CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761145Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-Disciplinary Review and Evaluation

Application Type	Original Biologics License Application
Application Number(s)	BLA 761145
Priority or Standard	Standard
Submit Date(s)	July 12, 2019
Received Date(s)	July 12, 2019
PDUFA Goal Date	May 12, 2020
Division/Office	DHM2/OOD
Review Completion Date	April 12, 2020
Established/Proper Name	Daratumumab
(Proposed) Trade Name	DARZALEX FASPRO (daratumumab and hyaluronidase-fihj)
Pharmacologic Class	Combination of daratumumab, a CD38 directed cytolytic antibody, and hyaluronidase, an endoglycosidase
Code Name	JNJ-54767414 (rHuPH20)
Applicant	Janssen Biotech, Inc.
Dosage Form	Subcutaneous injection
Applicant Proposed Dosing	1800mg daratumumab-30000U rHuPH20 per 15 mL vial
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with multiple myeloma: • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant. • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy. • in combination with pomalidomide and dexamethasone (b) (4) [redacted] • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
Recommendation on Regulatory Action	Approval for the indications specified below.

Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with multiple myeloma: • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant. • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy. • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality, OPDP=Office of Prescription Drug Promotion, OSI=Office of Scientific Investigations, OSE=Office of Surveillance and Epidemiology, DEPI= Division of Epidemiology, DMEPA=Division of Medication Error Prevention and Analysis, DRISK=Division of Risk Management

Glossary

ADRs	adverse drug reactions
AE	adverse event
ASCT	autologous stem cell transplantation
BLA	biologics license application
BW	body weight
CD38	cluster of differentiation 38
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum serum concentration
COA	clinical outcomes assessment
CR	complete response
CRF	case report form
CSR	clinical study report
C_{trough}	observed serum concentrations immediately prior to the next drug administration
CTSQ	Cancer Therapy Satisfaction Questionnaire
CV	coefficient of variation
CR	complete response
DBP	diastolic blood pressure
D-Kd	daratumumab, carfilzomib, and dexamethasone
DoR	duration of response
D-Pd	daratumumab, pomalidomide, and dexamethasone
D-Rd	daratumumab, lenalidomide, and dexamethasone
D-VRd	daratumumab, bortezomib, lenalidomide, and dexamethasone
D-VMP	daratumumab, bortezomib, melphalan, and prednisone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-R	exposure-response
FDA	Food and Drug Administration
GCP	good clinical practice
HR	hazard ratio or heart rate
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
IMiD	immunomodulatory drug/agent
IMWG	International Myeloma Working Group
IND	Investigational New Drug
INV	investigator
IRC	independent review committee
IRR	infusion-related reaction
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
M-protein	M-protein
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NDA	new drug application
NDMM	newly diagnosed multiple myeloma
NI	non-inferiority
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
rHuPH20	recombinant human hyaluronidase PH20
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
USPI	United States Package Insert/Prescribing Information
VGPR	very good partial response

1 Executive Summary

1.1 Product Introduction

Drug: Daratumumab and hyaluronidase (DARZALEX FASPRO)

Pharmacological Class: Daratumumab and hyaluronidase-fihj is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, an endoglycosidase. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc-mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis.

Proposed Indications:
Treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone (b) (4)
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Dosing Regimen: 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously (SC) into the abdomen over approximately 3 to 5 minutes according to the recommended schedule for the specific combination therapy or monotherapy regimens.

1.2 Conclusions on Substantial Evidence of Effectiveness

The review team recommends approval of DARZALEX FASPRO (daratumumab and hyaluronidase-fihj), according to the 21 Code of Federal Regulations (CFR) 314.126(a)(b) for the indication:

DARZALEX FASPRO is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, an endoglycosidase, for the treatment of adult patients with multiple myeloma:

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are

ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

The approval of daratumumab and hyaluronidase-fihj (henceforth referred to as daratumumab SC) in the above indications is based on the totality of evidence from Study MMY3012 (COLUMBA) supported by Study MMY2040 (PLEIADES), which demonstrate a favorable benefit-risk profile for the intended indications.

MMY3012 was a phase 3, multicenter, open-label, randomized, active-controlled trial evaluating the non-inferiority of daratumumab SC monotherapy as compared to daratumumab IV monotherapy in adult patients with multiple myeloma (MM) who had received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or whose MM was refractory to both a PI and an IMiD. Patients were randomized 1:1 to receive either daratumumab SC 1800 mg (N=263) or daratumumab IV 16 mg/kg (N=259) in 28-day cycles until disease progression or unacceptable toxicity.

MMY2040 was a phase 2, multicenter, open-label, single-arm, multicohort, non-randomized, combination therapy trial evaluating daratumumab SC in combination with: bortezomib, melphalan, and dexamethasone (D-VMP) in newly diagnosed transplant-ineligible patients with MM (N=67), in combination with lenalidomide and dexamethasone (D-Rd) in patients with RRMM and at least 1 prior line of therapy (N=65), and in combination with bortezomib, lenalidomide dexamethasone (D-VRd) in newly diagnosed transplant-eligible patients with MM (N=67).

Efficacy:
- MMY3012 included co-primary endpoints of overall response rate (ORR) and the maximum pre-dose trough concentration (C_{trough}) on Cycle 3 Day 1.
- The ORR was 41.1% for daratumumab SC vs. 37.1% for daratumumab IV (risk ratio 1.11; 95% Confidence Interval (CI): 0.89, 1.37).
- The geometric mean ratio comparing daratumumab SC to daratumumab IV for the maximum C_{trough} was 108% (90% CI: 96, 122).
- The primary endpoint for the D-VMP and D-Rd cohorts in MMY2040 was ORR.
- The ORR was 88.1% (95% CI: 77.8%, 94.7%) in the D-VMP cohort and 90.8% (95% CI: 81%, 96.5%) in the D-Rd cohort.

Safety:
- The overall safety profile of daratumumab SC was similar to daratumumab IV in MMY3012.
- Injection-site reactions are a new safety concern for daratumumab SC. In the pooled daratumumab SC monotherapy safety population (N=490) the incidence of injection-site reactions was 8%. All reactions were Grade 1-2 in severity, and the majority of were Grade 1

(mild) in severity.

- The rate of infusion reactions was lower in the daratumumab SC arm compared to the daratumumab IV arm (12.7% vs. 34.5%) in MMY3012.
- There was a higher incidence of neutropenia with daratumumab SC compared to daratumumab IV (19.2% vs. 13.6%), including severe (Grade 3-4) neutropenia (13.1% vs. 7.8%) in MMY3012.
- Patients with low body weight (BW) who received daratumumab SC had a higher incidence of Grade 3-4 neutropenia compared to patients with low BW who received daratumumab IV (27.3% vs. 4.8% in patients with BW ≤ 50 kg) in MMY3012.
- Despite the higher rates of neutropenia observed with daratumumab SC, there was not an increase in the incidence of infections in MMY3012; however, given the single arm design and small size of the patient cohorts in MMY2040, a definitive conclusion that there is no increase in the risk of infection could not be made.

Overall, the efficacy and safety results of MMY3012 and MMY2040 demonstrate an acceptable benefit-risk profile for daratumumab SC in the indicated patient populations.

1.3 Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies in the United States. MM is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years. Five-year survival rates for patients with MM are 52.2% (SEER 18 2009-2015). Despite the availability of multiple treatments, the majority of patients experiencing recurring remissions and relapses. The goal of treatment is often aimed at creating longer periods of time without disease progression. Improving outcomes in patients with relapsed/refractory disease is an unmet medical need.

Multiple treatment regimens are approved for use in MM, including alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies. Daratumumab (DARZALEX) is a CD38 -directed cytolytic antibody approved for multiple indications in combination with other MM drugs for the treatment of patients with newly diagnosed MM and in combination and as a single agent in patients with relapsed/refractory multiple myeloma, as specified in the DARZALEX USPI. Daratumumab (DARZALEX) is given as an intravenous infusion (IV) with administration times ranging from 3-7 hours depending on the volume of administration (henceforth referred to as daratumumab IV).

The Applicant 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 (henceforth referred to as daratumumab SC). Daratumumab SC offers patients with MM a different route of administration than daratumumab IV. Aside from the different route of administration, other aspects different in comparing daratumumab SC to daratumumab IV include: 1) combination with hyaluronidase and flat dose of SC daratumumab, and 2) SC administration takes place over 3-5 minutes.

The benefit-risk assessment for this BLA is primarily based on Study MMY3012 (COLUMBA); a phase 3, multicenter, open-label, randomized, active-controlled trial designed to evaluate the non-inferiority of daratumumab SC monotherapy as compared to daratumumab IV monotherapy in adult patients with multiple myeloma (MM) who had received at least 3 prior lines of therapy, including a PI and an IMiD, or whose MM was refractory to both a PI and an IMiD. Study MMY2040 (PLEIADES), a single arm multicohort combination therapy trial evaluating daratumumab SC in combination with bortezomib, melphalan, and dexamethasone (D-VMP), lenalidomide and dexamethasone (D-Rd), and bortezomib, lenalidomide, and dexamethasone (D-VRd), provided supportive evidence.

MMY3012 met its co-primary endpoint; non-inferiority of monotherapy of daratumumab SC over daratumumab IV for ORR and maximum C_{trough} at pre-dose Cycle 3 Day1. The ORR was 41.1% for daratumumab SC and 37.1% for daratumumab IV with a risk ratio of 1.11 (95% confidence interval [CI]: 0.89, 1.37). The geometric mean ratio comparing daratumumab SC (1800 mg) to daratumumab IV (16 mg/kg) for maximum trough

concentration (C_{trough} at pre-dose of Cycle 3 Day 1) was 108% (90% CI: 96%, 122%). MMY2040 met the protocol pre-specified hypotheses on their primary endpoints of ORR for the cohorts (D-VMP and D-Rd).

The safety profile of daratumumab SC in MMY3012 was overall similar to daratumumab IV with some notable exceptions: local injection site reactions were observed with daratumumab SC and the rate of infusion reactions was lower with daratumumab SC compared to daratumumab IV. Higher rates of neutropenia (>5% difference) as an adverse reaction were observed with daratumumab SC (13.1%) compared to daratumumab IV (7.8%). A higher incidence of Grade 3/4 neutropenia was observed for patients with lower body weight (BW) receiving daratumumab SC. In patients with BW 65 to < 51 kg, Grade 3/4 neutropenia was reported in 18.3% of patients in the daratumumab SC arm and 9.9% of patients in the daratumumab IV arm; in patients with BW ≤ 50 kg, Grade 3/4 neutropenia occurred in 27.3% and 4.8% of patients, respectively, in the two arms. Appropriate labeling is included for Dosage and Administration, the route of administration of daratumumab SC, and Warnings and Precautions for hypersensitivity and other administration reactions, neutropenia, thrombocytopenia, and embryo-fetal toxicity.

In conclusion, the efficacy and safety of daratumumab SC monotherapy was comparable to daratumumab IV monotherapy. Daratumumab SC offers a new dosing regimen and route of administration for patients with MM. FDA considered the totality of evidence from the available efficacy, safety and PK data from MMY3012 and MMY2040. The benefit-risk profile is acceptable in the populations as listed below.

