grade 2	50 (14.5%)	59 (17.1%)	19 (28.4%)	44 (15.5%)	57 (20.1%)	13 (20.0%)
Grade 3	182 (52.6%)	168 (48.6%)	28 (41.8%)	143 (50.5%)	136 (48.1%)	32 (49.2%)
Grade 4	71 (20.5%)	61 (17.6%)	15 (22.4%)	75 (26.5%)	60 (21.2%)	16 (24.6%)
Grade 5	19 (5.5%)	13 (3.8%)	2 (3.0%)	11 (3.9%)	9 (3.2%)	1 (1.5%)
TEAE leading to treatment discontinuation	17 (4.9%)	11 (3.2%)	2 (3.0%)	19 (6.7%)	16 (5.7%)	3 (4.6%)
TEAE leading to treatment discontinuation of daratumumab	23 (6.6%)	18 (5.2%)	3 (4.5%)	25 (8.8%)	19 (6.7%)	3 (4.6%)

Note: TEAE = treatment-emergent adverse event; Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: Primary analysis CSR data column is based on a median treatment duration of 14.7 months for the D-VMP group of MMY3007 and 13.1 months for the D-Rd group of MMY3003.

Modified from Mod5.3.5.3/ISS/AttTSFAE01C and AttTSFAE01D

All Grade adverse events

Monotherapy

All **drug-related TEAEs** were balanced between treatment groups (<5% difference in incidence) except neutropenia (daratumumab SC: 12.3%; daratumumab IV: 6.2%) and chills (5.4% and 11.6%, respectively; Attachment TSFAE03). A majority of all TEAEs in both treatment groups were assessed by the investigator to be related to study drug (50.8% and 57.8%, respectively – *see Table 49*).

Table 46: Most Common (At Least 10%) Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Total number of subjects with TEAE	230 (89.1%)	228 (87.7%)	259 (89.0%)
MedDRA System Organ Class / Preferred Term			
Infections and infestations	117 (45.3%)	119 (45.8%)	142 (48.8%)
Upper respiratory tract infection	25 (9.7%)	35 (13.5%)	41 (14.1%)
Blood and lymphatic system disorders	104 (40.3%)	110 (42.3%)	127 (43.6%)
Anaemia	60 (23.3%)	68 (26.2%)	72 (24.7%)
Neutropenia	35 (13.6%)	50 (19.2%)	54 (18.6%)
Thrombocytopenia	48 (18.6%)	48 (18.5%)	54 (18.6%)
Lymphopenia	17 (6.6%)	19 (7.3%)	29 (10.0%)
General disorders and administration site conditions	113 (43.8%)	102 (39.2%)	123 (42.3%)
Pyrexia	33 (12.8%)	34 (13.1%)	39 (13.4%)
Fatigue	27 (10.5%)	28 (10.8%)	33 (11.3%)
Chills	32 (12.4%)	15 (5.8%)	18 (6.2%)
Musculoskeletal and connective tissue disorders	86 (33.3%)	96 (36.9%)	114 (39.2%)
Back pain	32 (12.4%)	27 (10.4%)	35 (12.0%)
Gastrointestinal disorders	91 (35.3%)	81 (31.2%)	97 (33.3%)
Diarrhoea	28 (10.9%)	39 (15.0%)	45 (15.5%)
Nausea	28 (10.9%)	21 (8.1%)	26 (8.9%)
Respiratory, thoracic and mediastinal disorders	91 (35.3%)	58 (22.3%)	72 (24.7%)
Cough	33 (12.8%)	22 (8.5%)	27 (9.3%)
Dyspnoea	28 (10.9%)	14 (5.4%)	17 (5.8%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as the denominators.
Note: Adverse events are reported using MedDRA version 21.1.

Table 47: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Total number of subjects with Grade 3 or 4 TEAE	126 (48.8%)	118 (45.4%)	134 (46.0%)
MedDRA System Organ Class / Preferred Term			
Blood and lymphatic system disorders	72 (27.9%)	77 (29.6%)	86 (29.6%)
Thrombocytopenia	35 (13.6%)	36 (13.8%)	38 (13.1%)
Neutropenia	20 (7.8%)	34 (13.1%)	37 (12.7%)
Anaemia	36 (14.0%)	34 (13.1%)	35 (12.0%)
Lymphopenia	16 (6.2%)	13 (5.0%)	19 (6.5%)
Vascular disorders	17 (6.6%)	11 (4.2%)	14 (4.8%)
Hypertension	16 (6.2%)	8 (3.1%)	10 (3.4%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as the denominators.
Note: Adverse events are reported using MedDRA version 21.1.

Table 48: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set (Study 54767414 MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Total number of subjects with Grade 3 or 4 TEAE	39 (58.2%)	46 (68.7%)	51 (78.5%)
MedDRA system organ class/ Preferred term			
Blood and lymphatic system disorders	31 (46.3%)	38 (56.7%)	34 (52.3%)
Neutropenia	19 (28.4%)	21 (31.3%)	31 (47.7%)
Lymphopenia	11 (16.4%)	14 (20.9%)	8 (12.3%)
Thrombocytopenia	10 (14.9%)	23 (34.3%)	4 (6.2%)
Leukopenia	5 (7.5%)	4 (6.0%)	6 (9.2%)
Anaemia	3 (4.5%)	8 (11.9%)	3 (4.6%)
Infections and infestations	5 (7.5%)	8 (11.9%)	15 (23.1%)
Pneumonia	2 (3.0%)	3 (4.5%)	4 (6.2%)
Metabolism and nutrition disorders	3 (4.5%)	9 (13.4%)	8 (12.3%)
Hyperglycaemia	1 (1.5%)	1 (1.5%)	4 (6.2%)
Vascular disorders	1 (1.5%)	7 (10.4%)	1 (1.5%)
Hypertension	1 (1.5%)	4 (6.0%)	1 (1.5%)

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20). D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: Adverse events are reported using MedDRA version 21.1.

Modified from Mod5.3.5.2/MMY2040/Tab28

Table 49: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term: D-VMP and D-Rd; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040, MMY3003 and MMY2040)

	Primary Analysis	Through Month 6		Primary Analysis	Through Month 6	
	CSR MMY 3007 Dara IV + VMP	MMY 3007 Dara IV + VMP	MMY 2040 Dara SC + VMP	CSR MMY 3003 Dara IV + Rd	MMY 3003 Dara IV + Rd	MMY 2040 Dara SC + Rd
Analysis set: safety	346	346	67	283	283	65
Total number of subjects with Grade 3 or 4 TEAE	268 (77.5%)	239 (69.1%)	45 (67.2%)	229 (80.9%)	205 (72.4%)	49 (75.4%)
MedDRA system organ class/ Preferred term						
Blood and lymphatic system disorders	209 (60.4%)	184 (53.2%)	37 (55.2%)	162 (57.2%)	151 (53.4%)	33 (50.8%)
Thrombocytopenia	119 (34.4%)	98 (28.3%)	22 (32.8%)	36 (12.7%)	27 (9.5%)	4 (6.2%)
Neutropenia	138 (39.9%)	121 (35.0%)	20 (29.9%)	147 (51.9%)	137 (48.4%)	30 (46.2%)
Lymphopenia	26 (7.5%)	24 (6.9%)	14 (20.9%)	15 (5.3%)	15 (5.3%)	7 (10.8%)
Anaemia	55 (15.9%)	45 (13.0%)	8 (11.9%)	35 (12.4%)	24 (8.5%)	3 (4.6%)
Leukopenia	28 (8.1%)	27 (7.8%)	4 (6.0%)	8 (2.8%)	8 (2.8%)	5 (7.7%)
Infections and infestations	80 (23.1%)	56 (16.2%)	7 (10.4%)	80 (28.3%)	52 (18.4%)	12 (18.5%)
Pneumonia	39 (11.3%)	27 (7.8%)	2 (3.0%)	25 (8.8%)	15 (5.3%)	3 (4.6%)
Vascular disorders	19 (5.5%)	16 (4.6%)	7 (10.4%)	16 (5.7%)	14 (4.9%)	1 (1.5%)
Hypertension	14 (4.0%)	12 (3.5%)	4 (6.0%)	9 (3.2%)	8 (2.8%)	1 (1.5%)
Metabolism and nutrition disorders	43 (12.4%)	37 (10.7%)	8 (11.9%)	43 (15.2%)	26 (9.2%)	8 (12.3%)
Hyperglycaemia	10 (2.9%)	8 (2.3%)	1 (1.5%)	10 (3.5%)	9 (3.2%)	4 (6.2%)

Note: TEAE = treatment-emergent adverse event; Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.
Percentages are calculated with the number of subjects in each group as denominators. Adverse events are reported using MedDRA version 21.1.
Grade 3 or 4 adverse events shown are those reported in at least 5% of subjects in of subjects in D-VMP or D-Rd cohort of MMY2040, MMY3007, or MMY3003 through Month 6.
Note: Primary analysis CSR data column is based on a median treatment duration of 14.7 months for the D-VMP group of MMY3007 and 13.1 months for the D-Rd group of MMY3003.

Modified from Mod5.3.5.3/ISS/AttTSFAE04A, AttTSFAE04B, AttTSFAE03C, AttTSFAE03D; MMY3007 CSR, Attachment TSFAE03A, MMY3003 CSR, Table 31

Adverse events of special interest

Table 50: Treatment-emergent Infusion-related Reactions Reported in 1% or More of Subjects by System Organ Class, Preferred Term and Grade 3 or 4; Safety Analysis Set (Studies: MMY3012, MMY2040, MMY1004 Part 2, and MMY1008)

				Dara SC								
	Dara IV MMY3012			Pooled Monotherapy			Pooled Combination			Total		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Analysis set: safety	258			291			199			490		
Total number of subjects with treatment-emergent infusion-related reactions	89 (34.5%)	14 (5.4%)	0	37 (12.7%)	6 (2.1%)	0	15 (7.5%)	1 (0.5%)	0	52 (10.6%)	7 (1.4%)	0
Total number of subjects with treatment-emergent infusion-related reactions in more than 1 infusions	3 (1.2%)	0	0	1 (0.3%)	0	0	1 (0.5%)	1 (0.5%)	0	2 (0.4%)	1 (0.2%)	0
MedDRA System Organ Class / Preferred Term												
General disorders and administration site conditions	38 (14.7%)	2 (0.8%)	0	24 (8.2%)	1 (0.3%)	0	11 (5.5%)	0	0	35 (7.1%)	1 (0.2%)	0
Pyrexia	7 (2.7%)	1 (0.4%)	0	12 (4.1%)	0	0	10 (5.0%)	0	0	22 (4.5%)	0	0
Chills	30 (11.6%)	2 (0.8%)	0	13 (4.5%)	1 (0.3%)	0	4 (2.0%)	0	0	17 (3.5%)	1 (0.2%)	0
Chest discomfort	3 (1.2%)	0	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	43 (16.7%)	4 (1.6%)	0	13 (4.5%)	2 (0.7%)	0	2 (1.0%)	0	0	15 (3.1%)	2 (0.4%)	0
Dyspnoea	17 (6.6%)	2 (0.8%)	0	4 (1.4%)	1 (0.3%)	0	1 (0.5%)	0	0	5 (1.0%)	1 (0.2%)	0
Cough	9 (3.5%)	0	0	2 (0.7%)	1 (0.3%)	0	1 (0.5%)	0	0	3 (0.6%)	1 (0.2%)	0
Nasal congestion	11 (4.3%)	1 (0.4%)	0	3 (1.0%)	0	0	0	0	0	3 (0.6%)	0	0
Wheezing	3 (1.2%)	0	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0	0
Throat irritation	5 (1.9%)	0	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	0
Bronchospasm	7 (2.7%)	1 (0.4%)	0	0	0	0	0	0	0	0	0	0
Nasal oedema	3 (1.2%)	0	0	0	0	0	0	0	0	0	0	0

Table 50: Treatment-emergent Infusion-related Reactions Reported in 1% or More of Subjects by System Organ Class, Preferred Term and Grade 3 or 4; Safety Analysis Set (Studies: MMY3012, MMY2040, MMY1004 Part 2, and MMY1008)

				Dara SC								
	Dara IV MMY3012			Pooled Monotherapy			Pooled Combination			Total		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Analysis set: safety	258			291			199			490		
Vascular disorders	16 (6.2%)	6 (2.3%)	0	5 (1.7%)	4 (1.4%)	0	1 (0.5%)	0	0	6 (1.2%)	4 (0.8%)	0
Hypertension	9 (3.5%)	5 (1.9%)	0	4 (1.4%)	3 (1.0%)	0	0	0	0	4 (0.8%)	3 (0.6%)	0
Flushing	3 (1.2%)	0	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0	0
Hypotension	3 (1.2%)	0	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0	0
Infections and infestations	1 (0.4%)	0	0	0	0	0	2 (1.0%)	0	0	2 (0.4%)	0	0
Rhinitis	1 (0.4%)	0	0	0	0	0	2 (1.0%)	0	0	2 (0.4%)	0	0
Nervous system disorders	6 (2.3%)	1 (0.4%)	0	1 (0.3%)	0	0	1 (0.5%)	0	0	2 (0.4%)	0	0
Headache	5 (1.9%)	1 (0.4%)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	13 (5.0%)	1 (0.4%)	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	0
Nausea	5 (1.9%)	0	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	0
Vomiting	5 (1.9%)	1 (0.4%)	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	0
Skin and subcutaneous tissue disorders	9 (3.5%)	2 (0.8%)	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0	0
Pruritus	4 (1.6%)	0	0	0	0	0	0	0	0	0	0	0

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled monotherapy column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008; the pooled combination column includes subjects from all three cohorts in MMY2040.
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: Adverse events are reported using MedDRA version 21.1.