DARZALEX FASPRO for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

(b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MM is a plasma cell malignancy that accounts for approximately 17% of hematologic malignancies in the United States. • MM is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years. • Despite the availability of multiple treatments, myeloma is thought to be an incurable disease, with the majority of patients experiencing recurring remissions and relapses.	Improving outcomes in patients with relapsed/refractory disease is an unmet medical need.
Current Treatment Options	• Multiple treatment regimens are approved for use in MM including alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies. • Daratumumab (DARZALEX) is a CD38 -directed cytolytic antibody approved for the treatment of patients with newly diagnosed and relapsed/refractory MM, as specified in the DARZALEX USPI.	The subcutaneous (SC) formulation of daratumumab provides patients with a different dosing regimen (flat dose) and route of administration compared to intravenous (IV) daratumumab.
Benefit	• Study MMY3012 (COLUMBA) met its co-primary endpoints; non-inferiority of monotherapy of daratumumab SC vs. daratumumab IV for ORR and maximum trough concentration ($C_{trough)}$ pre-dose Cycle 3 Day1. • The ORR was 41.1% for daratumumab SC and 37.1% for daratumumab IV with a risk ratio of 1.11 (95% confidence interval [CI]: 0.89, 1.37). • The geometric mean ratio comparing daratumumab SC (1800 mg) to daratumumab IV (16 mg/kg) for maximum C_{trough} (pre-dose Cycle 3 Day 1) was 108% (90% CI: 96%, 122%). • Study MMY2040 (PLEIADES), the combination cohort study, met the protocol pre-specified hypotheses on the primary endpoint of ORR for the cohorts and is considered supportive.	The efficacy of daratumumab SC is comparable to daratumumab IV and exposures with flat dose daratumumab SC were similar to that achieved with daratumumab IV and across the bod weight range exposure differences did not appear to impact efficacy.
Risk and Risk Management	• Safety data from MMY3012 and MMY2040 showed the safety profile of daratumumab SC was comparable to daratumumab IV, except for increased injection site reactions and neutropenia with daratumumab SC in the monotherapy MMY3012 study.	There was a higher incidence of administration-related reactions with daratumumab SC and a higher incidence of Grade 3/4 neutropenia in patients with low body weight. This information is included in the USPI Warnings and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Higher rates of Grade 3/4 neutropenia were observed for daratumumab SC compared to daratumumab IV in MMY3012 (13.1% vs 7.8%); the difference in rates of neutropenia was higher in patients with low body weight (BW). In patients with BW 65 to < 51 kg, Grade 3/4 neutropenia was 18.3% in the daratumumab SC arm and 9.9% in the daratumumab IV arm; in patients with BW ≤ 50 kg, Grade 3/4 neutropenia was 27.3% and 4.8%, respectively.	Precautions. The safety profile of daratumumab SC is acceptable for the intended population. (b) (4)

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that was submitted as part of the application include:				Section where discussed, if applicable:
	X	Clinical outcome assessment (COA) data, such as:			
			X	Patient reported outcome (PRO)	Section 8.1.4 and Section 8.2.6
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other (Please specify)			
	Patient experience data that was not submitted in the application but was considered in this review.				

X Bindu Kanapuru, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
Multiple myeloma is an incurable malignant plasma cell disorder diagnosed annually in approximately 160,000 patients worldwide. The proliferation of myeloma cells causes displacement of normal bone marrow hematopoietic precursors and the overproduction of monoclonal proteins (M-proteins). 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).

Multiple myeloma is heterogeneous and genetically complex with a course that varies depending on both disease- and host-related factors. Typically, a chronic phase lasting several years is followed by an aggressive terminal phase. The coexistence of different tumor subclones at baseline displaying different drug sensitivities ultimately contributes to the development of drug resistance and disease progression (Barlogie 2014). Worldwide, 106,105 deaths were estimated in 2018 (Bray 2018), with approximately 12,770 patients dying from this disease annually in the United States (Siegel 2018).

The FDA's Assessment:
FDA agrees with the Applicant's analysis of condition.

2.2 Analysis of Current Treatment Options

The Applicant's Position:
Treatment choices for multiple myeloma vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors (Palumbo 2011). Current approved treatments are included in Table 1. With modern therapy, patients with standard risk multiple myeloma have an estimated median survival of 8 to 10 years (Rajkumar 2017).

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 proteasome inhibitors (PIs) and immunomodulatory drugs (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).

Daratumumab administered intravenously (DARZALEX; daratumumab IV, 16 mg/kg) has become a transformational therapy in multiple myeloma. In previous clinical trials and with postmarketing

exposure, daratumumab IV has been shown to be well-tolerated with manageable side effects. The most common adverse events (AEs) associated with daratumumab IV-based regimens are infusion-related reactions (IRRs). A larger volume (500 mL to 1000 mL) and a median infusion time of approximately 7 hours is required for the first infusion and 3 to 4 hours for subsequent infusions.

The Applicant 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 injected into the SC tissue of the abdomen over approximately 3 to 5 minutes. Daratumumab SC was developed to provide several potential benefits for both patients and healthcare providers, including:

- Shorter administration time giving additional flexibility and reducing treatment burden to the patient, as well as reducing health care professional time and resources spent on administration.
- Reduced burden and a reduced rate of IRRs are expected to improve patient satisfaction with daratumumab SC therapy.
- Daratumumab SC provides an alternative route of administration for patients with poor venous access and eliminates the need for repeated IV access and insertion of long-term central venous access devices.
- The smaller administration volume for daratumumab SC is expected to reduce the risk of volume overload in patients with cardiac or renal insufficiency.
- Reduced risk of errors, shorter preparation time, and complete content usage from vials are expected because daratumumab is a single, pre-mixed vial with a flat dose, compared with the daratumumab IV formulation that is dosed by body weight and requires multiple vials.

Table 1: Summary of Treatment Armamentarium Relevant to Multiple Myeloma

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Proteasome inhibitors						
VELCADE (bortezomib)	**1st line MM:** as monotherapy **2nd line MM**: as monotherapy; at least 1 prior therapy **3rd Line MM**: as monotherapy; at least 2 prior therapies	2008: standard approval 2005: standard approval 2003: accelerated approval	IV (1 mg/mL; 3-5 min bolus) or SC (2.5 mg/mL). Administer twice weekly (D1, D4, D8, D11, D22, D25, D29 and 32). QW in C5-C9 (D1, D8, D22, and D29). At least 72 hrs between consecutive doses.	**Previously untreated (IV)**: Median TTP: 20.7 mo Median PFS: 18.3 mo Median OS: NR ORR (CR+PR): 69% **Relapsed/refractory IV:** Median TTP: 6.2 mo ORR (CR+PR): 38% **Relapsed/refractory (SC vs IV, respectively):** ORR (CR+PR), 4 cycles: 43% vs 42% ORR (CR+PR), 8 cycles: 53% vs 51% Median TTP: 10.4 mo vs 9.4 mo Median PFS: 10.2 mo vs 8.0 mo 1-yr OS: 72.6% vs 76.7%	Peripheral neuropathy, hypotension, cardiac toxicity (acute development or exacerbation of CHF, new onset decreased LVEF), pulmonary toxicity (ARDS; ADIPD unknown etiology), PRES, TLS, hepatotoxicity, thrombocytopenia/ neutropenia, GI toxicity, thrombotic microangiopathy, embryo-fetal toxicity	
KYPROLIS (carfilzomib)	**2+ lines MM:** combination therapy	2016: standard approval	**In combination with dex** (40 mg IV D1, D8, D15; plus D22 on C1-C9): Carfilzomib 20/27 mg/m^2 IV on D1, D2, D8, D9, D15, D16 of 28-d cycle (20 mg/m^2 C1D2 and C1D2).	**Kd** PFS: 18.7 mo OS: 47.6 mo ORR: 77%	Cardiac toxicities, acute renal failure, TLS, pulmonary toxicity pulmonary hypertension, dyspnea, hypertension, venous thrombosis, infusion reactions, hemorrhage, thrombocytopenia, hepatic toxicity and hepatic failure, thrombotic microangiopathy, PRES	
	2+ lines MM combination therapy	2015: standard approval	**In combination with len** (25 mg PO, D1-D21) **+ dex** (40 mg PO or IV, D1, D8, D15, D22): Carfilzomib 20/27 mg/m^2 IV on D1, D2, D8, D9, D15, D16 of 28-d cycle (20 mg/m^2 C1D2 and C1D2).	**KRd:** PFS: 26.3 mo OS: 48.3 mo ORR: 87%		
	2+ lines MM: monotherapy	2012: accelerated approval	Administer carf 20 mg/m^2 IV on 2 consecutive days on D1, D2, D8, D9, D15, and D16 (28-d cycle). From C13, omit D8-D9 dose of carf. Escalate carf C1D8 to 27 mg/m^2 (weekly regimen) or 56 mg/m^2 (twice weekly regimen) until PD or unacceptable toxicity	***Twice weekly 20/56 mg/m^2 regimen:*** ORR (sCR+CR+VGPR+PR): 50% ***Once weekly 20/27 mg/m^2 regimen***: Study PX-171-003 A1 (N=266):		

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				ORR (CR+VGPR+PR): 23% Study PX-171-004 Part 2 (N=70): ORR (CR+VGPR+PR): 50%		
NINLARO (ixazomib)	**2nd line MM**: in combination with len and dex	2015: standard approval	Administer 4 mg PO qw on D1, D8, and D15 of a 28-d cycle. Starting dose of len: 25 mg daily on D1-D21. Starting dose of dex: 40 mg on D1, D8, D15, D22.	Median PFS: 20.6 mo ORR (PR+VGPR+CR): 78%	Thrombocytopenia, GI toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity, embryo- fetal toxicity	
Immunomodulatory drugs						
REVLIMID (lenalidomide)	As maintenance following autologous HSCT **1st line MM**: in combination with dex **2nd line MM**: in combination with dex	2017: standard approval 2015: standard approval 2006: standard approval	Administer 25 mg orally qd on D1-D21 (28-day cycles) in combination with dex	**Maintenance Study 1:** Median OS: 111.0 mo **Maintenance Study 2:** Median OS: 105.9 mo **1st Line**: Median PFS: 52.0 mo Median OS: 58.9 mo ORR (CR+VGPR+PR): 75.1% **2nd Line:** Median TTP: 13.9 mo ORR (CR+PR): 61%	Embryo-fetal toxicity, hematologic toxicity (neutropenia, thrombocytopenia), venous and arterial thromboembolism, second primary malignancies, hepatotoxicity, severe cutaneous reactions including hypersensitivity reactions, TLS, thyroid disorders	
POMALYST (pomalidomide)	**3rd line MM**: in combination with dex; at least 2 prior therapies including len and a PI (bort) and demonstrated PD on or within 60d of last therapy	2013: accelerated approval	Administer 4 mg once daily PO on D1-D21 (28-d cycles) until PD. Dex 40 mg PO qd on D1, D8, D15, D22.	ORR (CR+PR): 29.2%	Fetal risk, venous thromboembolism, hematologic toxicity, hypersensitivity reactions, dizziness and confusional state, neuropathy, risk of second primary malignancies	Avoid admin with CYP1A2, CYP3A or P-gp inhibitors / inducers