Modified from Mod5.3.5.3/ISS/AttTSFIRR03

Infusion-related reactions (IRRs):IRRs were defined as administration related systemic reactions, regardless of the route of administration.

Table 51: Treatment-emergent Cytopenia Adverse Events; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Neutropenia			
Any grade	35 (13.6%)	50 (19.2%)	54 (18.6%)
Grade 3 or 4	20 (7.8%)	34 (13.1%)	27 (12.7%)
Serious TEAE	1 (0.4%)	0	0
TEAE leading to treatment discontinuation	1 (0.4%)	0	0
TEAE leading to treatment modification[a]	9 (3.5%)	5 (1.9%)	6 (2.1%)
Febrile neutropenia			
Any grade	6 (2.3%)	3 (1.2%)	4 (1.4%)
Grade 3 or 4	6 (2.3%)	3 (1.2%)	4 (1.4%)
Serious TEAE	2 (0.8%)	1 (0.4%)	2 (0.7%)
TEAE leading to treatment discontinuation	0	1 (0.4%)	1 (0.3%)
TEAE leading to treatment modification[a]	0	1 (0.4%)	1 (0.3%)
Anaemia			
Any grade	60 (23.3%)	68 (26.2%)	72 (24.7%)
Grade 3 or 4	36 (14.0%)	34 (13.1%)	35 (12.0%)
Serious TEAE	4 (1.6%)	5 (1.9%)	5 (1.7%)
TEAE leading to treatment discontinuation	3 (1.2%)	2 (0.8%)	2 (0.7%)
TEAE leading to treatment modification[a]	5 (1.9%)	2 (0.8%)	2 (0.7%)
Lymphopenia			
Any grade	17 (6.6%)	19 (7.3%)	29 (10.0%)
Grade 3 or 4	16 (6.2%)	13 (5.0%)	19 (6.5%)
Serious TEAE	0	0	0
TEAE leading to treatment discontinuation	0	0	0
TEAE leading to treatment modification[a]	0	0	0
Thrombocytopenia			
Any grade	48 (18.6%)	48 (18.5%)	54 (18.6%)
Grade 3 or 4	35 (13.6%)	36 (13.8%)	38 (13.1%)
Serious TEAE	4 (1.6%)	3 (1.2%)	3 (1.0%)
TEAE leading to treatment discontinuation	5 (1.9%)	2 (0.8%)	2 (0.7%)
TEAE leading to treatment modification[a]	15 (5.8%)	20 (7.7%)	20 (6.9%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
TEAE=treatment-emergent adverse event.
[a] Adverse events reported as the reason for action of 'infusion delayed within the cycle', 'injection delayed within the cycle', 'infusion skipped', or 'injection skipped' on the daratumumab infusion CRF page, or for cycle delay on the cycle delay CRF page are summarized.
Note: Adverse events are reported using MedDRA version 21.1.
Note: Percentages are calculated with the number of subjects in each group as the denominators.

Modified from Mod5.3.5.3/ISS/AttTSFAE02, AttTSFAE04, AttTSFAE08, AttTSFAE11, AttTSFAE12

Table 52: Treatment-emergent Cytopenia Adverse Events; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Neutropenia			
Any grade	25 (37.3%)	25 (37.3%)	38 (58.5%)
Grade 3 or 4	19 (28.4%)	21 (31.3%)	31 (47.7%)
Serious TEAE	0	0	3 (4.6%)
TEAE leading to treatment discontinuation	0	0	0[b]
TEAE leading to treatment modification[a]	2 (3.0%)	5 (7.5%)	10 (15.4%)
Febrile neutropenia			
Any grade	2 (3.0%)	3 (4.5%)	2 (3.1%)
Grade 3 or 4	2 (3.0%)	3 (4.5%)	2 (3.1%)
Serious TEAE	1 (1.5%)	2 (3.0%)	1 (1.5%)
TEAE leading to treatment discontinuation	0	0	0
TEAE leading to treatment modification[a]	0	3 (4.5%)	1 (1.5%)
Anaemia			
Any grade	12 (17.9%)	24 (35.8%)	17 (26.2%)
Grade 3 or 4	3 (4.5%)	8 (11.9%)	3 (4.6%)
Serious TEAE	0	0	1 (1.5%)
TEAE leading to treatment discontinuation	0	0	0[b]
TEAE leading to treatment modification[a]	0	1 (1.5%)	1 (1.5%)
Lymphopenia			
Any grade	13 (19.4%)	14 (20.9%)	10 (15.4%)
Grade 3 or 4	11 (16.4%)	14 (20.9%)	8 (12.3%)
Serious TEAE	0	0	0
TEAE leading to treatment discontinuation	0	0	0
TEAE leading to treatment modification[a]	0	0	1 (1.5%)
Thrombocytopenia			
Any grade	26 (38.8%)	36 (53.7%)	21 (32.3%)
Grade 3 or 4	10 (14.9%)	23 (34.3%)	4 (6.2%)
Serious TEAE	1 (1.5%)	2 (3.0%)	1 (1.5%)
TEAE leading to treatment discontinuation	0	0	0[b]
TEAE leading to treatment modification[a]	2 (3.0%)	10 (14.9%)	0

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20). D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: Adverse events are reported using MedDRA version 21.1.
[a] Adverse events reported as the reason for action of 'injection delayed', 'injection skipped' on the daratumumab injection CRF page, or for cycle delay on the cycle delay CRF page are summarized
[b] One subject in D-Rd cohort whose end of treatment was progressive disease, had TEAEs of neutropenia, anemia, and thrombocytopenia that occurred at the time of discontinuation but were not included in the summary of discontinuation of (all) study treatment due to TEAEs.
Modified from Mod5.3.5.2/MMY2040/AttTSFAE02A, AttTSFAE03A, AttTSFAE04A, AttTSFAE05A, AttTSFAE05E

The incidence of severe **hemorrhagic TEAEs** was low and balanced between daratumumab SC and daratumumab IV in Study MMY3012 and similar for the D-VMP and D-Rd regimens in Study MMY2040 compared to historic data with the corresponding daratumumab IV combination regimens in Studies MMY3007 and MMY3003, respectively. The totality of data for Studies MMY3012 or MMY2040 did not indicate any clear evidence of a relationship between thrombocytopenia and Grade 3 or higher hemorrhagic events

Infections and infestations

Monotherapy

The overall incidence of infection and infestation TEAEs remained balanced between the daratumumab SC and daratumumab IV groups regardless of time of onset. In both treatment groups, the proportion of subjects with new onset infection and infestation TEAEs tended to be lower after 6 cycles of treatment (daratumumab SC: 20.3% for Cycles 7+ vs 28.5% and 27.4% for Cycles 1-2 and 3-6, respectively; daratumumab IV: 17.3% for Cycles 7+ vs 24.4% and 23.6% for Cycles 1-2 and 3-6, respectively) (Mod5.3.5.3/ISS/AttTSFINF02).

Most infection and infestation TEAEs were Grade 1 or 2, with the incidence of Grade 3 or 4 TEAEs low and similar for the daratumumab SC and daratumumab IV groups (10.4% and 11.2%, respectively). Pneumonia was the only Grade 3 or 4 infection TEAE reported in ≥2% of subjects in the daratumumab SC or daratumumab IV groups (2.7% and 3.9%, respectively) (Mod5.3.5.3/ISS/AttTSFINF01).

A small number of treatment-emergent infections were fatal, and this proportion was lower in the daratumumab SC group (3/119 subjects in the daratumumab SC and 10/117 subjects in the daratumumab IV group) (Mod5.3.5.1/MMY3012/Sec8.1.2.4.4).

Most infections were manageable and rarely led to treatment discontinuation (daratumumab SC, 1.2%; daratumumab IV, 3.5%) (Mod5.3.5.3/ISS/AttTSFAE11)

TSFAEINF01A: Summary of Treatment-emergent Adverse Events of Infections and Infestations by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3012)