Product (s) Name	**Relevant Indication**	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
						can impact exposure
THALOMID (thalidomide)	**1st line: in combination with dex**	May 2006: accelerated approval	Administer 200 mg PO qd with water in combination with dex. Dex 40 mg daily on D1-D4, D9-D12, and D17- D20 every 28 d.	Median TTP: 97.7 wks Median OS: NR ORR (CR+PR): 63%	Embryo-fetal toxicity, venous and arterial thromboembolism, drowsiness and somnolence, peripheral neuropathy, dizziness and orthostatic hypotension, neutropenia, thrombocytopenia, increased HIV viral load, bradycardia, SJS and toxic epidermal necrolysis, seizures, TLS, contraceptive risks, hypersensitivity	REMS
Histone deacetylase (HDAC) inhibitor						
FARYDAK (panobinostat)	**3rd line MM**: in combination with bort and dex; received at least 2 prior lines including bort and an IMiD	2015: accelerated approval	Administer 20 mg PO once every other day for 3 doses per wk in Wk 1 and 2 of each 21-d cycle. Wk 1-8: Bort 1.3 mg/m^2 IV, D1, D4, D8, and D11. Dex 20 mg PO; D1, D2, D4, D5, D8, D9, D11, D12. Weeks 9-16: Bort 1.3 mg/m^2 IV, D1 and D8. Dex 20 mg/m^2 PO; D1, D2, D8, D9.	Median PFS: 10.6 mo ORR (PR+nCR+CR): 58.5%	Diarrhea, cardiac toxicities (cardiac ischemic events, severe arrhythmias, ECG changes), hemorrhage, myelosuppression, infections, hepatotoxicity, embryo- fetal toxicity	
Anthracycline chemotherapy agent						
DOXIL (doxorubicin hydrochloride liposomal)	**2nd line MM**: in combination with bort	2007: standard approval	Administer 30 mg/m^2 IV over 60 min on D4 (after bort) of each 21-d cycle for 8 cycles or until PD or unacceptable toxicity.	Median TTP: 9.3 mo ORR (CR+PR): 48%	Cardiomyopathy, infusion-related reactions, hand-foot syndrome, secondary oral neoplasms	

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Monoclonal antibodies						
EMPLICITI (elotuzumab)	**2nd line MM**: in combination with len and dex	2015: BTD	Administer 10 mg/kg IV qw for the first 2 cycles and q2w thereafter (in conjunction with recommended dosing of len and low-dose dex).	Median PFS: 19.4 mo ORR (sCR+CR+VGPR+PR): 78.5% OS:43.7 mo	Infusion reactions, infections, second primary malignancies, hepatotoxicity, interference with determination of CR	
DARZALEX (daratumumab)	**1st line MM** (newly diagnosed): in combination with len and dex; ineligible for ASCT	2019: standard approval (RTOR)	Premedicate with corticosteroids, antipyretics, and antihistamines. **D-Rd:** Administer dara 16 mg/kg IV weekly for 8 wks, q2w for 8 additional doses, then q4w until PD. Len 25 mg PO D1-D21 of each cycle. Low-dose dex 40 mg/wk (or reduced dose 20 mg/wk) IV or PO	Median PFS: NR ORR (sCR+CR+VGPR+PR): 92.9%	Severe and/or serious infusion reactions including anaphylactic reactions; increases in neutropenia or thrombocytopenia induced by background therapy; infections and serious infections; potential for immunogenicity	Dara binds to CD38 found at low levels on RBCs and may result in a positive indirect Coombs test
	1st line MM: in combination with VMP; ineligible for ASCT	2018: standard approval	Premedicate with corticosteroids, antipyretics, and antihistamines. **Newly diagnosed:** **D-VMP**: Administer dara 16 mg/kg IV weekly for 6 wks, q3w for 16 additional doses, then q4w until PD. Bort 1.3 mg/m^2 SC q2w for C1 (6-wk cycle), then qw for C2-C9. Melphalan (9 mg/m^2 PO) and prednisone (60 mg/m^2 PO) on D1-D4 of C1-C9. **Relapsed/Refractory**: **D-Vd**: Administer dara 16 mg/kg IV weekly for 9 wks, q3w for 5 additional doses, then q4w until PD. Bort 1.3 mg/m^2 SC q2w for 8 cycles (21-d/cycle). Dex 20 mg PO D1, D2, D4, D5, D8, D9, D11, and D12 for 8 cycles (or reduced dose of 20 mg/wk). **D-Rd**: Administer dara 16 mg/kg IV weekly for 8 wks, q2w for 8 additional doses, then q4w until PD. Len 25 mg PO D1-D21 of each cycle. Low-dose dex 40 mg/wk (or reduced dose 20 mg/wk) IV or PO **D-Pd:** Administer dara 16 mg/kg IV weekly for 8 wks, q2w for 8 additional doses, then q4w until PD. Pom 4 mg PO qd D1-D21 of each cycle. Low-dose dex 40 mg/wk (or reduced dose 20 mg/wk)	D-VMP: Median PFS: NR ORR (sCR+CR+VGPR+PR): 90.9% D-Vd: Median PFS: NE ORR (sCR+CR+VGPR+PR): 79.3% OS: NR D-Rd: Median PFS: NE ORR (sCR+CR+VGPR+PR): 91.3% OS: NR D-Pd: ORR (sCR+CR+VGPR+PR): 59.2% Dara monotherapy: ORR: 29.2%		
	2nd line MM: in combination with dex and either bort or len	2016: BTD				
	3rd line MM: in combination with pom and dex; at least 2 prior therapies including len and a PI	2017: standard approval				
	4th line MM: as monotherapy; at least 3 prior therapies including a PI and IMiD or double- refractory to PI and IMiD	2015: BTD, accelerated approval				

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Conditioning and palliative treatment for multiple myeloma						
EVOMELA (melphalan)	Prior to conventional HPSCT; palliative therapy for pts with MM who cannot tolerate oral treatment	2016: standard approval	**Conditioning Treatment**: Administer 100 mg/m^2/day IV over 30 min for 2 consecutive d prior to ASCT. **Palliative Treatment**: Administer 16 mg/m^2 as a single IV dose over 15-20 min at 2-wk intervals for 4 doses, then after adequate recovery from toxicity, at 4-wk intervals	**Conditioning Treatment**: Improved ORR (from 79% prior to ASCT to 95% post-transplant) Increase in number of sCR (from 0 pts prior to ASCT to 16% at 90-d post-transplant) **Palliative treatment**: ORR with IV: 38% (vs 44% with PO treatment)	Bone marrow suppression, GI toxicity, hepatotoxicity, hypersensitivity, secondary malignancies, embryo-fetal toxicity, infertility	
Alkylating agent						
CYTOXAN (cyclophosphamide)	**1st line MM**: as combination therapy with bortezomib and dexamethasone in patients eligible for SCT as well as patients ineligible for SCT	1959: standard approval	**Variation 1:** ***Cycles 1 and 2:*** Cyclophosphamide: Oral: 300 mg/m^2/day on D1, D8, D15, and D22 Bortezomib: IV: 1.5 mg/m^2/day on D1, D8, D15, and D22 Dexamethasone: Oral: 40 mg/day on D1-D4, D9-D12, and D17-D20 *Repeat cycle every 28 d for 2 cycles* ***Cycles 3 and 4:*** Cyclophosphamide: Oral: 300 mg/m^2/day on D1, D8, D15, and D22 Bortezomib: IV: 1.5 mg/m^2/day on D1, D8, D15, and D22 Dexamethasone: Oral: 40 mg/day on D1, D8, D15, and D22 *Repeat cycle every 28 d for 2 cycles* **Variation 2:** Cyclophosphamide: Oral: 300 mg/m^2/day on	**CyBorD Regimen as described in NCCN MM Guidelines:** **Reeder et al:** ORR: 88% CR rate: 39% 5-year PFS: 42% OS: 70% **German DSMM Xia study:** ORR: 84% PR rate: 71.5% CR Rate: 12.5% **EVOLUTION study:** ORR: 75% CR rate: 22% 1-year PFS: 93%	Neutropenia, nausea and vomiting, alopecia, abdominal discomfort, diarrhea	

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			D1, D8, D15, and D22 Bortezomib: IV: 1.3 mg/m^2/day on D1, D4, D8, and D11 Dexamethasone: Oral: 40 mg/day on D1-D4, D9-D12, and D17-D20 *Repeat cycle every 28 d for 4 cycles total*			

ADIPD=acute diffuse infiltrative pulmonary disease; ARDS=acute respiratory distress syndrome; ASCT=autologous stem cell transplantation; bort=bortezomib; BTD=break through designation; C=cycle; carf=carfilzomib; CHF=congestive heart failure; CR=complete response; CRCL=creatinine clearance; CYP=cytochrome P450; d=day; dara=daratumumab; DC=discontinuation; dex=dexamethasone; G-CSF=granulocyte colony stimulating factor; SRE=skeletal-related event; GI=gastrointestinal; hr=hour; HSCT=hematopoietic stem cell transplantation; IMiD=immunomodulatory drug; IV=intravenous; len=lenalidomide; LVEF=left ventricular ejection fraction; min=minutes; MM=multiple myeloma; mo=month; NCCN= National Comprehensive Cancer Network; nCR=near complete response; NR=not reached; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PI=proteasome inhibitor; PO=per os; pom=pomalidomide; PR=partial response; PRES=posterior reversible encephalopathy syndrome; pts=patients; qd=once daily; q2w=once every 2 weeks; q3w=once every 3 weeks; q4w=once every 4 weeks; qw=every week; RBCs=red blood cells; REMS=Risk Evaluation and Mitigation Strategies; RTOR=real time oncology review; SC=subcutaneous; sCR=stringent complete response; SJS=Stevens Johnson syndrome; TLS=tumor lysis syndrome; TTP=time to progression; VGPR=very good partial response; VMP=bortezomib, melphalan, and prednisone; wk=week; yr=year

[a] Accelerated approval or standard approval.
[b] Initial course for patients with no hematologic deficiency.
[c] Many other regimens of IV and oral cyclophosphamide have been reported. Adjust dose in accordance with antitumor activity and/or leukopenia.
[d] When included in combination with combined cytotoxic regimens, it may be necessary to reduce the dose of cyclophosphamide as well as the other drugs.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of current treatment options. FDA agrees with the list of treatment options in Table 1, but also notes that selinexor received accelerated approval in 2019 for an indication in patients with relapsed or refractory MM (RRMM) with at least 4 prior lines of therapy whose disease is refractory to at least 2 PIs, at least 2 IMiDs and an anti-CD38 mAb. FDA agrees that a SC formulation of daratumumab represents a new route of administration that may provide potential benefits to patients, such as a shorter administration time, reduced rate of IRRs, alternative route of administration for patients with poor venous access, and smaller volume of administration.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
DARZALEX (daratumumab) 16 mg/kg IV administration (hereafter referred to as daratumumab IV) was granted accelerated approval by the US FDA on 16 November 2015 as monotherapy for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD. Full approval was granted by FDA on 21 November 2016, along with the following indications: in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone for the treatment of patients with multiple myeloma who have received ≥1 prior therapy. Additional approvals were received on 16 June 2017 in combination with pomalidomide/dexamethasone for the treatment of multiple myeloma in patients who have received ≥2 prior therapies and on 7 May 2018 for daratumumab in combination with VMP for the treatment of patients with newly-diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT). Most recently on 27 June 2019, daratumumab was approved in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for ASCT.
(b) (4)

The FDA's Assessment:
Since submission of this BLA, DARZALEX received approval for an additional indication in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant. The Applicant did not request this indication in the current BLA. It was still under review at the time this application was submitted. Otherwise, FDA agrees with the Applicant's presentation of the regulatory and marketing history of daratumumab.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of the presubmission/submission regulatory activity for IND 125541 is provided in Table 2.

Table 2: Daratumumab Presubmission/Submission Regulatory Activity

Activity	Date	Comment
Type B Meeting	07 Nov 2016	Meeting request submitted. Purpose: to obtain agreement with Agency on the Phase 3 study design (54767414MMY3012 [MMY3012]) to support the use of daratumumab co-formulated with rHuPH20 administered by SC injection (daratumumab SC) (Serial No. 0177).
	20 Jan 2017	Briefing book submitted (Serial No. 0204).