	Dara IV			Dara SC		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Analysis set: safety	258			260		
Total number of subjects with TEAE of Infections and Infestations	117 (45.3%)	29 (11.2%)	10 (3.9%)	119 (45.8%)	27 (10.4%)	3 (1.2%)
MedDRA Preferred Term						
Upper respiratory tract infection	25 (9.7%)	2 (0.8%)	0	35 (13.5%)	0	0
Nasopharyngitis	16 (6.2%)	0	0	18 (6.9%)	0	0
Sinusitis	4 (1.6%)	0	0	10 (3.8%)	0	0
Bronchitis	8 (3.1%)	0	0	9 (3.5%)	2 (0.8%)	0
Pneumonia	16 (6.2%)	10 (3.9%)	1 (0.4%)	9 (3.5%)	7 (2.7%)	0
Urinary tract infection	9 (3.5%)	3 (1.2%)	1 (0.4%)	9 (3.5%)	0	0
Lower respiratory tract infection	5 (1.9%)	2 (0.8%)	0	8 (3.1%)	4 (1.5%)	0
Respiratory tract infection	2 (0.8%)	1 (0.4%)	0	8 (3.1%)	2 (0.8%)	0
Influenza	7 (2.7%)	0	0	7 (2.7%)	3 (1.2%)	0
Lung infection	4 (1.6%)	2 (0.8%)	1 (0.4%)	5 (1.9%)	4 (1.5%)	0
Oral herpes	2 (0.8%)	0	0	4 (1.5%)	0	0
Viral infection	1 (0.4%)	0	0	4 (1.5%)	0	0
Herpes zoster	3 (1.2%)	0	0	3 (1.2%)	0	0
Rhinitis	4 (1.6%)	0	0	3 (1.2%)	0	0
Sepsis	4 (1.6%)	4 (1.6%)	2 (0.8%)	3 (1.2%)	3 (1.2%)	0
Septic shock	4 (1.6%)	1 (0.4%)	3 (1.2%)	3 (1.2%)	1 (0.4%)	2 (0.8%)
Abscess limb	0	0	0	2 (0.8%)	0	0
Cellulitis	0	0	0	2 (0.8%)	0	0
Fungal infection	0	0	0	2 (0.8%)	0	0
Hepatitis B reactivation	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	0
Pharyngitis	3 (1.2%)	0	0	2 (0.8%)	0	0
Salmonellosis	0	0	0	2 (0.8%)	0	0
Acute sinusitis	2 (0.8%)	0	0	1 (0.4%)	0	0
Bacterial infection	0	0	0	1 (0.4%)	0	0
Candida infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Chronic sinusitis	0	0	0	1 (0.4%)	0	0
Clostridium difficile infection	0	0	0	1 (0.4%)	0	0
Corona virus infection	0	0	0	1 (0.4%)	0	0
Cystitis	0	0	0	1 (0.4%)	0	0
Cytomegalovirus infection	0	0	0	1 (0.4%)	0	0
Escherichia urinary tract infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Eye infection	0	0	0	1 (0.4%)	0	0
Folliculitis	1 (0.4%)	0	0	1 (0.4%)	0	0
Furuncle	0	0	0	1 (0.4%)	1 (0.4%)	0
Gingivitis	2 (0.8%)	0	0	1 (0.4%)	0	0
Haemophilus infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Herpes simplex	1 (0.4%)	0	0	1 (0.4%)	0	0
Hordeolum	0	0	0	1 (0.4%)	0	0
Infection	4 (1.6%)	1 (0.4%)	0	1 (0.4%)	0	0
Labyrinthitis	0	0	0	1 (0.4%)	0	0
Listeriosis	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
Meningitis cryptococcal	0	0	0	1 (0.4%)	1 (0.4%)	0
Nail infection	0	0	0	1 (0.4%)	0	0
Neutropenic sepsis	0	0	0	1 (0.4%)	1 (0.4%)	0
Onychomycosis	0	0	0	1 (0.4%)	0	0
Ophthalmic herpes zoster	0	0	0	1 (0.4%)	1 (0.4%)	0
Oral candidiasis	1 (0.4%)	0	0	1 (0.4%)	0	0
Oral fungal infection	0	0	0	1 (0.4%)	0	0
Otitis externa	0	0	0	1 (0.4%)	0	0
Otitis media	0	0	0	1 (0.4%)	0	0
Otitis media acute	0	0	0	1 (0.4%)	0	0
Paronychia	2 (0.8%)	0	0	1 (0.4%)	0	0
Periodontitis	0	0	0	1 (0.4%)	0	0
Tinea cruris	0	0	0	1 (0.4%)	0	0
Bacteraemia	1 (0.4%)	1 (0.4%)	0	0	0	0
Campylobacter gastroenteritis	1 (0.4%)	1 (0.4%)	0	0	0	0
Chronic tonsillitis	1 (0.4%)	0	0	0	0	0
Conjunctivitis	2 (0.8%)	0	0	0	0	0
Diarrhoea infectious	1 (0.4%)	0	0	0	0	0
Ear infection	1 (0.4%)	0	0	0	0	0
Gastroenteritis	3 (1.2%)	0	0	0	0	0
Genital herpes	1 (0.4%)	0	0	0	0	0
Mastoiditis	2 (0.8%)	1 (0.4%)	0	0	0	0
Meningitis pneumococcal	1 (0.4%)	1 (0.4%)	0	0	0	0
Mucosal infection	1 (0.4%)	0	0	0	0	0
Necrotising fasciitis	1 (0.4%)	1 (0.4%)	0	0	0	0
Pneumocystis jirovecii pneumonia	2 (0.8%)	2 (0.8%)	1 (0.4%)	0	0	0
Respiratory syncytial virus infection	2 (0.8%)	0	0	0	0	0
Rhinovirus infection	3 (1.2%)	0	0	0	0	0
Skin infection	1 (0.4%)	0	0	0	0	0
Staphylococcal infection	1 (0.4%)	0	0	0	0	0
Staphylococcal sepsis	1 (0.4%)	1 (0.4%)	0	0	0	0
Tinea pedis	1 (0.4%)	0	0	0	0	0
Vulvovaginitis	1 (0.4%)	0	0	0	0	0

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as denominators.

Combination therapy

In each daratumumab SC combination therapy cohort of Study MMY2040, the majority of infection and infestation TEAEs were assessed as Grade 1 or 2 in severity.

D-VMP cohort: The incidence of Grade 3 or 4 infection and infestation TEAEs was 11.9%, with pneumonia being the most common of these events (4.5%) (Mod5.3.5.2/MMY2040/AttTSFAEINF01). Treatment was discontinued for 2 subjects (3.0%) in this cohort due to a Grade 3 or 4 infection TEAE (pneumonitis and neutropenic sepsis) (Mod5.3.5.2/MMY2040/AttTSFAE05A), the latter of which subsequently worsened to Grade 5 (Mod5.3.5.2/MMY2040/Sec7.1.2.4.6).

D-Rd cohort: The incidence of Grade 3 or 4 infection and infestation TEAEs was 23.1%, with pneumonia being the most common of these events (6.2%) (Mod5.3.5.2/MMY2040/AttTSFAEINF01). Treatment was discontinued for 2 subjects (3.1%) in this cohort due to a Grade 3 or 4 infection TEAEs (Grade 3 or 4 pneumonia in both) (Mod5.3.5.2/MMY2040/AttTSFAE05A).

D-VRd cohort: The incidence of Grade 3 or 4 infection and infestation TEAEs was 7.5%, with pneumonia being the only such event reported in >1 subject in this cohort (3.0%) (TSFAEINF01). Treatment was not discontinued for any subject in this cohort due to a Grade 3 or 4 infection TEAE (TSFAE05A).

TSFAEINF01: Summary of Grade 3 or 4 Treatment-emergent Adverse Events of Infections and Infestations by Preferred Term and Relationship; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd		D-VMP		D-Rd	
	Total	Related	Total	Related	Total	Related
Analysis set: all treated	67		67		65	
Total number of subjects with Grade 3 or 4 TEAE of Infections and Infestations	5 (7.5%)	3 (4.5%)	8 (11.9%)	3 (4.5%)	15 (23.1%)	8 (12.3%)
MedDRA preferred term						
Pneumonia	2 (3.0%)	1 (1.5%)	3 (4.5%)	1 (1.5%)	4 (6.2%)	2 (3.1%)
Infection	1 (1.5%)	1 (1.5%)	0	0	1 (1.5%)	1 (1.5%)
Pneumococcal sepsis	1 (1.5%)	0	0	0	0	0
Urinary tract infection	1 (1.5%)	0	1 (1.5%)	0	0	0
Urosepsis	1 (1.5%)	1 (1.5%)	0	0	0	0
Bronchitis	0	0	0	0	1 (1.5%)	1 (1.5%)
Central nervous system infection	0	0	0	0	1 (1.5%)	0
Escherichia pyelonephritis	0	0	1 (1.5%)	0	0	0
Gastroenteritis	0	0	0	0	1 (1.5%)	0
Infection parasitic	0	0	1 (1.5%)	0	0	0
Influenza	0	0	0	0	2 (3.1%)	2 (3.1%)
Lower respiratory tract infection	0	0	0	0	2 (3.1%)	1 (1.5%)
Lung infection	0	0	0	0	1 (1.5%)	1 (1.5%)
Neutropenic sepsis	0	0	2 (3.0%)	2 (3.0%)	0	0
Pharyngitis	0	0	0	0	1 (1.5%)	0
Sepsis	0	0	0	0	2 (3.1%)	1 (1.5%)
Upper respiratory tract infection	0	0	0	0	1 (1.5%)	0

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: Adverse events are reported using MedDRA version 21.1.

[TSFAEINF01.RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TSFAEINF01.SAS] 29MAR2019, 18:07

A similar proportion of subjects in the daratumumab SC (23.6%) and daratumumab IV (20.8%) groups received a transfusion of any type of blood product (most commonly packed RBCs) although the number of transfusions was higher in the daratumumab IV group (daratumumab SC: 193; daratumumab IV: 318) (see Table TSITRSF01/CSR). There were more transfusion days, which is a more precisely defined measure compared to "transfusion events", in the IV arm, where there were more AEs of anaemia, mainly driven by four heavily treated patients.

TSFAEINF01A: Summary of Treatment-emergent Adverse Events of Infections and Infestations by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3012)

	Dara IV			Dara SC		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Analysis set: safety	258			260		
Total number of subjects with TEAE of Infections and Infestations	117 (45.3%)	29 (11.2%)	10 (3.9%)	119 (45.8%)	27 (10.4%)	3 (1.2%)
MedDRA Preferred Term						
Upper respiratory tract infection	25 (9.7%)	2 (0.8%)	0	35 (13.5%)	0	0
Nasopharyngitis	16 (6.2%)	0	0	18 (6.9%)	0	0
Sinusitis	4 (1.6%)	0	0	10 (3.8%)	0	0
Bronchitis	8 (3.1%)	0	0	9 (3.5%)	2 (0.8%)	0
Pneumonia	16 (6.2%)	10 (3.9%)	1 (0.4%)	9 (3.5%)	7 (2.7%)	0
Urinary tract infection	9 (3.5%)	3 (1.2%)	1 (0.4%)	9 (3.5%)	0	0
Lower respiratory tract infection	5 (1.9%)	2 (0.8%)	0	8 (3.1%)	4 (1.5%)	0
Respiratory tract infection	2 (0.8%)	1 (0.4%)	0	8 (3.1%)	2 (0.8%)	0
Influenza	7 (2.7%)	0	0	7 (2.7%)	3 (1.2%)	0
Lung infection	4 (1.6%)	2 (0.8%)	1 (0.4%)	5 (1.9%)	4 (1.5%)	0
Oral herpes	2 (0.8%)	0	0	4 (1.5%)	0	0
Viral infection	1 (0.4%)	0	0	4 (1.5%)	0	0
Herpes zoster	3 (1.2%)	0	0	3 (1.2%)	0	0
Rhinitis	4 (1.6%)	0	0	3 (1.2%)	0	0
Sepsis	4 (1.6%)	4 (1.6%)	2 (0.8%)	3 (1.2%)	3 (1.2%)	0
Septic shock	4 (1.6%)	1 (0.4%)	3 (1.2%)	3 (1.2%)	1 (0.4%)	2 (0.8%)
Abscess limb	0	0	0	2 (0.8%)	0	0
Cellulitis	0	0	0	2 (0.8%)	0	0
Fungal infection	0	0	0	2 (0.8%)	0	0
Hepatitis B reactivation	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	0
Pharyngitis	3 (1.2%)	0	0	2 (0.8%)	0	0
Salmonellosis	0	0	0	2 (0.8%)	0	0
Acute sinusitis	2 (0.8%)	0	0	1 (0.4%)	0	0
Bacterial infection	0	0	0	1 (0.4%)	0	0
Candida infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Chronic sinusitis	0	0	0	1 (0.4%)	0	0
Clostridium difficile infection	0	0	0	1 (0.4%)	0	0
Corona virus infection	0	0	0	1 (0.4%)	0	0
Cystitis	0	0	0	1 (0.4%)	0	0
Cytomegalovirus infection	0	0	0	1 (0.4%)	0	0
Escherichia urinary tract infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Eye infection	0	0	0	1 (0.4%)	0	0
Folliculitis	1 (0.4%)	0	0	1 (0.4%)	0	0
Furuncle	0	0	0	1 (0.4%)	1 (0.4%)	0
Gingivitis	2 (0.8%)	0	0	1 (0.4%)	0	0
Haemophilus infection	1 (0.4%)	0	0	1 (0.4%)	0	0
Herpes simplex	1 (0.4%)	0	0	1 (0.4%)	0	0
Hordeolum	0	0	0	1 (0.4%)	0	0
Infection	4 (1.6%)	1 (0.4%)	0	1 (0.4%)	0	0
Labyrinthitis	0	0	0	1 (0.4%)	0	0
Listeriosis	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
Meningitis cryptococcal	0	0	0	1 (0.4%)	1 (0.4%)	0
Nail infection	0	0	0	1 (0.4%)	0	0
Neutropenic sepsis	0	0	0	1 (0.4%)	1 (0.4%)	0
Onychomycosis	0	0	0	1 (0.4%)	0	0
Ophthalmic herpes zoster	0	0	0	1 (0.4%)	1 (0.4%)	0
Oral candidiasis	1 (0.4%)	0	0	1 (0.4%)	0	0
Oral fungal infection	0	0	0	1 (0.4%)	0	0
Otitis externa	0	0	0	1 (0.4%)	0	0
Otitis media	0	0	0	1 (0.4%)	0	0
Otitis media acute	0	0	0	1 (0.4%)	0	0
Paronychia	2 (0.8%)	0	0	1 (0.4%)	0	0
Periodontitis	0	0	0	1 (0.4%)	0	0
Tinea cruris	0	0	0	1 (0.4%)	0	0
Bacteraemia	1 (0.4%)	1 (0.4%)	0	0	0	0
Campylobacter gastroenteritis	1 (0.4%)	1 (0.4%)	0	0	0	0
Chronic tonsillitis	1 (0.4%)	0	0	0	0	0
Conjunctivitis	2 (0.8%)	0	0	0	0	0
Diarrhoea infectious	1 (0.4%)	0	0	0	0	0
Ear infection	1 (0.4%)	0	0	0	0	0
Gastroenteritis	3 (1.2%)	0	0	0	0	0
Genital herpes	1 (0.4%)	0	0	0	0	0
Mastoiditis	2 (0.8%)	1 (0.4%)	0	0	0	0
Meningitis pneumococcal	1 (0.4%)	1 (0.4%)	0	0	0	0
Mucosal infection	1 (0.4%)	0	0	0	0	0
Necrotising fasciitis	1 (0.4%)	1 (0.4%)	0	0	0	0
Pneumocystis jirovecii pneumonia	2 (0.8%)	2 (0.8%)	1 (0.4%)	0	0	0
Respiratory syncytial virus infection	2 (0.8%)	0	0	0	0	0
Rhinovirus infection	3 (1.2%)	0	0	0	0	0
Skin infection	1 (0.4%)	0	0	0	0	0
Staphylococcal infection	1 (0.4%)	0	0	0	0	0
Staphylococcal sepsis	1 (0.4%)	1 (0.4%)	0	0	0	0
Tinea pedis	1 (0.4%)	0	0	0	0	0
Vulvovaginitis	1 (0.4%)	0	0	0	0	0

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as denominators.

Serious adverse event/deaths/other significant events

Deaths

Table 53: Treatment-emergent Adverse Events with Outcome Death by Preferred Term; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY 3012		
	Dara IV	Dara SC	Pooled Dara SC
Analysis set: safety	258	260	291
Total number of subjects with TEAE with outcome death	17 (6.6%)	14 (5.4%)	14 (4.8%)
MedDRA Preferred Term			
General physical health deterioration	3 (1.2%)	4 (1.5%)	4 (1.4%)
Septic shock	3 (1.2%)	2 (0.8%)	2 (0.7%)
Respiratory failure	0	2 (0.8%)	2 (0.7%)
Cardiac failure	1 (0.4%)	1 (0.4%)	1 (0.3%)
Cardiac failure chronic	0	1 (0.4%)	1 (0.3%)
Cardiopulmonary failure	0	1 (0.4%)	1 (0.3%)
Cerebral infarction	0	1 (0.4%)	1 (0.3%)
Febrile neutropenia	0	1 (0.4%)	1 (0.3%)
Listeriosis	0	1 (0.4%)	1 (0.3%)
Renal failure	0	1 (0.4%)	1 (0.3%)
Sepsis	2 (0.8%)	0	0
Brain oedema	1 (0.4%)	0	0
Circulatory collapse	1 (0.4%)	0	0
Hepatitis B reactivation	1 (0.4%)	0	0
Hypercalcaemia	1 (0.4%)	0	0
Lung infection	1 (0.4%)	0	0
Pneumocystis jirovecii pneumonia	1 (0.4%)	0	0
Pneumonia	1 (0.4%)	0	0
Urinary tract infection	1 (0.4%)	0	0

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
Note: Percentages are calculated with the number of subjects in each group as the denominators.
Note: Adverse events are reported using MedDRA version 21.1.

Modified from Mod5.3.5.3/ISS/AttTSFAE13

As of the cutoff date for Study MMY2040, few deaths (4 across 3 cohorts) occurred within 30 days of the last dose, and each of these deaths were due to an AE (ie, Grade 5 TEAE) (Mod5.3.5.2/MMY2040/ Sec7.1.2.1):

- D-VMP cohort: Two deaths (3.0%) (neutropenic sepsis, pneumonitis)
- D-Rd cohort: One death (1.5%) (myocardial infarction)
- D-VRd cohort: One death (1.5%) (respiratory failure)

In the monotherapy study deaths due to AEs were similar in the two arms (6.6% and 5.4% in IV and SC arms, respectively, see Table 59).

There were no deaths in studies MMY1004 (Part 2; 25 patients) or MMY1008 (6 patients), which are also part of the pooled daratumumab SC cohort in the SCS.

There were four deaths in study MMY2040; two in the D-VMP cohort, and one each in the D-Rd and D-VRd cohort of which the causality is impossible to determine.

Serious adverse events

Monotherapy

All serious TEAEs were balanced between treatment groups (<5% difference in incidence; Attachment TSFAE06). Although ≥1 serious TEAE(s) was reported for approximately 30% of subjects in both treatment groups, the incidence of any specific preferred term being reported as serious was low, with only pneumonia being reported at ≥2% incidence in either treatment group (Table 60).

Table 54 **Summary of Most Common (≥2%) Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set (Study 54767414MMY3012)**

	Dara IV	Dara SC
Analysis set: safety	258	260
Total number of subjects with serious TEAE	76 (29.5%)	68 (26.2%)
MedDRA system organ class / preferred term		
Infections and infestations	34 (13.2%)	27 (10.4%)
Pneumonia	11 (4.3%)	7 (2.7%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE=treatment-emergent adverse event
Note: Percentages are calculated with the number of subjects in each group as denominators.
Note: Adverse events are reported using MedDRA version 21.1.
[TSFAE04C.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TSFAE04C.SAS] 05MAR2019, 16:38

Combination therapy

The SOC Infections and infestations and General disorders and administration site conditions were the most frequent SAEs by SOC in Study 2040 (Table 31/CSR), and for D-VMP and D-Rd the SOC Infections and infestations is lower than in the historical controls. (**Table 61**)

Table 55 **Summary of Most Common (At Least 2%) Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set (Study 54767414MMY2040)**

	D-VRd	D-VMP	D-Rd
Analysis set: all treated	67	67	65
Total number of subjects with serious TEAE	19 (28.4%)	25 (37.3%)	26 (40.0%)
MedDRA system organ class/ Preferred term			
General disorders and administration site conditions	6 (9.0%)	6 (9.0%)	5 (7.7%)
Pyrexia	4 (6.0%)	5 (7.5%)	2 (3.1%)
Fatigue	2 (3.0%)	0	1 (1.5%)
Infections and infestations	5 (7.5%)	8 (11.9%)	14 (21.5%)
Pneumonia	1 (1.5%)	3 (4.5%)	4 (6.2%)
Influenza	0	1 (1.5%)	3 (4.6%)
Neutropenic sepsis	0	2 (3.0%)	0
Upper respiratory tract infection	0	0	2 (3.1%)
Respiratory, thoracic and mediastinal disorders	4 (6.0%)	2 (3.0%)	2 (3.1%)
Pulmonary embolism	2 (3.0%)	0	1 (1.5%)
Gastrointestinal disorders	3 (4.5%)	3 (4.5%)	2 (3.1%)
Vomiting	2 (3.0%)	0	0
Diarrhoea	0	1 (1.5%)	2 (3.1%)
Blood and lymphatic system disorders	2 (3.0%)	4 (6.0%)	4 (6.2%)
Febrile neutropenia	1 (1.5%)	2 (3.0%)	1 (1.5%)
Thrombocytopenia	1 (1.5%)	2 (3.0%)	1 (1.5%)
Neutropenia	0	0	3 (4.6%)
Cardiac disorders	1 (1.5%)	2 (3.0%)	4 (6.2%)
Cardiac failure	0	1 (1.5%)	2 (3.1%)
Vascular disorders	1 (1.5%)	2 (3.0%)	0
Hypotension	1 (1.5%)	2 (3.0%)	0
Renal and urinary disorders	0	1 (1.5%)	4 (6.2%)
Acute kidney injury	0	1 (1.5%)	2 (3.1%)

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab and recombinant human hyaluronidase PH20 for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: Adverse events are reported using MedDRA version 21.1.

[TSFAE04C.RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TSFAE04C.SAS] 29MAR2019, 18:06

Table 56 **Most Common (At Least 2%) Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term: D-VMP and D-Rd; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040, MMY3003 and MMY2040)**

	Primary Analysis	Through Month 6		Primary Analysis	Through Month 6	
	CSR MMY 3007 Dara IV + VMP	MMY 3007 Dara IV + VMP	MMY 2040 Dara SC + VMP	CSR MMY 3003 Dara IV + Rd	MMY 3003 Dara IV + Rd	MMY 2040 Dara SC + Rd
Analysis set: safety	346	346	67	283	283	65
Total number of subjects with serious TEAE	144 (41.6%)	115 (33.2%)	24 (35.8%)	138 (48.8%)	99 (35.0%)	23 (35.4%)
MedDRA system organ class/ Preferred term						
General disorders and administration site conditions	15 (4.3%)	14 (4.0%)	6 (9.0%)	14 (4.9%)	6 (2.1%)	4 (6.2%)
Pyrexia	5 (1.4%)	5 (1.4%)	5 (7.5%)	8 (2.8%)	3 (1.1%)	2 (3.1%)
Infections and infestations	80 (23.1%)	61 (17.6%)	6 (9.0%)	85 (30.0%)	56 (19.8%)	9 (13.8%)
Neutropenic sepsis	0	0	2 (3.0%)	1 (0.4%)	0	0
Pneumonia	35 (10.1%)	23 (6.6%)	2 (3.0%)	26 (9.2%)	14 (4.9%)	3 (4.6%)
Influenza	3 (0.9%)	2 (0.6%)	0	8 (2.8%)	5 (1.8%)	2 (3.1%)
Blood and lymphatic system disorders	15 (4.3%)	14 (4.0%)	4 (6.0%)	17 (6.0%)	11 (3.9%)	4 (6.2%)
Febrile neutropenia	2 (0.6%)	2 (0.6%)	2 (3.0%)	12 (4.2%)	8 (2.8%)	1 (1.5%)
Thrombocytopenia	5 (1.4%)	4 (1.2%)	2 (3.0%)	1 (0.4%)	0	1 (1.5%)
Neutropenia	3 (0.9%)	3 (0.9%)	0	2 (0.7%)	2 (0.7%)	3 (4.6%)
Vascular disorders	5 (1.4%)	5 (1.4%)	2 (3.0%)	6 (2.1%)	5 (1.8%)	0
Hypotension	1 (0.3%)	1 (0.3%)	2 (3.0%)	1 (0.4%)	1 (0.4%)	0
Cardiac disorders	18 (5.2%)	11 (3.2%)	2 (3.0%)	9 (3.2%)	6 (2.1%)	4 (6.2%)
Cardiac failure	1 (0.3%)	0	1 (1.5%)	0	0	2 (3.1%)
Renal and urinary disorders	5 (1.4%)	4 (1.2%)	1 (1.5%)	6 (2.1%)	3 (1.1%)	4 (6.2%)
Acute kidney injury	3 (0.9%)	3 (0.9%)	1 (1.5%)	3 (1.1%)	2 (0.7%)	2 (3.1%)

Note: TEAE = treatment-emergent adverse event; Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.

Percentages are calculated with the number of subjects in each group as denominators. Adverse events are reported using MedDRA version 21.1.

Serious TEAEs shown are those reported in at least 2% of subjects in of subjects in D-VMP or D-Rd cohort of MMY2040, MMY3007, or MMY3003 through Month 6.

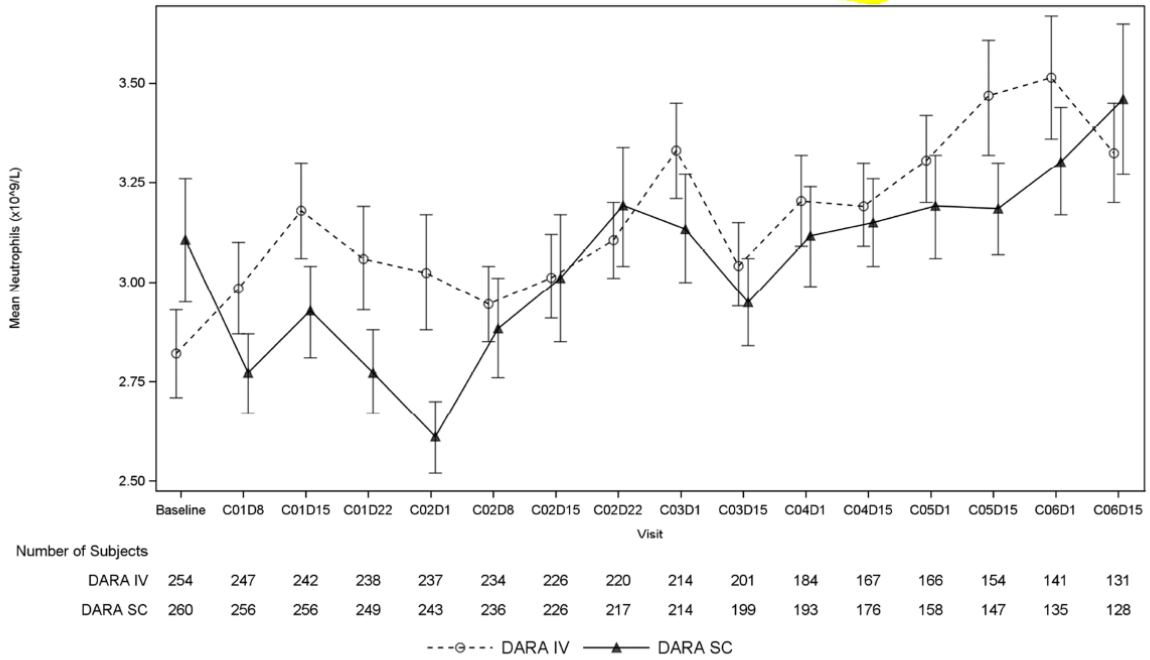
Note: Primary analysis CSR data column is based on a median treatment duration of 14.7 months for the D-VMP group of MMY3007 and 13.1 months for the D-Rd group of MMY3003.