	23 Feb 2017	End of Phase 2 meeting to obtain agreement with Agency on the Phase 3 study design (MMY3012) to support use of daratumumab SC.
Pharmacokinetics (PK) and Safety Data Submitted	12 Sep 2017	Submission of PK and safety data for daratumumab SC 1800 mg based on data from 25 subjects who have received at least 1 dose of daratumumab SC and 20 subjects (18 were PK-evaluable) who reached C3D1 at the clinical data cutoff (03 Aug 2017) from Study MMY1004. Data were submitted for review prior to initiating Phase 3 studies using daratumumab SC (Serial No. 0278).
Protocol submitted	04 Oct 2017	The initial protocol for Study MMY3012 was submitted (Serial No. 0288).
Type B Pre-BLA Meeting	14 Sep 2018	Meeting request submitted. Purpose: to seek FDA's agreement on the proposed format, content, and planned efficacy/safety analyses of the planned initial BLA for daratumumab SC, including Phase 3 Study MMY3012 (Serial No. 0410).
	24 Oct 2018	Briefing book submitted (Serial No. 0426).
	18 Dec 2018	Pre-BLA meeting to obtain agreement with the Agency regarding the proposed content, format, and planned efficacy/safety analyses on planned initial BLA for daratumumab SC. Following clear preliminary comments from FDA dated 13 Dec 2018, the scheduled Type B teleconference for 18 Dec 2018 was subsequently cancelled.
Final Statistical Analysis Plan	01 Nov 2018	The final SAP for Study MMY3012 submitted (Serial No. 0431).
	15 Feb 2019	Response to IR, received 28 January 2019, regarding SAP submitted (Serial No. 0467).
Type B Pre-BLA Meeting	02 Nov 2018	Meeting request submitted. Purpose: to obtain Agency feedback on CMC content for the initial BLA for daratumumab SC to further guide drug substance and drug product development to enable readiness for BLA submission (Serial No. 0432).
	07 Dec 2018	Briefing book submitted (Serial No. 0441).
	24 Jan 2019	Pre-BLA face-to-face CMC meeting to obtain Agency feedback on CMC content for the initial BLA for daratumumab SC to further guide drug substance and drug product development to enable readiness for BLA submission.
Proprietary Name Review	25 May 2017	Request for Proprietary Name Review submitted – Primary name: DARZALEX® (b) (4)
	20 Nov 2017	Propriety Name DARZALEX® (b) (4) unacceptable.
	04 Feb 2019	Updated Request for Proprietary Name Review submitted - Primary Name: DARZALEX FASPRO; Alternate Name: DARZALEX (b) (4)
Assessment Aid Pilot Program Submitted	26 Feb 2019	Janssen requested participation for this BLA in the Assessment Aid pilot program (Serial No. 0473).
BLA submission	12 Jul 2019	Complete submission of BLA 761145.

BLA=Biologics Licensing Application; C=cycle; CMC=chemistry, manufacturing, and controls; D=day; daratumumab SC=daratumumab co-formulated with rHuPH20 administered by SC administration; FDA=Food and Drug Administration; IND=Investigational New Drug Application; IR=information request; PK=pharmacokinetic; SC=subcutaneous

The FDA's Assessment:

FDA agrees with the Applicant's table summarizing the presubmission/submission regulatory activity for IND 125541.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations

The FDA's Assessment:
No clinical site inspections were conducted for this application.

4.2 Product Quality

The Applicant's Position:
There are no impurities over the ICH Q3 A/B thresholds that haven't been qualified.

The FDA's Assessment:
Refer to the Office of Product Quality review for specific recommendations regarding the product quality and PMR/PMCs. The FDA Product Quality review team recommended approval.

4.3 Clinical Microbiology

The FDA's Assessment:
Refer to the Office of Microbiology review for specific recommendations regarding the drug product microbiology and PMR/PMCs. The FDA Microbiology review team recommended approval.

4.4 Devices and Companion Diagnostic Issues

The FDA's Assessment:
Not applicable.

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Complete nonclinical toxicology programs were conducted for daratumumab and rHuPH20. Since daratumumab only cross reacts with human and chimpanzee CD38 and conducting additional studies is banned in this species (Federal Register 2016; Vermij 2003), the nonclinical toxicology studies for daratumumab SC only evaluated the local tolerance of the formulation in the rabbit and mini-pig. No additional nonclinical safety concerns were identified in the rabbit and mini-pig studies using daratumumab SC, supporting the use of this formulation in clinical studies.

The FDA's Assessment:

We agree with the Applicant's assessment of the nonclinical studies conducted with daratumumab, including the local tolerance studies of the SC formulation in the rabbit and mini-pig. Based on the lack of a relevant species for toxicological testing and the completed studies conducted to date, we also agree that no additional nonclinical studies are needed to support approval of the SC formulation of daratumumab. Labeling changes were made to reflect current labeling practices for the PLLR format and to have consistency across the labels for CD38-directed cytolytic antibodies. Changes include adding a Warning and Precaution for Embryo-Fetal Toxicity, updating the Animal Data section in Section 8.1 with data from CD38 knockout animal models (mice and frogs), and adding language regarding the treatment in combination with embryo-fetal toxic agents.

X Emily Place, PhD, MPH	X Brenda Gehrke, PhD
Primary Clinical Reviewer	Clinical Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:
The Office of Clinical Pharmacology has reviewed the information contained in BLA 761145 and recommends approval. Key review issues are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The proposed dosage regimen of daratumumab SC 1800 mg is supported by non-inferiority to the approved daratumumab IV 16 mg/kg established with efficacy (overall response rate, ORR) and pharmacokinetics (PK) as co-primary endpoints in Study MMY3012. The ORR was 41.1% for the daratumumab SC and 37.1% for the daratumumab IV with a ratio of 1.11 (95% confidence interval [CI]: 0.89, 1.37). The geometric mean ratio comparing daratumumab SC (1800 mg) to daratumumab IV (16 mg/kg) for maximum trough concentration (C_{trough} at pre-dose of Cycle 3 Day 1) was 108% (90% CI: 96%, 122%).
General dosing instructions	1800 mg of daratumumab with 30000 units recombinant human hyaluronidase PH 20 (rHuPH20) subcutaneously injected over approximately 3 to 5 minutes. In combination with lenalidomide (4-week cycle dosing regimen) and low dose-dexamethasone and for monotherapy: QW (week 1 to 8), Q2W (week 9 to 24), Q4W (week 25 onwards) In combination with bortezomib, melphalan and prednisone ([VMP], 6-week cycle dosing regimen): QW (week 1 to 6), Q3W (week 7 to 54), Q4W (week 55 onwards) With bortezomib and dexamethasone (3-week cycle dosing regimen): QW (week 1 to 9), Q3W (week 10 to 24), Q4W (week 25 onwards)
Dosing in patient subgroups (intrinsic and extrinsic factors)	No daratumumab dose individualization is recommended based on intrinsic and extrinsic factors. For patients with body weight (BW) ≤ 50 kg, monitor neutrophil counts for neutropenia. Daratumumab SC achieved equal or higher maximum C_{trough} (pre-dose of Cycle 3 Day 1) and comparable efficacy across BW groups, as compared to daratumumab IV. A higher incidence of Grade 3/4 neutropenia was observed in the daratumumab SC arm than in the daratumumab IV arm for patients with lower BW (≤ 50 kg: SC 27.3% vs IV 4.8%). The majority of the Grade 3/4 treatment emergent adverse effect (TEAE)

	neutropenia occurred in Cycles 1 and 2 and did not continue into later cycles beyond Cycle 6. More patients in the daratumumab SC arm had Grade 3/4 TEAE neutropenia events that resolved without G-CSF treatment than that in the IV arm. Neutropenia was clinically manageable with G-CSF treatment. Clinically consequential infection AEs were similar between the daratumumab SC and daratumumab IV treatment arms. The range of daratumumab exposures (maximum C_{trough}) across BW groups following 1800 mg daratumumab SC was within the range of exposures after administration of 16 mg/kg daratumumab IV across different monotherapy studies. The totality of the data supports a flat dose of 1800 mg daratumumab SC across all BW groups.
Immunogenicity	One patient (1/426, 0.2%) tested positive for anti-daratumumab antibodies and neutralizing antibodies after receiving daratumumab SC. The incidence of anti-rHuPH20 antibodies was 6.4% (27/420). The anti-rHuPH20 antibodies were non-neutralizing and had no impact on daratumumab exposure.
Labeling	Generally acceptable upon the applicant's agreement to the FDA revisions on the label with specific content and formatting change recommendations.

Post-Marketing Requirements and Commitments: None

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical development program of daratumumab SC is based on demonstration of non-inferiority of pharmacokinetics (PK) using maximum C_{trough} (Cycle 3 Day 1 Ctrough), and efficacy in terms of response rate (overall response rate [ORR]) compared to the approved daratumumab IV 16 mg/kg administration following the same dosing schedule. The objective of the PK program was to select a daratumumab SC dose that provides similar or higher C_{trough} compared to daratumumab IV 16 mg/kg for the key PK-predictive efficacy endpoint, of maximum Ctrough (Cycle 3 Day 1 predose). The PK data from Study 54767414MMY1004 (MMY1004) showed that the 1800 mg daratumumab SC dose consistently provided similar or higher C_{trough} values after the 2nd weekly administration and throughout the dosing schedule as compared to daratumumab IV 16 mg/kg. The data from Study 54767414MMY1008 (MMY1008) demonstrated

that Japanese subjects achieved similar exposures with daratumumab SC 1800 mg as subjects in Study MMY1004, supporting the inclusion of Japanese subjects in Phase 2 and 3 clinical studies. Study MMY2040 evaluated the clinical benefit, PK, and immunogenicity of daratumumab SC administered in combination with standard multiple myeloma regimens (D-VMP, D-VRd, and D-Rd).

The randomized, monotherapy clinical study, 54767414MMY3012 (MMY3012), demonstrated that the average ±SD maximum C_{trough} (Cycle 3 Day 1 predose) for the PK-evaluable population (subjects who received all 8 doses in Cycles 1 and 2 and provided a predose sample on Cycle 3 Day 1 within 8 hours prior to dosing) was higher for daratumumab SC (593±306 µg/mL, N=149) versus daratumumab IV (522±226 µg/mL, N=146). The lower limit of the geometric means ratio for maximum C_{trough} (107.93% [90% CI: 95.74%, 121.67%]) was higher than 80%, thereby demonstrating non-inferiority of daratumumab SC to daratumumab IV in terms of PK. In the Phase 2 combination study, daratumumab SC 1800 mg consistently resulted in comparable C_{trough} values to historical data with D-Rd and D-VMP, where such comparisons were possible.

Exposure-response analyses for efficacy demonstrated a similar relationship between Cycle 3 Day 1 C_{trough} for daratumumab SC 1800 mg as for daratumumab IV 16 mg/kg. For combination therapies, a high ORR was observed consistently across the studied concentrations range, indicating that maximum efficacy in terms of ORR has been attained for daratumumab SC. Subgroup analyses of Cycle 3 Day 1 C_{trough} (maximum C_{trough}) showed that the flat dose of daratumumab SC 1800 mg achieved adequate exposure for all bodyweight subgroups, as the maximum C_{trough} (Cycle 3 Day 1 predose) exceeded the 236 µg/mL threshold (Xu 2017) previously established in daratumumab IV studies as necessary for 99% target saturation.

The exposure-safety analyses for monotherapy studies with daratumumab SC 1800 mg demonstrated a similar relationship between drug exposure (peak concentrations after first dose, overall peak concentration) and safety endpoints (serious adverse events [SAEs], Grade 3 or higher treatment-emergent adverse events [TEAEs], and neutropenia) compared with daratumumab IV 16 mg/kg. There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs, and neutropenia). No exposure-response (E-R) relationship for safety was apparent for combination therapy. In addition, subgroup analysis based on weight did not demonstrate a relationship between neutropenia, infections and infestations and body weight.

These subgroup analyses support the conclusion that no dose modifications are necessary for daratumumab SC on the basis of weight.

The incidence of treatment-emergent anti-daratumumab antibodies was 0.2% (1/426). The 1 subject that was positive for anti-daratumumab antibodies also had transient neutralizing antibodies, but these did not appear to affect daratumumab exposures.

The incidence of baseline anti-rHuPH20 antibodies was 4.3% (18/420) and treatment-emergent non-neutralizing antibodies was 6.4% (27/420). 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™. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures.

The FDA's Assessment:

FDA agrees that daratumumab concentrations following the SC 1800 mg dose were non-inferior to the IV regimen of 16 mg/kg as the lower bound of the 90% CI of the geometric mean ratio (GMR) was greater than 80%, which met the non-inferiority criteria for the co-primary PK endpoint.

FDA does not agree with the Applicant's statement: "subgroup analysis based on weight did not demonstrate a relationship between body weight and neutropenia, infections and infestations."

Subgroup analyses showed that the flat dose of daratumumab SC 1800 mg resulted in an 81% higher mean maximum C_{trough} than the BW-based dose of daratumumab IV 16 mg/kg for patients with BW ≤ 50 kg (Table 3). Overall, administration of daratumumab SC 1800 mg resulted in the maximum C_{trough} (pre-dose on Cycle 3 Day 1) exceeding the 236 µg/mL threshold previously established in daratumumab IV studies to reach 99% target saturation.

Table 3: Maximum Ctrough (pre-dose on Cycle 3 Day 1) for Dara SC vs Dara IV by BW Groups

Maximum Ctrough (µg/mL)	≤ 50 kg		> 50 to 65 kg		> 65 to 85 kg		> 85 kg	
	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC	Dara IV	Dara SC
n	10	9	40	38	63	63	33	39
Mean (SD)	572 (107)	1033 (401)	445 (221)	684 (305)	543 (239)	537 (273)	562 (216)	494 (224)
Geometric mean (%CV)	563 (19%)	960 (39%)	385 (50%)	611 (45%)	480 (44%)	459 (51%)	510 (38%)	405 (45%)
SC/IV mean ratio (%)	**181%**		**154%**		**99%**		**88%**	

Source: FDA reviewer's independent analysis

Across these BW groups and treatment arms, higher grade 3/4 neutropenia was observed for patients with lower BW receiving daratumumab SC (Table 4). For patients with BW ≤ 50 kg, a higher incidence of Grade 3/4 neutropenia was observed in the daratumumab SC arm than in the daratumumab IV arm (SC: 27.3% vs IV: 4.8%).

Table 4: Incidence of Grade 3/4 Neutropenia by BW Groups for Dara IV vs Dara SC

BW groups	Incidence of Grade 3/4 Neutropenia	
	Dara IV	Dara SC
≤ 50 kg	4.8% (1/21)	27.3% (6/22)
>50 to 65 kg	9.9% (7/71)	18.3% (13/71)
>65 to 85 kg	8.6% (9/105)	9.8% (10/102)
> 85 kg	4.9% (3/61)	7.7% (5/65)
Total	**7.8% (20/258)**	**13.1% (34/260)**

Source: FDA reviewer's independent analysis

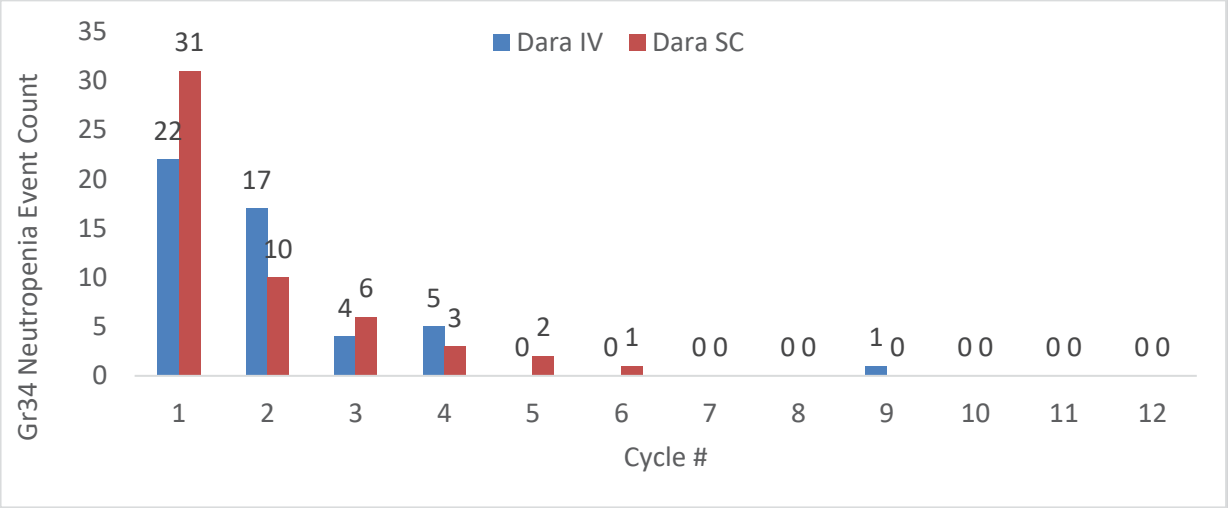
The different rates of neutropenia between the IV and SC arms may in part be explained by the use of G-CSF to treat neutropenia. Table 5 listed the percentage of patients that had TEAE Grade 3/4 neutropenia were treated with G-CSF for the daratumumab IV and SC arms. More patients in the IV arm with TEAE Grade 3/4 neutropenia were treated with G-CSF than those in the SC arm (for patients with BW ≤ 50 kg, ≤ 65 kg, and all patients). In other words, more patients in the daratumumab SC arm had Grade 3/4 neutropenia events that resolved without G-CSF treatment. Additionally, the majority of the Grade 3/4 neutropenia events occurred in Cycles 1 and 2, were resolved overtime either by G-CSF treatment or self-recovery and did not continue into later cycles beyond Cycle 6 for both the IV and SC arms (Figure 1).

Table 5: Percentage of Patients with Grade 3/4 Neutropenia Treated with G-CSF

BW Cutoff	Percentage of patients with TEAE Grade 3/4 Neutropenia treated with G-CSF	
	Dara IV	Dara SC
≤ 50 kg	100% (1/1)	67% (4/6)
≤ 65 kg	100% (8/8)	47% (9/19)
All pts	85% (17/20)	47% (16/34)

Source: FDA reviewer's independent analysis

Figure 1: Grade 3/4 TEAE Neutropenia Event Counts vs Cycle for All Patients



Source: FDA reviewer's independent analysis

Despite the higher incidence of Grade 3/4 neutropenia in the lower BW groups, FDA agrees with the Applicant's position that dose reductions for patients weighing less than 50 kg is not recommended based on the following:

- The majority of the Grade 3/4 TEAE neutropenia occurred in Cycles 1 and 2 and did not continue into later cycles beyond Cycle 6 (Figure 1).
- More patients in the daratumumab SC arm had Grade 3/4 TEAE neutropenia events resolved without G-CSF treatment than that in the IV arm.
- Neutropenia was clinically manageable with G-CSF treatment.

- The incidence of TEAE Grade 3/4 neutropenia (13%) observed in Study MMY3012 daratumumab SC patients was similar to those (12%) in the previous registrational daratumumab IV monotherapy studies.
- Treatment discontinuation due to AEs were comparable between daratumumab SC and daratumumab IV.
- Although a higher rate of neutropenia was observed for patients with lower BW (≤50 kg) who received daratumumab SC, clinically consequential infection AEs (Grade 3/4 infections, infection SAEs, infection AEs leading to discontinuation) were comparable to patients with higher BW received daratumumab SC as well as daratumumab IV in patients within the same BW category.
- The range of daratumumab exposures (maximum C_{trough}) across BW groups following 1800 mg daratumumab SC was within the range of exposures after administration of 16 mg/kg daratumumab IV across different monotherapy studies.

FDA agrees with the Applicant's immunogenicity assessment. One patient (1/426, 0.2%) tested positive for treatment-emergent anti-daratumumab antibodies and neutralizing antibodies in the daratumumab SC treatment arm. The incidence of treatment-emergent anti-rHuPH20 antibodies was 6.4% (27/420) and none of the anti-rHuPH20 antibodies were classified as neutralizing. Anti-rHuPH20 antibodies had no impact on daratumumab exposure.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

The dose of daratumumab SC monotherapy and in combination with standard multiple myeloma therapy is a flat dose of 1800 mg using the same dosing schedule as daratumumab IV 16 mg/kg (DARZALEX USPI).

The FDA's Assessment:

FDA agrees with the Applicant's proposed dosage of 1800 mg daratumumab SC with the same dosing schedule as 16 mg/kg daratumumab IV. Patients with BW ≤ 50 kg should be monitored for increased neutropenia.

6.2.2.2 Therapeutic Individualization

The Applicant's Position:

Therapeutic individualization is not recommended on the basis of body weight or any other intrinsic (age, sex, renal or hepatic impairment, myeloma subtype [IgG or non-IgG], baseline albumin) or extrinsic (e.g., drug interactions) factors.

Subgroup analyses of PK showed higher exposure for lower body weight (≤65 kg) and lower exposure for higher body weight (>85 kg) subgroup. However, the range of C_{trough} across body

weights were within the range previously observed for the approved daratumumab IV 16 mg/kg dosing regimens and the PK variability did not translate to differences in efficacy or the overall safety profile. The benefit-risk profile observed with daratumumab SC supports flat-dose administration of daratumumab SC 1800 mg across body weight subgroups.

- At the recommended dose of daratumumab SC 1800 mg, and the same dosing schedule of daratumumab IV 16 mg/kg, the predicted target saturation at the maximal trough concentration was highly consistent (e.g., >97.5%) across the different body weight subgroups, although there may be some difference in the predicted maximal trough concentrations among the subgroups.
- ORR results in higher body weight patients were consistent with overall results.
- Higher exposure in lower body weight group did not result in clinically significant safety issues.

The FDA's Assessment:
FDA concurs with the Applicant that therapeutic individualization is not necessary based on the following intrinsic factors: age, sex, renal or hepatic impairment, myeloma subtype (IgG or non-IgG), baseline albumin or extrinsic (e.g., drug interactions) factors. Dose adjustment based on body weight is not recommended. However, patients with BW≤50kg should be monitored for increased neutropenia and treated with G-CSF if necessary. Refer to Section 6.2.1 for detailed rationales.

6.2.2.3 Outstanding Issues

The Applicant's Position:
The Applicant does not believe there are any outstanding issues from clinical pharmacology perspective.