Modified from Mod5.3.5.3/ISS/AttTSFAE04C, AttTSFAE04D, AttTSFAE09A, AttTSFAE09B

Laboratory findings

Haematology

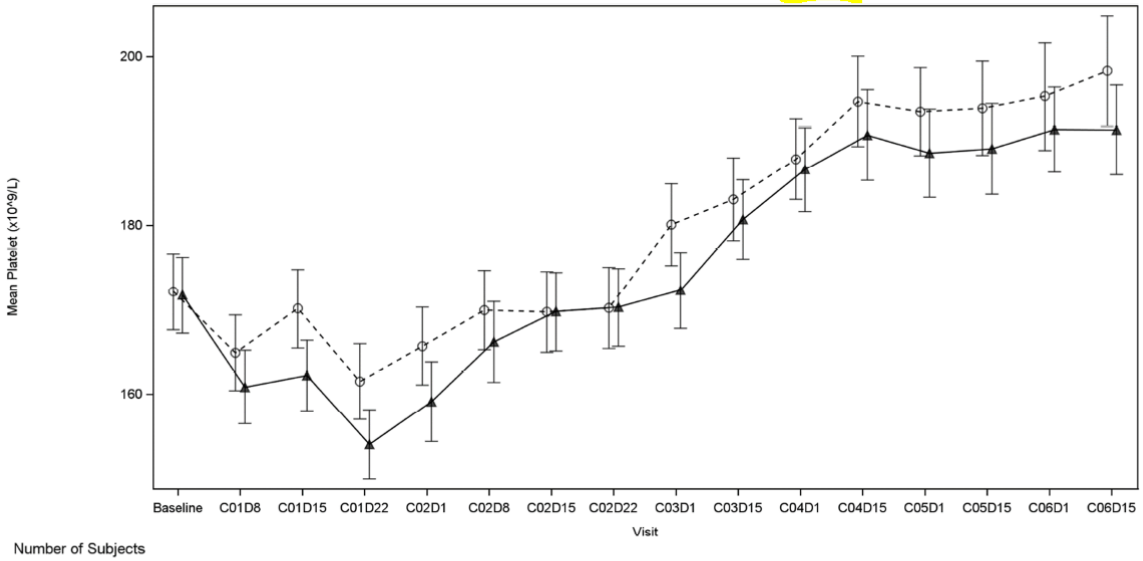
Figure 18 **Line Plot of Mean Neutrophils Over Time (Cycles 1 to 6) – Safety Analysis Set (Study 54767414MMY3012)**



Number of Subjects	Baseline	C01D8	C01D15	C01D22	C02D1	C02D8	C02D15	C02D22	C03D1	C03D15	C04D1	C04D15	C05D1	C05D15	C06D1	C06D15
DARA IV	254	247	242	238	237	234	226	220	214	201	184	167	166	154	141	131
DARA SC	260	256	256	249	243	236	226	217	214	199	193	176	158	147	135	128

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Mean neutrophils (x10E9/L) values at each time point are plotted with the error bars of mean +/- standard error.
[GSFLAB02.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\GSFLAB02.SAS] 05MAR2019, 16:33

Figure 19 Line Plot of Mean Platelets Over Time (Cycles 1 to 6) – Safety Analysis Set (Study 54767414MMY3012)



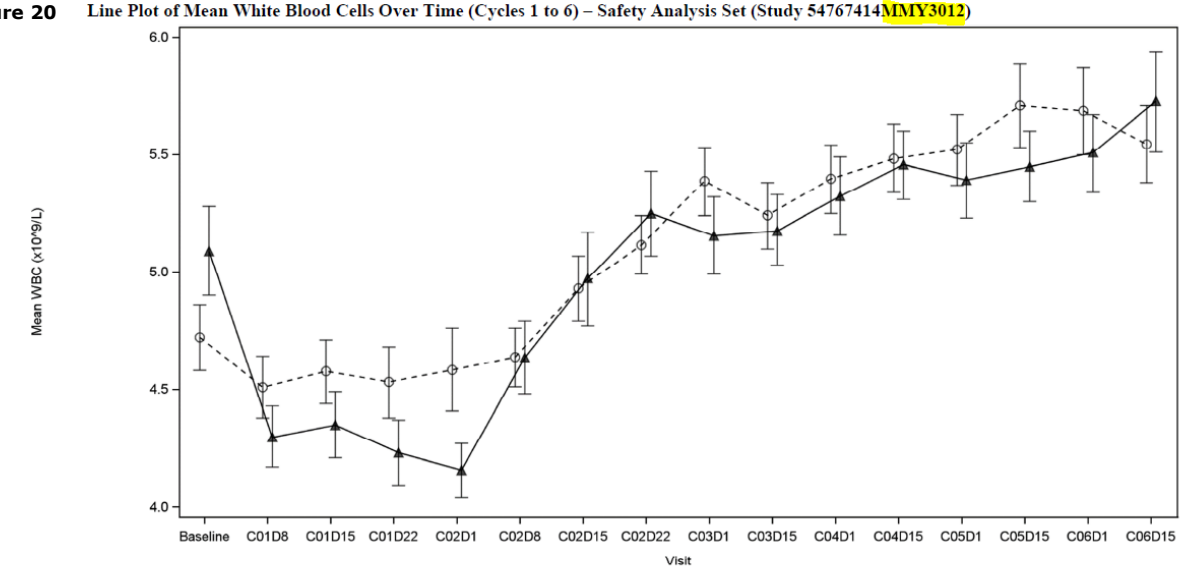
Number of Subjects

DARA IV	254	248	242	238	237	234	226	223	214	201	184	168	166	154	141	131
DARA SC	260	257	256	250	245	238	226	218	216	200	193	177	158	147	136	128

---⊖--- DARA IV ——▲—— DARA SC

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Mean platelets (x10E9/L) values at each time point are plotted with the error bars of mean +/- standard error.
[GSFLAB04.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\GSFLAB04.SAS] 05MAR2019, 16:34

Figure 20 Line Plot of Mean White Blood Cells Over Time (Cycles 1 to 6) – Safety Analysis Set (Study 54767414MMY3012)



Number of Subjects

DARA IV	254	248	242	238	237	234	226	223	214	201	184	168	166	154	141	131
DARA SC	260	257	256	250	245	238	226	218	216	200	193	177	158	147	136	128

---⊖--- DARA IV ——▲—— DARA SC

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: WBC=white blood cell
Mean WBC (x10E9/L) values at each time point are plotted with the error bars of mean +/- standard error.
[GSFLAB05.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\GSFLAB05.SAS] 05MAR2019, 16:34

Clinical Chemistry

Monotherapy

The worst toxicity grades observed during treatment for chemistry parameters were balanced (<5% difference in incidence) between treatment groups except for Grade 1 creatinine high (daratumumab SC: 31.3%; daratumumab IV: 25.2%) and Grade 1 hyponatremia (20.1% and 28.9%, respectively; Table 63).

Grade 3 or 4 abnormal chemistry values were uncommon, with only Grade 3 hyponatremia (6.7%) and Grade 3 hyperglycemia (5.1%) having incidence ≥5% (both in the daratumumab SC group).

No subject in either treatment group met criteria for drug-induced liver injury.

Combination therapy

In Study MMY2040, treatment-emergent Grade 3 or 4 biochemistry laboratory abnormalities were infrequent (<5%) in all treatment cohorts with the exception of Grade 3 low sodium and Grade 3 high creatinine in the D-VMP cohort (11.9% and 6.0%, respectively)

Treatment-emergent Grade 3 or 4 elevations in hepatic laboratory parameters were rare in each cohort, and no subject in Study MMY2040 met the criteria for drug-induced liver injury (Mod5.3.5.2/MMY2040/Sec7.2.1.2.1).

Table 57 **Summary of Worst Toxicity Grade During Treatment in Chemistry – Safety Analysis Set (Study 54767414MMY3012)**

	Dara IV Toxicity Grade, n (%)						Dara SC Toxicity Grade, n (%)					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	258						260					
Biochemistry												
ALT high	246 (95.3%)	202 (82.1%)	40 (16.3%)	1 (0.4%)	3 (1.2%)	0	255 (98.1%)	208 (81.6%)	42 (16.5%)	1 (0.4%)	4 (1.6%)	0
AST high	241 (93.4%)	192 (79.7%)	46 (19.1%)	1 (0.4%)	2 (0.8%)	0	253 (97.3%)	212 (83.8%)	38 (15.0%)	1 (0.4%)	2 (0.8%)	0
Creatinine high	246 (95.3%)	142 (57.7%)	62 (25.2%)	34 (13.8%)	5 (2.0%)	3 (1.2%)	256 (98.5%)	140 (54.7%)	80 (31.3%)	28 (10.9%)	7 (2.7%)	1 (0.4%)
Sodium high (Hypernatremia)	246 (95.3%)	230 (93.5%)	14 (5.7%)	2 (0.8%)	0	0	254 (97.7%)	239 (94.1%)	13 (5.1%)	2 (0.8%)	0	0
Sodium low (Hyponatremia)	246 (95.3%)	163 (66.3%)	71 (28.9%)	0	12 (4.9%)	0	254 (97.7%)	185 (72.8%)	51 (20.1%)	0	17 (6.7%)	1 (0.4%)
Potassium high (Hyperkalemia)	246 (95.3%)	215 (87.4%)	21 (8.5%)	8 (3.3%)	1 (0.4%)	1 (0.4%)	256 (98.5%)	227 (88.7%)	22 (8.6%)	3 (1.2%)	4 (1.6%)	0
Potassium low (Hypokalemia)	246 (95.3%)	204 (82.9%)	0	34 (13.8%)	8 (3.3%)	0	256 (98.5%)	210 (82.0%)	0	41 (16.0%)	5 (2.0%)	0
Bilirubin high	246 (95.3%)	224 (91.1%)	13 (5.3%)	7 (2.8%)	1 (0.4%)	1 (0.4%)	256 (98.5%)	240 (93.8%)	15 (5.9%)	1 (0.4%)	0	0
Alkaline phosphatase high	246 (95.3%)	190 (77.2%)	54 (22.0%)	2 (0.8%)	0	0	255 (98.1%)	202 (79.2%)	45 (17.6%)	7 (2.7%)	1 (0.4%)	0
Uric acid high (Hyperuricemia)	243 (94.2%)	164 (67.5%)	71 (29.2%)	0	0	8 (3.3%)	254 (97.7%)	178 (70.1%)	67 (26.4%)	0	0	9 (3.5%)
Corrected calcium high (Hypercalcemia)	252 (97.7%)	200 (79.4%)	39 (15.5%)	6 (2.4%)	5 (2.0%)	2 (0.8%)	256 (98.5%)	194 (75.8%)	40 (15.6%)	9 (3.5%)	10 (3.9%)	3 (1.2%)
Corrected calcium low (Hypocalcemia)	252 (97.7%)	175 (69.4%)	51 (20.2%)	18 (7.1%)	7 (2.8%)	1 (0.4%)	256 (98.5%)	184 (71.9%)	49 (19.1%)	12 (4.7%)	1 (0.4%)	10 (3.9%)
Glucose high (Hyperglycemia)	245 (95.0%)	234 (95.5%)	0	0	9 (3.7%)	2 (0.8%)	254 (97.7%)	241 (94.9%)	0	0	13 (5.1%)	0
Glucose low (Hypoglycemia)	245 (95.0%)	233 (95.1%)	11 (4.5%)	1 (0.4%)	0	0	254 (97.7%)	246 (96.9%)	8 (3.1%)	0	0	0
Albumin low (Hypoalbuminemia)	245 (95.0%)	195 (79.6%)	23 (9.4%)	27 (11.0%)	0	0	251 (96.5%)	205 (81.7%)	18 (7.2%)	27 (10.8%)	1 (0.4%)	0

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events
Note: For each parameter, the total column includes all subjects with available data at both baseline and postbaseline, including those whose toxicity grade did not worsen during treatment; percentages in the total column are calculated with the number of treated subjects in each group as denominators. Percentages for toxicity grade columns are calculated with the number of subjects in the total column as denominators. For each subject and each parameter, the worst toxicity grade is selected.
Note: The laboratory toxicity grades are derived based on the NCI CTCAE Version 4.03.
Note: For glucose high (hyperglycemia), Grade 3 or 4 hyperglycemia were graded regardless of whether subject was fasting or not; Grade 1 or 2 would require that the subject fasted and hence they are missing in the table since there was no fasting status information collected for this study.