The FDA's Assessment:
FDA concurs.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
The pharmacokinetics and immunogenicity of daratumumab SC 1800 mg dosed as monotherapy or in combination with other standard therapies in subjects with multiple myeloma were evaluated in 2 Phase 1/1b monotherapy studies (MMY1004, MMY1008), 1 monotherapy Phase 3 study (MMY3012), and 1 combination therapy Phase 2 study (MMY2040). A pooled population PK analysis and E-R (efficacy, safety) analyses were performed to support registration of the daratumumab SC 1800 mg formulation. A brief summary of the general clinical pharmacology and PK characteristics is provided below.

The randomized Phase 3 Study MMY3012 established the non-inferiority of daratumumab SC. The results for the co-primary endpoints are summarized below:

The average (SD) maximum C_{trough} (Cycle 3 Day 1 predose) was higher for daratumumab SC [593 (306) µg/mL, N=149] versus daratumumab IV [522 (226) µg/mL, N=146], and the geometric means ratio for maximum C_{trough} was 107.93% (90% CI: 95.74%, 121.67%), demonstrating non inferiority of daratumumab SC treatment.

Absorption

Following daratumumab SC 1800 mg administration, peak concentrations were observed at about 70 to 72 hours (MMY1004). The highest trough concentration was generally observed at the end of the weekly dosing regimen for both monotherapy and combination therapy (MMY3012, MMY2040), with mean trough concentrations similar or higher than daratumumab IV 16 mg/kg (MMY3012). For the same treatment schedule, simulated daratumumab SC monotherapy showed lower peaks than daratumumab IV, and a more moderate peak-to-trough fluctuation than daratumumab IV (ratio of 1.2 for daratumumab SC vs 1.7 for daratumumab IV for Cycle 3 Day 1 dose (9th dose). The absolute bioavailability of daratumumab SC 1800 mg estimated using pooled population PK analysis is approximately 69%. The first order rate constant of absorption for daratumumab after 3 to 5 minutes of SC administration was estimated to be 0.012 $hour^{-1}$.

Distribution

The mean estimated volume of distribution for the central compartment (V1) is 5.25 L (36.9% CV) and 3.78 L for the peripheral compartment, suggesting localization to the vascular system with limited extravascular tissue distribution.

Metabolism and Excretion

Daratumumab is cleared by parallel linear and nonlinear saturable, target-mediated clearance. The model estimated mean linear clearance is 4.96 mL/hours (58.7% CV), which is close to the clearance of non-specific endogenous IgG reported in the literature (Ryman 2017).

The model-derived geometric mean half-life associated with linear elimination was 20.4 (22.4% CV) days based on post hoc PK estimates. Similar to previous daratumumab IV studies, steady state appears to be reached approximately 5 months into the every 4 weeks dosing at the recommended dose and schedule (1800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

Intrinsic/Extrinsic Factors and Specific Populations

- The clearance of daratumumab is not expected to be different as a result of the change in

formulation or route of administration.

- A pooled population PK analysis was performed to evaluate the effect of intrinsic factors (i.e., age, sex, race, renal impairment, hepatic impairment, baseline albumin, Eastern Cooperative Oncology Group [ECOG] status, and type of myeloma [IgG or non-IgG]) on Cycle 3 Day 1 Ctrough of daratumumab for monotherapy and combination therapy. The effect of the intrinsic factors on exposure was not found to be clinically important for any of the evaluated intrinsic factors. Consistent with findings from previous daratumumab IV studies, the lower exposure seen in IgG subjects or subjects with lower baseline albumin concentrations did not translate into a clinically relevant effect on the efficacy and safety. Therefore, no dose adjustment is recommended based on these factors.

Drug Interactions

No dedicated clinical drug-drug interaction studies were performed for daratumumab SC, and no interactions with concomitant medications are expected. Daratumumab SC used as monotherapy and in combination with standard myeloma therapy appears to yield similar exposure as monotherapy.

Exposure-Response Analysis

E-R analyses were performed for selected efficacy and safety endpoints. For monotherapy, the E-R relationship between Cycle 3 Day 1 C_{trough} and ORR was similar for both daratumumab SC and daratumumab IV. Daratumumab SC produced higher trough concentrations in both responders and non-responders, and slightly higher ORRs compared with the approved daratumumab IV regimen. For combination therapies, a high ORR was observed consistently across the studied concentration range, indicating that maximum efficacy (ORR) has been attained for daratumumab SC. Cross-study comparisons with data from Study MMY3007 (subjects received daratumumab IV, bortezomib, melphalan, and prednisone [D-VMP]) and Study MMY3003 (subjects received daratumumab IV, lenalidomide, and dexamethasone [D-Rd]) indicated a similar E-R relationship for efficacy between daratumumab SC and daratumumab IV for both D-VMP and D-Rd combinations.

The exposure-safety analyses for monotherapy studies with daratumumab SC 1800 mg demonstrated a similar relationship between drug exposure (peak concentration after first dose, overall peak concentration) and safety endpoints (SAEs, Grade 3 or higher TEAEs, and neutropenia) compared with daratumumab IV 16 mg/kg. There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs, and neutropenia). The results were consistent with the clinical analysis, where a similar safety profile was observed for daratumumab SC 1800 mg compared with daratumumab IV 16 mg/kg.

No E-R relationship for safety was apparent for combination therapy. Comparisons with historical IV data from Studies MMY3003 (D-Rd) and MMY3007 (D-VMP) indicate similar incidence of SAEs and Grade 3 or higher TEAEs for daratumumab SC subjects across the exposure range.

Neutropenia

The E-R analysis using the exposure metrics of maximum serum concentration (C_{max}) values after first dose (not confounded by dose interruption or dose delay) demonstrated no apparent relationship between incidence of neutropenia and exposure after daratumumab SC 1800 mg monotherapy.

Although higher incidence of neutropenia was observed at lower body weights following daratumumab SC 1800 mg administration, a flat relationship was observed between body weight and infections (for any-grade and Grade 3 or higher infections).

Flat Dosing Across Body Weight Subgroups

Most monoclonal antibodies have a large therapeutic window, which enables a flat-dose regimen (Bai 2012). As expected, trough concentrations were slightly higher in subjects with lower body weight (≤65 kg) and lower in subjects with higher body weight (>85 kg) compared with subjects with body weight between 65 and 85 kg following flat dosing with daratumumab SC. The 1800 mg dose achieved adequate exposure for all body weight subgroups and the range of trough concentrations across body weights were within the range previously observed (36 to 1764 µg/mL for Cycle 3 Day 1 C_{trough}) for the approved daratumumab IV 16 mg/kg dosing regimens (Study 54767414MMY2002 [hereafter referred to as MMY2002], Attachment TPKCONC01). Peak concentrations (C_{max}) after Cycle 3 Day 1 dose for the lower body weight subgroup (≤65 kg) for daratumumab SC 1800 mg were comparable to the higher body weight subgroup (>85 kg) for daratumumab IV 16 mg/kg, but in general, the C_{max} values for the overall population were lower for daratumumab SC.

The mean Cycle 3 Day 1 C_{trough} in the lower body weight subgroup (≤65 kg) of daratumumab SC was 60% higher than in the daratumumab IV subgroup. However, in the E-R analysis for safety, no relationship was apparent between exposures and SAEs, Grade 3 or higher TEAEs, or neutropenia. For the higher body weight (>85 kg) subgroup, average Cycle 3 Day 1 C_{trough} was 12% lower than the daratumumab IV subgroup with comparable efficacy between daratumumab SC and IV subgroups. The PK variability in body weight subgroups did not translate to differences in efficacy or the overall safety profile.

Pharmacodynamics

In Study MMY3012, similar reductions in natural killer cells and CD38-Tregs were observed after administration of daratumumab SC or daratumumab IV. While the proportion of CD38-myeloid-derived suppressor cells exhibited a decreasing trend, the variability remained largely unchanged irrespective of the route of administration. An expansion of CD8+ T cells was also observed. These data suggest that daratumumab acts via a similar mechanism of action regardless of the route of administration.

Electrocardiograms

In 2 clinical studies with daratumumab IV (Study GEN501 and in IV Study SMM2001 in subjects with smoldering MM; GEN501 CSR; SMM2001 CSR), a review of the QT intervals corrected using Fridericia's formula and the PK/pharmacodynamic relationship revealed that daratumumab has no clinically meaningful effect on electrocardiographic parameters (GEN501 CSR, Section 4.2.5 and 5.2.5). No additional QT analyses were performed for daratumumab SC 1800 mg as the range of concentrations was within that observed previously for daratumumab IV 16 mg/kg.

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment on general pharmacology and pharmacokinetics characterization of daratumumab SC.

FDA finds the Applicant's population PK analysis acceptable for labeling the PK characteristics of daratumumab. The Applicant's population PK model suggests higher exposures for patients with lower body weight administered a fixed SC dose of 1800 mg.

The Agency does not agree with the Applicant's conclusion on the exposure-response analysis for Grade 3/4 neutropenia. See Section 6.3.2.3 and/or Appendix 18.3 for further details.

Higher incidence of Grade 3/4 neutropenia was observed for patients with lower BW following daratumumab SC 1800 mg administration. As in the daratumumab IV arm, most of the Grade 3/4 neutropenia events in the daratumumab SC arm occurred in Cycles 1 and 2 and did not continue into later cycles beyond Cycle 6 (Figure 1). They were resolved overtime either by G-CSF treatment or self-recovery. More patients in the daratumumab SC arm had Grade 3/4 TEAE neutropenia events resolved without G-CSF treatment than that in the IV arm suggesting the neutropenia events occurred in the daratumumab SC arm at a flat dose of 1800 mg are generally manageable with or without G-CSF treatment.

FDA agrees with the Applicant's assessment that similar reductions in NK cells and Tregs were observed between daratumumab SC and daratumumab IV, indicating that daratumumab acts via a similar mechanism of action regardless of the route of administration.

FDA concurs with the Applicant's position that daratumumab IV has no clinically meaningful effect on electrocardiographic (ECG) parameters; therefore, it is acceptable to not perform additional QT analyses for daratumumab SC 1800 mg as the range of concentrations for daratumumab SC 1800 mg was within that observed previously for daratumumab IV 16 mg/kg.

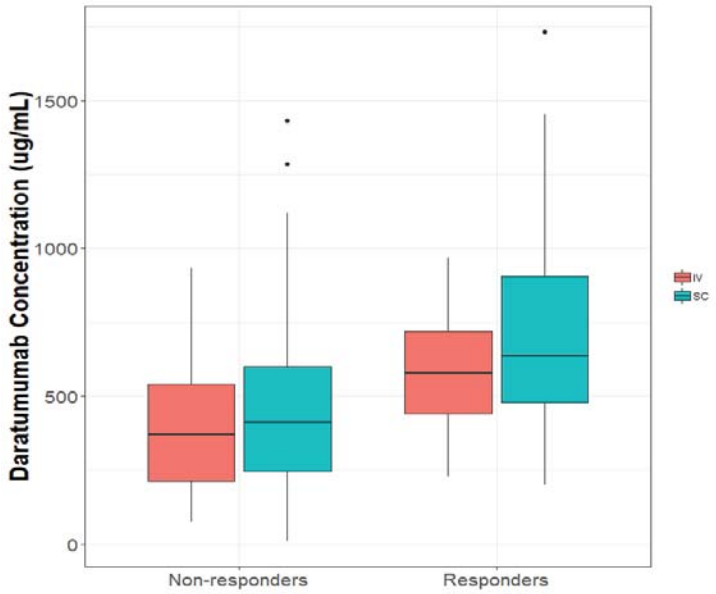
6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

The relationship between ORR and Cycle 3 Day 1 trough concentration suggested a similar exposure-efficacy relationship for daratumumab SC as for daratumumab IV. Daratumumab SC produced higher trough concentrations in both responders and non-responders, and slightly higher ORRs compared with the approved daratumumab IV regimen (Figure 2). These results suggest that an optimum therapeutic exposure is reached by daratumumab SC at 1800 mg compared with daratumumab IV at 16 mg/kg.

Figure 2: Box Plot for Daratumumab Maximum Trough Concentrations for Non-responders and Responders After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy



IV=intravenous; SC=subcutaneous.
Source: Mod2.7.2/Fig21

For combination therapy, a high ORR was observed consistently across the studied concentration range, indicating that maximum efficacy in terms of ORR has been attained for daratumumab SC 1800 mg. Cross-study comparisons with data from Studies MMY3003 (in which subjects received D-Rd]) and MMY3007 (in which subjects received daratumumab IV, bortezomib, melphalan, and prednisone [D-VMP]) indicated a similar E-R relationship for efficacy between daratumumab SC and daratumumab IV for both D-Rd and D-VMP combinations.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Overall, the population PK and E-R analyses support the selected daratumumab SC 1800 mg dose regimen for the treatment of multiple myeloma. The PK data for monotherapy and combination therapies indicate the following:

- The range of exposures across all daratumumab SC studies fell within the exposure range observed in the approved daratumumab IV regimen.
- None of the investigated factors (i.e., age, sex, race, renal impairment, hepatic impairment, baseline albumin, ECOG status, and type of myeloma) had clinically relevant effects on daratumumab exposure. Therefore, no dose adjustment is recommended based on these factors.
- The simulated trough concentrations following 6 weekly doses of daratumumab SC 1800 mg for combination therapy (D-VMP, D-Rd, D-VRd), were similar to those following monotherapy.
- The exposure-response relationship for efficacy was similar for daratumumab SC and daratumumab IV regimens.
- The incidence of anti-daratumumab and anti-rHuPH20 antibodies was low, and consistent with reported literature.
- No relationship was apparent between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs, and neutropenia).

The population PK and E-R analyses also support the flat daratumumab SC 1800 mg dosing strategy for patients with multiple myeloma:

- Body weight had a statistically significant effect on both linear clearance and central volume of distribution, but not on nonlinear clearance after daratumumab SC administration, which is consistent with previous population PK models after daratumumab IV administration.
- Similar efficacy in terms of ORR was observed across the body weight range evaluated after the flat daratumumab SC dose regimen for both monotherapy and combination therapy.
- Overall, exposures across the range of body weights were adequate for efficacy, and the higher exposures in the lower body weight group were within the range of exposures observed for the approved daratumumab IV regimen.

The dose of daratumumab SC monotherapy and in combination with standard multiple myeloma therapies is a flat dose of 1800 mg using the same dosing schedule as daratumumab IV 16 mg/kg (DARZALEX USPI).

The FDA's Assessment:

FDA agrees that the non-inferior trough concentrations and clinical efficacy and safety support the flat dose of daratumumab SC 1800 mg using the same dosing schedule as daratumumab IV 16 mg/kg as monotherapy and in combination with standard multiple myeloma therapies for patients with multiple myeloma.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

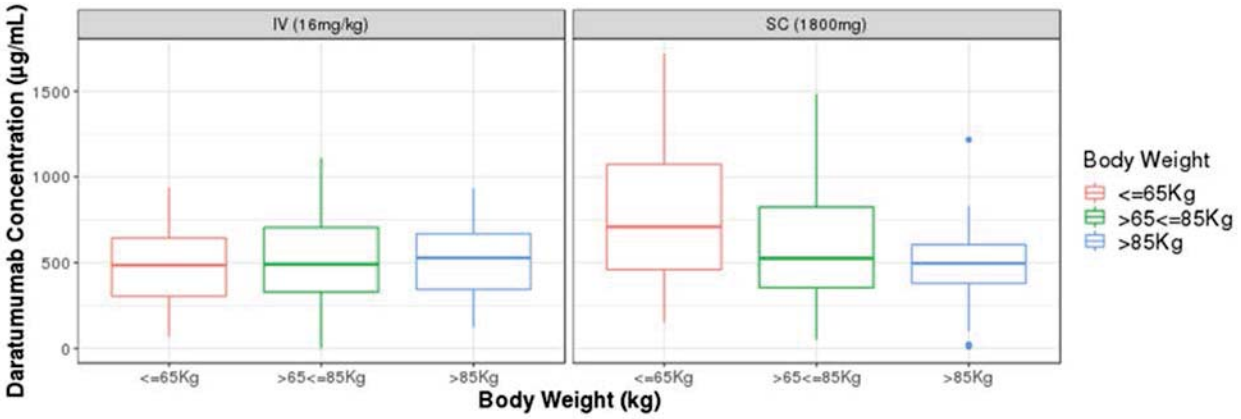
The Applicant's Position:

None of the investigated intrinsic factors (i.e., age, sex, race, region, 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 concentration appear to have lower exposure, clinical analyses demonstrated that the lower daratumumab concentration 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 concentration have been observed in the previous studies for daratumumab IV monotherapy (popPK 2015).

Similarly with combination therapy, none of the investigated intrinsic factors (age, sex, race, region, renal impairment, hepatic impairment, and ECOG status) had clinically relevant effects on the exposure to daratumumab. Similar to previous daratumumab IV studies and compared to monotherapy, the covariate effects on exposure were generally smaller (<25% difference among subgroups). Therefore, no dose adjustment for these covariates is required.

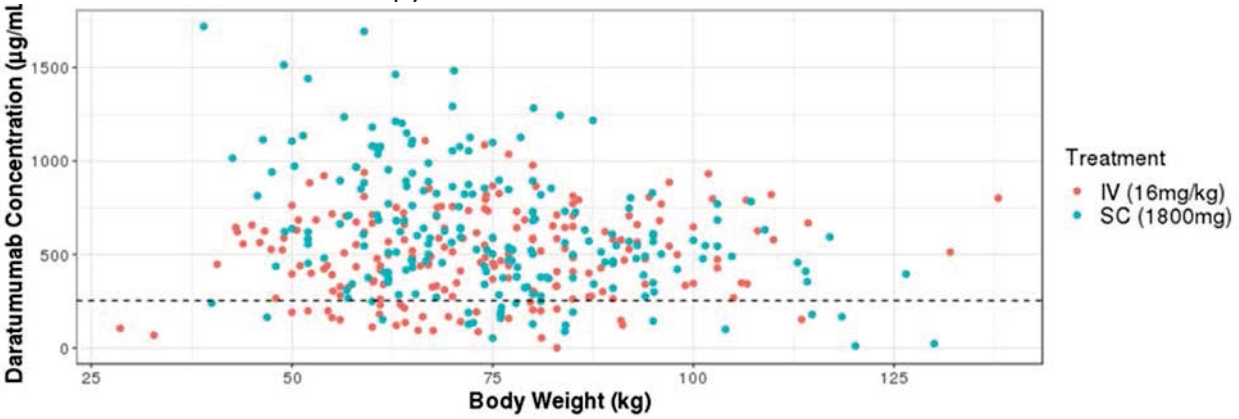
As exposure differences were identified between various body weight subgroups, a detailed analysis was further performed to understand the clinical impact. The flat-dose administration of daratumumab SC achieved adequate exposure for all body weight subgroups, as the maximum C_{trough} (Cycle 3 Day 1 predose) exceeded the 236 µg/mL threshold (Xu 2017) previously established in daratumumab IV studies as necessary for 99% target saturation. Within each body weight subgroup, there was considerable overlap in the observed maximum C_{trough} (Cycle 3 Day 1 predose) values for both treatment groups (Figure 3, Figure 4). The mean observed concentrations of daratumumab for the lowest 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 group (>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.
The mean concentration of daratumumab in the middle body weight group (>65 to 85 kg) was comparable between treatment groups. The spread of trough concentrations across body weight subgroups observed with daratumumab SC (Figure 3, Figure 4) was similar to previously observed data from daratumumab IV 16 mg/kg (Cycle 3 Day 1 C_{trough}: 36 to 1764 µg/mL [Study MMY2002]).

Figure 3: Boxplot 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: Mod2.7.2/Fig18

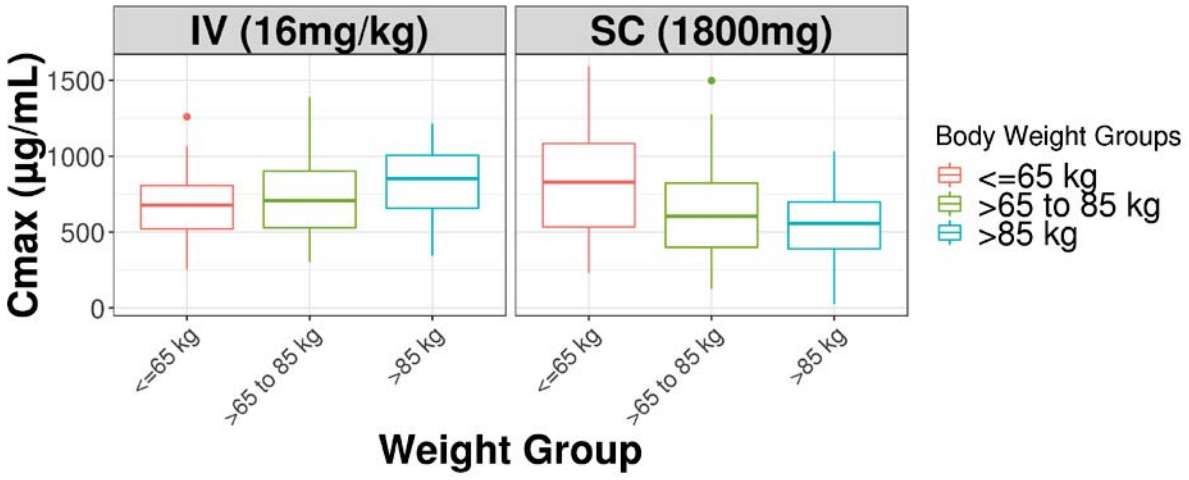
Figure 4: Observed Daratumumab Trough Concentrations After 8 Weekly Doses Across the Range of Studied Body Weights After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration for Monotherapy



IV=intravenous; SC=subcutaneous.
Note: Black dashed line represents the concentration of daratumumab at which the 99% (EC99TAR) target saturation is achieved.
Source: Mod2.7.2/Fig19

The simulated peak concentrations (Cmax after Cycle 3 Day 1 dose) for the lower body weight subgroup (≤65 kg) for monotherapy daratumumab SC 1800 mg were comparable to the simulated Cmax in the higher body weight subgroup (>85 kg) for daratumumab IV 16 mg/kg (Figure 5), but in general, the Cmax values for the overall population were lower for daratumumab SC.

Figure 5: Boxplot of Simulated Cmax Following Daratumumab SC 1800 mg and Daratumumab IV 16 mg/kg Dosing on Cycle 3 Day 1 (9th dose) by Body Weight Subgroups for Monotherapy



Cmax=maximum plasma concentration; IV=intravenous; SC=subcutaneous.
Source: Mod5.3.3.5/PPK/Fig20

Similarly, when daratumumab SC was dosed in combination with standard small molecule combinations (MMY2040), the exposure in the lower body weight group was highest, with lower exposure seen in the highest body weight group (>85 kg). In both clinical studies (MMY3012, MMY2040), the PK variability did not translate to any differences in ORR or safety.