[TSFLAB03.RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TSFLAB03.SAS] 05MAR2019, 16:40

Source: Modified from Attachment TSFLAB03.

Safety in special populations

Table 58 : Safety in Special Populations; Safety Analysis Set (Study 54767414MMY3012)

	Age <65		Age 65-74		Age 75-84		Age 85+	
	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC
Analysis set: safety	99	118	100	95	51	47	8	0
Total AEs	87 (87.9%)	98 (83.1%)	92 (92.0%)	85 (89.5%)	43 (84.3%)	45 (95.7%)	8 (100.0%)	0
Serious AEs Total	34 (34.3%)	33 (28.0%)	23 (23.0%)	22 (23.2%)	17 (33.3%)	13 (27.7%)	2 (25.0%)	0
Fatal	7 (7.1%)	5 (4.2%)	4 (4.0%)	6 (6.3%)	5 (9.8%)	3 (6.4%)	1 (12.5%)	0
Hospitalization/prolong existing hospitalization	31 (31.3%)	30 (25.4%)	23 (23.0%)	21 (22.1%)	16 (31.4%)	12 (25.5%)	2 (25.0%)	0
Life-threatening	9 (9.1%)	5 (4.2%)	4 (4.0%)	5 (5.3%)	5 (9.8%)	4 (8.5%)	1 (12.5%)	0
Disability/incapacity	1 (1.0%)	4 (3.4%)	1 (1.0%)	1 (1.1%)	1 (2.0%)	0	0	0
Other (medically significant)	4 (4.0%)	6 (5.1%)	0	3 (3.2%)	0	1 (2.1%)	0	0
AE leading to drop-out	8 (8.1%)	6 (5.1%)	8 (8.0%)	8 (8.4%)	4 (7.8%)	4 (8.5%)	1 (12.5%)	0
Psychiatric disorders	7 (7.1%)	3 (2.5%)	7 (7.0%)	9 (9.5%)	9 (17.6%)	9 (19.1%)	2 (25.0%)	0
Nervous system disorders	23 (23.2%)	17 (14.4%)	23 (23.0%)	18 (18.9%)	11 (21.6%)	13 (27.7%)	2 (25.0%)	0
Accidents and injuries	9 (9.1%)	8 (6.8%)	10 (10.0%)	11 (11.6%)	6 (11.8%)	5 (10.6%)	3 (37.5%)	0
Cardiac disorders	5 (5.1%)	6 (5.1%)	5 (5.0%)	8 (8.4%)	5 (9.8%)	5 (10.6%)	2 (25.0%)	0
Vascular disorders	14 (14.1%)	8 (6.8%)	18 (18.0%)	9 (9.5%)	8 (15.7%)	7 (14.9%)	1 (12.5%)	0
Cerebrovascular disorders[a]	0	3 (2.5%)	0	1 (1.1%)	1 (2.0%)	0	0	0
Infections and infestations	46 (46.5%)	49 (41.5%)	44 (44.0%)	44 (46.3%)	24 (47.1%)	26 (55.3%)	3 (37.5%)	0
Anticholinergic syndrome	23 (23.2%)	20 (16.9%)	18 (18.0%)	22 (23.2%)	10 (19.6%)	12 (25.5%)	4 (50.0%)	0
Increase in ECOG score[b]	24 (24.2%)	25 (21.2%)	27 (27.0%)	20 (21.1%)	12 (23.5%)	13 (27.7%)	2 (25.0%)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	10 (10.1%)	5 (4.2%)	7 (7.0%)	11 (11.6%)	3 (5.9%)	6 (12.8%)	2 (25.0%)	0
Circulatory collapse	1 (1.0%)	0	0	0	0	0	0	0
Clavicle fracture	1 (1.0%)	0	0	0	1 (2.0%)	0	0	0
Dizziness	5 (5.1%)	2 (1.7%)	3 (3.0%)	5 (5.3%)	1 (2.0%)	4 (8.5%)	1 (12.5%)	0
Fall	0	1 (0.8%)	1 (1.0%)	4 (4.2%)	0	0	2 (25.0%)	0
Femoral neck fracture	0	1 (0.8%)	0	0	0	0	0	0

Table 59: ***Safety in Special Populations; Safety Analysis Set (Study 54767414MMY3012)***

	Age <65		Age 65-74		Age 75-84		Age 85+	
	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC

Femur fracture	0	0	2 (2.0%)	1 (1.1%)	0	0	0	0
Hip fracture	0	0	0	0	0	1 (2.1%)	0	0
Humerus fracture	1 (1.0%)	1 (0.8%)	0	0	0	1 (2.1%)	0	0
Presyncope	0	0	0	1 (1.1%)	0	0	0	0
Pubis fracture	0	0	1 (1.0%)	0	0	0	0	0
Radius fracture	0	0	1 (1.0%)	0	0	0	0	0
Rib fracture	2 (2.0%)	0	0	0	1 (2.0%)	0	0	0
Spinal compression fracture	0	0	0	0	2 (3.9%)	0	0	0
Sternal fracture	0	0	0	1 (1.1%)	0	0	0	0
Syncope	0	0	1 (1.0%)	0	0	1 (2.1%)	0	0
Upper limb fracture	0	1 (0.8%)	0	0	0	0	0	0
Other AEs appearing more frequently in older patients	52 (52.5%)	54 (45.8%)	58 (58.0%)	54 (56.8%)	29 (56.9%)	39 (83.0%)	6 (75.0%)	0
Chills	9 (9.1%)	6 (5.1%)	12 (12.0%)	4 (4.2%)	10 (19.6%)	5 (10.6%)	1 (12.5%)	0
Cough	14 (14.1%)	6 (5.1%)	12 (12.0%)	8 (8.4%)	5 (9.8%)	8 (17.0%)	2 (25.0%)	0
Decreased appetite	4 (4.0%)	4 (3.4%)	4 (4.0%)	3 (3.2%)	3 (5.9%)	5 (10.6%)	0	0
Diarrhoea	9 (9.1%)	13 (11.0%)	11 (11.0%)	14 (14.7%)	5 (9.8%)	12 (25.5%)	3 (37.5%)	0
Insomnia	3 (3.0%)	2 (1.7%)	4 (4.0%)	6 (6.3%)	6 (11.8%)	6 (12.8%)	0	0
Musculoskeletal pain	1 (1.0%)	3 (2.5%)	4 (4.0%)	2 (2.1%)	2 (3.9%)	4 (8.5%)	1 (12.5%)	0
Nausea	9 (9.1%)	3 (2.5%)	10 (10.0%)	6 (6.3%)	8 (15.7%)	12 (25.5%)	1 (12.5%)	0
Neutropenia	17 (17.2%)	21 (17.8%)	12 (12.0%)	17 (17.9%)	5 (9.8%)	12 (25.5%)	1 (12.5%)	0
Oedema peripheral	3 (3.0%)	2 (1.7%)	5 (5.0%)	3 (3.2%)	5 (9.8%)	4 (8.5%)	0	0
Pneumonia	9 (9.1%)	2 (1.7%)	4 (4.0%)	3 (3.2%)	3 (5.9%)	4 (8.5%)	0	0
Upper respiratory tract infection	13 (13.1%)	16 (13.6%)	11 (11.0%)	10 (10.5%)	1 (2.0%)	9 (19.1%)	0	0
Urinary tract infection	2 (2.0%)	0	2 (2.0%)	5 (5.3%)	5 (9.8%)	4 (8.5%)	0	0
Vomiting	8 (8.1%)	5 (4.2%)	9 (9.0%)	4 (4.2%)	0	5 (10.6%)	3 (37.5%)	0

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[a]includes cerebral infarction, cerebrovascular accident, cerebrovascular insufficiency and transient ischaemic attack.
[b]The study did not assess QoL measures; Thus, ECOG is utilized as a measure of the subject's health status. Note: Percentages are calculated with the number of subjects in each subgroup as the denominators.

Weight

Monotherapy

The distribution of subjects by baseline body weight was comparable for the pooled daratumumab SC group and daratumumab IV group for Study MMY3012, ie, ~36% for those weighing ≤65 kg, ~40% for those weighing >65 to 85 kg, and ~24% for those weighing >85 kg.

- The overall incidence of TEAEs of any grade was higher in the ≤65 kg subgroup for the pooled daratumumab SC group compared with the daratumumab IV group of Study MMY3012 (95.2% vs 89.1%), and this difference was driven primarily by Grade 1 and 2 TEAEs (43.8% and 38.1%, respectively) (Table 66).
- For each body weight subgroup, the overall incidences of maximum Grade 3 or 4 TEAEs, maximum Grade 5 TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation for the pooled daratumumab SC group were either similar to or lower than corresponding incidences observed in the daratumumab IV group of Study MMY3012.

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Table 60: Overview of Treatment-emergent Adverse Events by Baseline Weight; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY3012 Dara IV n (%)				Pooled Dara SC n (%)			
	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg
Analysis set: safety	258	92	105	61	291	105	115	71
Any TEAE	230 (89.1%)	82 (89.1%)	94 (89.5%)	54 (88.5%)	259 (89.0%)	100 (95.2%)	102 (88.7%)	57 (80.3%)
Serious TEAE	76 (29.5%)	28 (30.4%)	33 (31.4%)	15 (24.6%)	74 (25.4%)	25 (23.8%)	31 (27.0%)	18 (25.4%)
Maximum toxicity grades of TEAE								
Grade 1	23 (8.9%)	9 (9.8%)	11 (10.5%)	3 (4.9%)	22 (7.6%)	11 (10.5%)	8 (7.0%)	3 (4.2%)
Grade 2	81 (31.4%)	26 (28.3%)	32 (30.5%)	23 (37.7%)	102 (35.1%)	35 (33.3%)	42 (36.5%)	25 (35.2%)
Grade 3	81 (31.4%)	33 (35.9%)	27 (25.7%)	21 (34.4%)	97 (33.3%)	39 (37.1%)	36 (31.3%)	22 (31.0%)
Grade 4	28 (10.9%)	8 (8.7%)	16 (15.2%)	4 (6.6%)	24 (8.2%)	9 (8.6%)	10 (8.7%)	5 (7.0%)
Grade 5	17 (6.6%)	6 (6.5%)	8 (7.6%)	3 (4.9%)	14 (4.8%)	6 (5.7%)	6 (5.2%)	2 (2.8%)
TEAE leading to treatment discontinuation	21 (8.1%)	6 (6.5%)	9 (8.6%)	6 (9.8%)	18 (6.2%)	8 (7.6%)	8 (7.0%)	2 (2.8%)
Infusion-related reactions	89 (34.5%)	27 (29.3%)	38 (36.2%)	24 (39.3%)	52 (10.6%)	18 (11.3%)	18 (8.8%)	16 (12.7%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
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.

Modified from Mod5.3.5.3/ISS/AttTSFAE01S05, AttTSFIRR01, AttTSFIRR02

Table 61: Treatment-emergent Adverse Events of Neutropenia, Febrile Neutropenia and Infections/Infestations by Baseline Weight; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY3012 Dara IV n (%)				Pooled Dara SC n (%)			
	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg
Analysis set: safety	258	92	105	61	291	105	115	71

Table 61: Treatment-emergent Adverse Events of Neutropenia, Febrile Neutropenia and Infections/Infestations by Baseline Weight; Safety Analysis Set (Monotherapy Studies: MMY3012, MMY1004 Part 2, and MMY1008)

	MMY3012 Dara IV				Pooled Dara SC			
	n (%)				n (%)			
	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg	Total	≤ 65 kg	>65 kg to 85 kg	>85 kg
Neutropenia								
Any grade TEAE	35 (13.6%)	13 (14.1%)	13 (12.4%)	9 (14.8%)	54 (18.6%)	25 (23.8%)	17 (14.8%)	12 (16.9%)
Grade 3 or 4 TEAE	20 (7.8%)	8 (8.7%)	9 (8.6%)	3 (4.9%)	37 (12.7%)	20 (19.0%)	11 (9.6%)	6 (8.5%)
Serious TEAE	1 (0.4%)	0	1 (1.0%)	0	0	0	0	0
TEAE leading to treatment discontinuation	1 (0.4%)	0	0	1 (1.6%)	0	0	0	0
Febrile Neutropenia								
Any grade TEAE	6 (2.3%)	2 (2.2%)	4 (3.8%)	0	4 (1.4%)	2 (1.9%)	1 (0.9%)	1 (1.4%)
Grade 3 or 4 TEAE	6 (2.3%)	2 (2.2%)	4 (3.8%)	0	4 (1.4%)	2 (1.9%)	1 (0.9%)	1 (1.4%)
Serious TEAE	2 (0.8%)	0	2 (1.9%)	0	2 (0.7%)	0	1 (0.9%)	1 (1.4%)
TEAE leading to treatment discontinuation	0	0	0	0	1 (0.3%)	0	1 (0.9%)	0
Grade 5 TEAEs related to neutropenia								
Febrile neutropenia	0	0	0	0	1 (0.3%)	0	1 (0.9%)	0
Infections/Infestations SOC								
Any grade TEAE	117 (45.3%)	41 (44.6%)	43 (41.0%)	33 (54.1%)	142 (48.8%)	55 (52.4%)	53 (46.1%)	34 (47.9%)
Grade 3 or 4 TEAE	29 (11.2%)	11 (12.0%)	12 (11.4%)	6 (9.8%)	29 (10.0%)	10 (9.5%)	11 (9.6%)	8 (11.3%)
Serious TEAE	34 (13.2%)	12 (13.0%)	13 (12.4%)	9 (14.8%)	29 (10.0%)	10 (9.5%)	11 (9.6%)	8 (11.3%)
TEAE leading to treatment discontinuation	9 (3.5%)	3 (3.3%)	3 (2.9%)	3 (4.9%)	3 (1.0%)	1 (1.0%)	2 (1.7%)	0

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); the pooled Dara SC column includes subjects from MMY3012 SC group, MMY1004 Part 2, and MMY1008.
Key: TEAE=treatment-emergent adverse event.
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.

Modified from Mod5.3.5.3/ISS/AttTSFAE02S05, AttTSFAE04S05, AttTSFAE08S05, AttTSFAE11S05, AttTSFAE13S05

Combination therapy

Table 62 **Summary of Treatment-emergent Neutropenia Adverse Events Up to Month 6 by Baseline Weight: DVMP; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040)**

	MMY 3007 Dara IV + VMP				MMY 2040 Dara SC + VMP			
	Total	≤65 kg	>65 kg to 85 kg	>85 kg	Total	≤65 kg	>65 kg to 85 kg	>85 kg
Analysis set: safety	346	129	172	45	67	32	25	10
Neutropenia TEAEs								
Any grade TEAE	153 (44.2%)	65 (50.4%)	78 (45.3%)	10 (22.2%)	24 (35.8%)	14 (43.8%)	6 (24.0%)	4 (40.0%)
Grade 3 or 4 TEAE	121 (35.0%)	53 (41.1%)	60 (34.9%)	8 (17.8%)	20 (29.9%)	12 (37.5%)	5 (20.0%)	3 (30.0%)
TEAE leading to treatment discontinuation	0	0	0	0	0	0	0	0
Serious neutropenia-related TEAEs[a]								
Febrile neutropenia	2 (0.6%)	0	2 (1.2%)	0	2 (3.0%)	0	1 (4.0%)	1 (10.0%)
Neutropenic sepsis	0	0	0	0	2 (3.0%)	1 (3.1%)	0	1 (10.0%)

Note: TEAE = treatment-emergent adverse event; Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.

[a] No subject in the D-VMP cohort of Study MMY2040 had a serious TEAE of neutropenia, while 3 subjects in the D-VMP cohort of MMY3007 had a serious TEAE of neutropenia.

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

Modified from Mod5.3.5.3/ISS/AttTSFAE02A1_Cut, AttTSFAE04A1, AttTSFAE09A1, AttTSFAE11A1

Table 63 **Summary of Treatment-emergent Neutropenia Adverse Events Up to Month 6 by Baseline Weight: DRd; Safety Analysis Set (Combination Therapy Studies: MMY3003 and MMY2040)**

	MMY 3003 Dara IV + Rd				MMY 2040 Dara SC + Rd			
	Total	≤65 kg	>65 kg to 85 kg	>85 kg	Total	≤65 kg	>65 kg to 85 kg	>85 kg
Analysis set: safety	283	94	121	65	65	9	33	23
Neutropenia TEAEs								
Any grade TEAE	156 (55.1%)	54 (57.4%)	66 (54.5%)	34 (52.3%)	38 (58.5%)	6 (66.7%)	20 (60.6%)	12 (52.2%)
Grade 3 or 4 TEAE	137 (48.4%)	47 (50.0%)	58 (47.9%)	30 (46.2%)	30 (46.2%)	3 (33.3%)	17 (51.5%)	10 (43.5%)
TEAE leading to treatment discontinuation	0	0	0	0	0	0	0	0
Serious neutropenia-related TEAEs								
Febrile neutropenia	8 (2.8%)	1 (1.1%)	6 (5.0%)	1 (1.5%)	1 (1.5%)	0	1 (3.0%)	0
Neutropenia	2 (0.7%)	1 (1.1%)	1 (0.8%)	0	3 (4.6%)	0	3 (9.1%)	0

Note: TEAE = treatment-emergent adverse event; Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); Rd = lenalidomide/dexamethasone.

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

Note: There were 3 subjects in study MMY3003 with missing baseline weight.

Modified from Mod5.3.5.3/ISS/AttTSFAE02B1_Cut, AttTSFAE04B1, AttTSFAE09B1, AttTSFAE11B1

Immunological events

The issue with immunological events and ADA is discussed above.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Monotherapy

Discontinuation of study treatment due to a TEAE(s) was reported at similarly low rates in the daratumumab SC (6.9%) and daratumumab IV (8.1%) groups in Study MMY3012 (*see Table 49*), as was the proportion of subjects who were discontinued from treatment due to a Grade 3 or 4 TEAE (4.2% and 5.0%, respectively). Those TEAEs (any grade) leading to discontinuation of study treatment in 1% or more of subjects in either

treatment group were thrombocytopenia (daratumumab SC, 0.8%; daratumumab IV, 1.9%), anemia (0.8% and 1.2%, respectively), and septic shock (0.8% and 1.2%, respectively).

Combination therapy

TSFAE05A: Summary of Treatment-emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term and Grade 3/4; All Treated Analysis Set (Study 54767414MMY2040)

	D-VRd		D-VMP		D-Rd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: all treated	67		67		65	
Total number of subjects with TEAE leading to treatment discontinuation	1 (1.5%)	0	2 (3.0%)	2 (3.0%)	3 (4.6%)	2 (3.1%)
MedDRA system organ class / Preferred term						
Respiratory, thoracic and mediastinal disorders	1 (1.5%)	0	1 (1.5%)	1 (1.5%)	0	0
Respiratory failure	1 (1.5%)	0	0	0	0	0
Pneumonitis	0	0	1 (1.5%)	1 (1.5%)	0	0
Cardiac disorders	0	0	0	0	1 (1.5%)	0
Myocardial infarction	0	0	0	0	1 (1.5%)	0
Infections and infestations	0	0	1 (1.5%)	1 (1.5%)	2 (3.1%)	2 (3.1%)
Neutropenic sepsis	0	0	1 (1.5%)	1 (1.5%)	0	0
Pneumonia	0	0	0	0	2 (3.1%)	2 (3.1%)

Key: TEAE = treatment-emergent adverse event. Dara-SC = daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated. D-VRd = Dara-SC, bortezomib, lenalidomide, and dexamethasone. D-VMP = Dara-SC, bortezomib, melphalan, and prednisone. D-Rd = Dara-SC, lenalidomide, and dexamethasone.
Note: Percentages are calculated with the number of subjects in each cohort as denominators.
Note: Adverse events are reported using MedDRA version 21.1.

[TSFAE05A.RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TSFAE05A.SAS] 29MAR2019, 18:07

Comparison to Historic Data with Daratumumab IV:

- D-VMP Regimens
  - The overall incidence of TEAEs leading to discontinuation through Month 6 was low and similar for Studies MMY2040 (3.0%) and MMY3007 (3.2%).
- D-Rd Regimens
  - The overall incidence of TEAEs leading to discontinuation through Month 6 was low and similar for Studies MMY2040 (4.6%) and MMY3003 (5.7%).

Post marketing experience

Daratumumab SC has not been authorized for use in any country worldwide.

2.6.1. Discussion on clinical safety

The main focus of the safety evaluation is on the pivotal study MMY3012 as this is a phase 3, open-label, randomised study.

For study MMY3012 (N=260) and the daratumumab SC pooled monotherapy population (N=291) the reasons for discontinuation, the overall percentage of subjects who remained on treatment, the number of cycles received, median duration of treatment, and median relative dose intensity were consistent with those reported for the daratumumab IV treatment.

Study MMY2040, where daratumumab was given as SC treatment in combination with other well-established treatments (D-VRd, D-VMP, D-Rd) used in combination with daratumumab IV and compared to historical data,

is considered supportive although important for the safety evaluation of daratumumab SC in these combinations. The median follow-up duration in Study MMY2040 with daratumumab SC was 7-10 months shorter than those for historical daratumumab IV data from the primary analyses of the D-VMP group (Study MMY3007) and the D-Rd group (Study MMY3003). Therefore, the comparison of daratumumab SC and daratumumab IV combination safety profiles from these studies are based on data collected from the first dose of study treatment up to the end of month 6 for each subject.

The overall TEAE profile for subjects treated with daratumumab SC in the randomised comparative study, MMY3012, and in the Pooled Monotherapy Safety analysis set was comparable to that for the daratumumab IV treatment group of MMY3012 (Table 49). TEAEs (all grades and grade 3-4) were balanced with <5% difference in incidence except for the incidence of neutropenia, which was higher in the daratumumab SC groups (Study MMY3012 and pooled; Table 52 and Table 53). Despite this, the AEs in the SOC Infections and Infestations were similar although with Upper respiratory tract infections (only grade 1-2) being higher in the SC arm. SAEs and discontinuations related to febrile neutropenia were low and comparable as was the use of hematopoietic growth factors. In the monotherapy study deaths due to AEs and SAEs were similar in the two arms. The safety profile is reflected in the SPC.

In the combination therapy study (the D-VMP and D-Rd regimens) SAEs, Grade 3 or 4 TEAEs, and TEAEs leading to discontinuation were similar to that reported for the same combination therapy regimens in Studies MMY3007 and MMY3003, respectively (IV), see Table 51. Cytopenias were the most common Grade 3 or 4 TEAEs in all 3 cohorts but the incidence was similar or lower when compared to historical data for neutropenia, anaemia and thrombocytopenia, and the SOC Infections and infestations were similar or lower in the SC arms. In the combination study the results were compared to historical data, which is not ideal, but there is no obvious biological explanation why the results from the monotherapy study (MMY3012) would not be applicable in combination treatments that has previously been used in combination with daratumumab IV.

Treatment with daratumumab SC in study MMY3012 was associated with a significant lower risk of IRRs both overall and grade 3-4. The reduction in IRRs is considered a major therapeutic advantage with relation to safety.

All injection-site reactions in monotherapy study MMY3012 and combination therapy study MMY2040 were grade 1 and 2 and none led to treatment discontinuation. These reactions are considered a minor disadvantage especially in light of the reduced incidence of IRRs.

Regarding weight and the use of a flat dose: Daratumumab SC was administered as a flat dose of 1800 mg, regardless of body weight, whereas daratumumab IV is administered at a weight-based dose of 16 mg/kg. For the $\leqslant$65 kg group comparable concentration-time profiles independent of SC or IV administration were not seen: C_{trough} daratumumab SC values are markedly increased from Cycle 3 Day 1 and onwards (see the pharmacology section). A higher incidence of any grade and grade 3 or 4 neutropenia in the pooled SC group was observed and corresponded to a higher incidence of all grade AEs in the SOC Infections/Infestations but comparable grade 3 or 4 AEs and SAEs in the $\leqslant$65 kg subgroup (in this SOC) leading to the difference in neutropenia being of minor clinical relevance.

2.6.2. Conclusions on the clinical safety

The safety profile of daratumumab is well known and clinically manageable, it is overall as reflected in the SmPC. The median duration of administration of Dara SC was considerably shorter than for Dara IV, and Dara SC had a significantly lower incidence of IRR compared with Dara IV. A higher incidence of any grade and grade 3 or 4 neutropenia in the pooled SC group was observed and corresponded to a higher incidence of all grade AEs in the SOC Infections/Infestations, but this was not associated with any clinically meaningful differences in sequelae such as infections. No new safety signals were observed, all OC's have been addressed by the MAH in a satisfactory manner.

2.7. Risk Management Plan

Safety concerns

*Table 64**. Summary of the Safety Concerns***

Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	Immunogenicity
Missing information	Use in pregnancy and lactation
	Reproductive and developmental toxicity

Pharmacovigilance plan

Table 65: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Investigate new method for detecting antidrug antibodies Ongoing	Improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab.	Immunogenicity	Final report	1st Quarter 2020

Key: PSUR = Periodic Safety Update Report.

Risk minimisation measures

Table 66 Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4 and 4.5 • PL Section 2 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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions.

Table 66 Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Immunogenicity	Routine risk minimization measures: • SmPC Section 5.1 Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Investigation of a new method for detecting antidrug antibodies to improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab. Final report 1st Quarter 2020.
Use in pregnancy and lactation	Routine risk minimization measures: • SmPC Section 4.6 • PL Section 2 Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

Table 66 Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Reproductive and developmental toxicity	Routine risk communication: • SmPC Section 5.3. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

Key: DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; rHuPH20 = recombinant human hyaluronidase enzyme PH20;

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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 Agency web-portal.

2.9. Product information

Please refer to the PI attachment.

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Darzalex IV formulation. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Darzalex (daratumumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The new pharmaceutical form and new route of administration (1800 mg solution for subcutaneous injection) of Darzalex is indicated:

Daratumumab Subcutaneous solution for injection is indicated:

- 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, 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.
- 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.

3.1.2. Available therapies and unmet medical need

Treatment options for multiple myeloma are dependent on age, performance status, comorbidity, suitability for intensive treatment as well as aggressiveness of the disease and related prognostic factors. Current treatments include different combinations of chemotherapy, proteasome inhibitors, immunomodulatory drugs, high dose chemotherapy and ASCT and monoclonal antibodies such as daratumumab IV and elotuzumab IV. Most treatment regimens include a glucocorticoid.

In the past years, multiple targeted therapies and immunotherapies including second generation IMiDs and PIs and monoclonal antibodies (daratumumab IV) were approved for the treatment of myeloma or entered of clinical testing (Larocca 2017). With modern therapy, patients with standard risk multiple myeloma have an estimated median survival of 8 to 10 years (Rajkumar 2018). Despite advances in treatment options, multiple myeloma remains incurable. With each successive relapse, the chance of response and the duration of response typically decrease. Ultimately the disease becomes refractory or patients develop intolerability to PIs and IMiDs. Patients who are refractory to both a PI and an IMiD have a dismal prognosis and median survival is only approximately 8 to 9 months (Kumar 2012; Usmani 2016).

Therefore, besides from novel therapeutic strategies to improve and deepen ORR, treatment modalities minimising the toxicities and treatment duration that are associated with current treatment options are needed.

3.1.3. Main clinical studies

The submission is mainly based on a phase 3 multicentre, randomized, open-label efficacy (non-inferiority), safety and pharmacokinetics study comparing monotherapy daratumumab IV to daratumumab SC in 522 patients with a relapsed or refractory multiple myeloma. Further submitted were a phase 2 study evaluating daratumumab SC in combination with standard treatment regimens in patients newly diagnosed with multiple myeloma (eligible and ineligible to ASCT) and relapsed patients, a phase 1b dose-escalation study and a phase 1 study of daratumumab SC in Japanese patients with a relapsed or refractory multiple myeloma.

3.2. Favourable effects

Co-Primary endpoints:

The ORR was 41.1% for daratumumab SC and 37.1% for daratumumab IV (incidence ratio 1.11 (90% CI: 0.89, 1.37), $p < 0.0001$).

The observed mean exposure (C_{trough} at Cycle 3 Day 1 in Study MMY3012) of daratumumab was comparable after SC and IV administration by Pop PK analyses: 463 (86.1-1109) vs. 499 (9.97-1720) µg/ml.

Key secondary endpoint:

A reduction in the IRRs was shown in the daratumumab SC group (12.7%) compared to daratumumab IV (34.5%); odds ratio=0.28 (95% CI: 0.18, 0.44); $p<0.0001$.

3.3. Uncertainties and limitations about favourable effects

Sex, IgG myeloma, baseline albumin and body weight were identified as significant covariates for daratumumab SC exposure and in the Pop PK analysis. There is a concern with regard to lower exposure in extreme high body weight SC patients (>120 kg) and potential loss of efficacy. While no dose modifications can currently be recommended, the risk of possible reduced efficacy in patients with body weight >120 kg has been adequately reflected in section 4.4 of the SmPC..

3.4. Unfavourable effects

A higher incidence of any grade and grade 3 or 4 neutropenia in the pooled daratumumab SC group was observed Despite this, the AEs in the SOC 'Infections and Infestations' were similar..

No new clinically relevant safety concerns were identified for daratumumab SC. The safety profile for daratumumab SC, administered at a flat dose of 1800 mg, is generally consistent with the well-characterized safety profile for daratumumab 16 mg/kg IV.

3.5. Uncertainties and limitations about unfavourable effects

There are no relevant uncertainties related to unfavourable effects.

3.6. Effects Table

Table 67. Effects Table for Darzalex data cut-off: 08-jan 2019

Effect	Short Description	Unit	Treatment (daratumumab SC, N=263)	Control (daratumumab IV, N=259)	Uncertainties / Strength of evidence	References
Favourable Effects						
Objective response rate (ORR)	Proportion of subjects with PR or CR	%	41.1	37.1	Relative Risk 1.11 90% CI: 0.89, 1.37	Study MMY3012
C_{trough}	Plasma daratumumab concentration before administration in cycle 3	µg/ml	499	463	Geometric mean ratio 107.93% (90% CI: 95.74%, 121.67%)	Study MMY3012
Infusion-related reactions (IRR)	Proportion of subjects with at least one IRR	%	12.7%	34.5%	Odds Ratio: 0.28 (95% CI: 0.18, 0.44, p<0.0001)	
Unfavourable Effects						
Neutropenia	Grade 3-4	Proportion of subjects (%) with at least one AE	13.6	7.8		Study MMY3012
Infections	All grades	Proportion of subjects (%) with at least one AE	45.8	45.3		Study MMY3012
Neutropenia	All grades	Proportion of subjects (%) with at least one AE	19.2	13.6		Study MMY3012

Abbreviations: SC: subcutaneous administration. IV: intravenous administration (here, infusion). AE: adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results for ORR and C_{trough} indicate that the efficacy of daratumumab SC is not inferior to daratumumab IV, which is authorised for treatment of patients with multiple myeloma (see 3.1.1 for exact indications). Compared with daratumumab IV, daratumumab SC had a lower incidence of IRR when administered as monotherapy and at the same schedule as daratumumab IV, and this has relevance for patients. While a higher incidence of any grade and grade 3 or 4 neutropenia was observed in the pooled daratumumab SC group, compared to daratumumab IV, this was not associated with clinically meaningful differences in sequelae such as infections or discontinuations. The availability of daratumumab in the pharmaceutical form for subcutaneous administration is considered a major benefit to the patients, because this route of administration reduces the treatment burden for patients and healthcare providers.

The efficacy results for daratumumab SC in combination with standard backbone combination therapy in supportive studies indicated comparability to previously approved combination therapies using daratumumab IV.

While daratumumab IV dosing is weight-based, daratumumab SC was administered as a flat dose of 1800 mg. Subgroup analyses across body weight distribution showed similar efficacy pertaining ORR. In addition, the MAH commits to evaluate clinical trial data to further characterize efficacy and exposure of the daratumumab subcutaneous formulation in patients with body weight >120 kg and:

a) Conduct subgroup analysis of subjects with body weight >120 kg in ongoing randomized studies to further characterize the impact of body weight >120 kg on exposure and efficacy outcomes.

b) Submit these data as part of a Type II variation, reflecting the conclusions of this analysis by 1Q2023 (interim results presented with the PBRER in 1Q2021 and 1Q2022).

In conclusion, daratumumab SC was well tolerated both as monotherapy and in combination with standard background MM therapy. The AEs of daratumumab SC are well known and considered manageable, no new clinically relevant safety concerns were identified for the daratumumab SC.

3.7.2. Balance of benefits and risks

Daratumumab, administered as an IV infusion, has a favourable balance of benefits and risks in the relapsed/refractory setting of multiple myeloma (MM), as well as in newly-diagnosed patients, ineligible to HDT and ASCT.

In the present submission, daratumumab SC is shown to be non-inferior to daratumumab IV in terms of ORR, to be associated with fewer IRRs and to have a C_{trough} that is comparable after SC and IV administration. No new safety signals were raised, and the AEs were considered clinically manageable. Furthermore, the duration of administration of daratumumab SC was considerably shorter than for daratumumab IV, which is considered a benefit to the patients.

Therefore, the favourable effects of daratumumab SC outweigh the risks.

3.8. Conclusions

The overall B/R of Darzalex (daratumumab) subcutaneous formulation is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Imnovid, Farydak, Kyprolis, Ninlaro, within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Darzalex 1800 mg solution for subcutaneous injection is favourable in the following indication:

DARZALEX is indicated:

- 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, 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.
- 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.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Darzalex subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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 Agency web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of DARZALEX (daratumumab) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, aiming at increasing awareness about the Important Identified Risk of "Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)" and providing guidance on how to manage it.

The MAH shall ensure that in each MS where DARZALEX (daratumumab) is marketed, all HCPs and patients who are expected to prescribe, dispense and receive this product have access to/are provided with the below.

The HCPs and Blood Banks educational materials, shall contain the following key elements:

o The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;
o The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:

o All patients should be typed and screened prior to start treatment with daratumumab; alternatively, phenotyping may also be considered;
o Daratumumab-mediated positive indirect Coombs test (interfering with cross-matching of blood) may persist for up to 6 months after the last product's infusion, therefore, the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended;
o Daratumumab bound to Red Blood Cells (RBCs) may mask the detection of antibodies to minor

antigens in the patient's serum;
- The determination of a patient's ABO and Rh blood type are not impacted;
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, genotyping may also be considered;
- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices;
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the interference with indirect antiglobulin tests;
- Reference to the need to consult the Summary of Product Characteristics (SmPC);
- Reference to the need of giving the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

The Patient Alert Card, shall contain the following key elements:
- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using DARZALEX (daratumumab), and that this treatment is associated with the Important Identified Risk of Interference for blood typing (minor antigen) (Positive Indirect Coombs' test), which might persist for up to 6 months after the last product's infusion, and a clear reference that the patient should continue to carry this card until 6 months after the treatment has ended;
- Contact details of the DARZALEX (daratumumab) prescriber;
- Reference to the need to consult the Package Leaflet (PL).