The variability in exposure between flat dosing and body weight-based dosing is generally moderate compared with the pharmacodynamic, safety, or efficacy effects. Most mAbs have a large therapeutic window; therefore, the flat-dose regimen (does not require individualization by body weight) provides benefit over the body weight-based dosing schedule (Wang 2009; Bai 2012; Hendrikx 2017). The within-subgroup variability in PK was within the range of variability observed for the larger population for daratumumab IV, which demonstrated a wide therapeutic window for both efficacy and safety.

The FDA's Assessment:

FDA concurs with the Applicant that no dose adjustment is recommended for daratumumab SC 1800 mg as monotherapy or in combination with standard multiple myeloma therapies based on the following intrinsic factors: age, sex, race, region, renal impairment, hepatic impairment, and ECOG status.

Dose adjustment based on body weight is not recommended. However, patients with BW ≤ 50kg should be monitored for increased neutropenia and treated accordingly.

The FDA's Assessment in Section 6.2.1 highlights three key points supporting this recommendation:

- Subgroup analyses showed that the flat dose of daratumumab SC 1800 mg resulted in an 81% higher mean maximum C_{trough} than the BW-based dose of daratumumab IV 16 mg/kg for patients with BW ≤ 50 kg and an increasing trend of exposures when decreasing body weight

within the SC arm (Table 3).

- Across these BW groups and treatment arms, higher incidence of Grade 3/4 neutropenia was observed for patients with lower BW receiving SC daratumumab. For patients with BW ≤ 50 kg, a higher incidence of Grade 3/4 neutropenia was observed in the daratumumab SC arm than in the daratumumab IV arm (SC: 27.3% vs IV: 4.8%) (Table 4).
- The difference in rates of neutropenia between the IV and SC treatment arms may in part be explained by the use of G-CSF to treat for neutropenia. More patients in the daratumumab SC arm had Grade 3/4 TEAE neutropenia events resolved without G-CSF treatment than that in the IV arm (Table 5). Most of the Grade 3/4 neutropenia events occurred in Cycles 1 and 2 and did not continue into later cycles beyond Cycle 6 (Figure 1) and were resolved overtime either by G-CSF treatment or self-recovery.

The FDA's Assessment in Section 6.2.1 also indicates the key reasons why no dose reduction of 1800 mg daratumumab SC is recommended in patients with BW ≤ 50 kg.

In addition, the following points also support no change to the proposed dosing regimen of 1800 mg SC.

No BW – ORR relationship was observed. Despite the difference in exposure between daratumumab IV and daratumumab SC across BW groups, the ORRs were comparable between daratumumab IV and SC arms within the same BW category as well as across BW groups within the daratumumab SC treatment arm (Table 6). In the Phase 2 combination study MMY2040, the flat dose of 1800 mg daratumumab SC consistently resulted in comparable C_{trough} values to historical data from daratumumab IV for the same combination dosage regimens (e.g. D-Rd and D-VMP).

Table 6: ORR and 95% CI by BW Groups for Dara IV vs Dara SC

BW groups	Daratumumab IV		Daratumumab SC	
	ORR %(n/N)	95% CI	ORR %(n/N)	95% CI
BW ≤ 50 kg	47.6% (10/21)	(26.3%, 69.0%)	31.8% (7/22)	(12.4%, 51.3%)
50 kg < BW ≤ 65 kg	35.2% (25/71)	(24.1%, 46.3%)	47.9% (34/71)	(36.3%, 59.5%)
65 kg < BW ≤ 85 kg	39.0% (41/105)	(29.7%, 48.4%)	37.3% (38/102)	(27.9%, 46.6%)
BW > 85 kg	32.8% (20/61)	(21.0%, 44.6%)	43.9% (29/66)	(32.0%, 55.9%)

Source: FDA reviewer's independent analysis.
n: patient number with Complete response (CR) or Partial response (PR)
N: total patient number in BW groups

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Since daratumumab SC is administered by a non-oral route, no food-drug interactions are anticipated.

As a mAb that binds with high affinity to a unique epitope on CD38, daratumumab is not

anticipated to alter drug-metabolizing enzymes or transporters in terms of inhibition or induction, thereby interactions with small molecules are unlikely. The metabolism and elimination of daratumumab is expected to be similar to endogenous IgGs, via degradation and unlikely to be impacted by drugs that do not affect the expression of CD38.

The potential of drug interactions with small molecules typically used in multiple myeloma was assessed in a previous study (Study MMY1001) with daratumumab IV 16 mg/kg. The PK of bortezomib, pomalidomide, and thalidomide when dosed in combination with daratumumab (MMY1001) or without daratumumab (literature values) were found to be comparable. The PK of daratumumab dosed IV in combination therapy studies (Studies MMY1001, MMY3003, MMY3004, and MMY3007), were similar to monotherapy studies. Thus, there is no interaction between daratumumab and small molecules used in combination (bortezomib, pomalidomide, and thalidomide). No dedicated drug-drug interaction studies were performed with daratumumab SC, but daratumumab data from the combination therapies Study MMY2040 were compared with monotherapy daratumumab SC and the exposures were similar.

The FDA's Assessment:
FDA concurs with the Applicant's position.

X Yibo Wang, PhD/Hongshan Li, PhD
Clinical Pharmacology Reviewers

X Justin Earp, PhD/Hong Zhao, PhD
Clinical Pharmacology Team Leaders

7 Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Position:
The efficacy and safety of daratumumab SC is supported by 2 key clinical studies (MMY3012, MMY2040) and 2 supportive studies (MMY1004, MMY1008). Details for these studies are provided in Table 7.

The FDA's Assessment:
FDA agrees with the summary of the pivotal trials, MMY3012 and MMY2040, and supportive trials, MMY1004 and MMY1008 as presented in Table 7 and notes the following additional details:

- MMY3012 was designed to assess the non-inferiority of daratumumab SC monotherapy as compared to daratumumab IV monotherapy.
- The patient population for MMY3012 consisted of patients with relapsed/refractory MM (RRMM), who had at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent.
- The patient population for the D-VMP cohort in MMY2040 consisted of patients with newly diagnosed MM (NDMM) who were not considered candidates for high-dose chemotherapy and autologous stem cell transplantation (ASCT) due to either age ≥65, or in patients <65 years, the presence of important comorbid conditions that would make ASCT intolerable.
- The patient population for the D-Rd cohort in MMY2040 consisted of patients with RRMM who had at least 1 prior line of therapy.
- The patient population for MMY1004 consisted of patients with RRMM who had at least 2 prior lines of therapy, including a PI and an IMiD.
- Although the Applicant submitted the results of MMY1004 and MMY1008, these trials were not included in the FDA analysis of efficacy or safety due to the small patient numbers, different patient populations, and different doses and formulations of daratumumab SC evaluated in these trials.

Table 7: Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
54767414 MMY3012	NCT03277105	Open-label, randomized, active-controlled, Phase 3, multicenter, international study of SC vs IV administration of daratumumab	Dara SC group: 1800 mg SC qw in C1 and C2, q2w in C3 to C6, and q4w thereafter until PD or unacceptable toxicity Dara IV group: 16 mg/kg IV qw in C1 and C2, q2w in C3 to C6, and q4w thereafter until PD or unacceptable toxicity	**Co-primary efficacy endpoint**: ORR **Co-primary PK endpoint**: maximum C_{trough} (Cycle 3 Day 1 predose) **Secondary endpoints**: rate of IRRs, PFS, VGPR or better response rate; OS	Median duration of treatment: Dara SC: 4.75 mo; Dara IV: 5.36 mo Median overall follow-up: 7.46 mo	N=522 Dara SC: 263 Dara IV: 259	Relapsed or refractory MM	147 sites; 18 countries
Uncontrolled Study to Support Efficacy and Safety								
54767414 MMY2040	NCT03412565	Open-label, nonrandomized, Phase 2 multicenter study to investigate the efficacy and safety of daratumumab SC in combination with established multiple myeloma regimens	Dara SC (120 mg/mL daratumumab + 2000 U/mL rHuPH20) D-VRd: treat with 4 cycles (21-d cycles). HSC collection after C4 and ASCT off protocol. D-VMP: Treat on a 42-d cycle for C1-C9 and on a 28-d cycle for C10+, until PD or unacceptable toxicity D-Rd: Treat (28-d cycles) until PD or unacceptable toxicity	**Primary efficacy endpoint (D-VMP and D-Rd cohorts)**: ORR **Primary endpoint (D-VRd cohort)**: response rate (VGPR or better) **Key secondary endpoints:** Rate of VGPR or better (D-VMP and D-Rd cohorts), ORR (D-VRd cohort), PK and immunogenicity	Median duration of treatment: D-VRd: 2.6 mo D-VMP: 6.5 mo D-Rd: 7.0 mo Median overall follow-up: D-VRd: 3.94 mo D-VMP: 6.90 mo D-Rd: 7.13 mo	N=199 D-VRd: 67 D-VMP: 67 D-Rd: 65	D-VRd: Newly diagnosed MM, transplant eligible D-VMP: newly diagnosed MM, ineligible for transplant D-Rd: relapsed or refractory MM	43 sites; 8 countries
Studies to Support Safety								
54767414 MMY1004	NCT02519452	Open-label, nonrandomized,	Daratumumab (SC infusion with rHuPH20)	**Primary objectives:** Part 1: PK and safety	Median duration of	N=78	Relapsed or refractory	11 sites; 6 countries

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		multicenter, dose escalation Phase 1b study to evaluate the PK, safety, and antitumor activity of daratumumab SC	(Dara-MD); Daratumumab (SC injection with rHuPH20) (Dara-CF; also known as daratumumab SC [Dara SC]) Part 1: Dara-MD 1200 mg (Cohort 1) or 1800 mg (Cohort 2) qw in C1 and C2, q2w in C3 to C6, and q4w until PD or unacceptable toxicity Part 2: Dara SC (Cohort 4) 1800 mg, qw in C1 and C2, q2w in C3 to C6, and q4w until PD or unacceptable toxicity.	of the Dara-MD SC formulation Part 2: PK and safety of Dara SC Part 3: safety of Dara SC without pre-dose and postdose corticosteroids **Secondary objectives:** immunogenicity of Dara SC; CR rate, ORR (PR or better), DoR, TTR	treatment: 12.0 mo; Median overall follow-up: 14.19 mo 8	Part 1: 53 ***Cohort 1*** (1200 mg Dara-MD): ***Cohort 2*** (1800 mg Dara-MD): 45 Part 2: ***Cohort 4*** (1800 mg Dara SC): 25 Part 3: 0	MM	
54767414 MMY1008	NCT03242889	Open-label, nonrandomized, Phase 1, multicenter study to evaluate the tolerability and safety of Dara-CF (also known as daratumumab SC [Dara SC]) in Japanese subjects	Daratumumab 1800 mg, SC, qw in C1 and C2, q2w in C3 to C6, then q4w thereafter until PD or unacceptable toxicity.	**Primary objective**: tolerability and safety of Dara SC **Secondary objectives**: PK, immunogenicity, clinical efficacy outcomes (ORR), DoR, TTR	Median duration of treatment: 12.45 mo; Median overall follow-up: 12.9 mo	N=6	Relapsed or refractory MM	4 sites; 1 country (Japan)

ASCT=autologous stem cell transplantation; C=cycle; CR=complete response; Dara=daratumumab; Dara-CF= daratumumab co-formulated with rHuPH20 preparation (daratumumab SC); Dara-MD=daratumumab mixed with rHuPH20 (intermediate formulation of daratumumab SC); DoR=duration of response; D-Rd=daratumumab, lenalidomide, dexamethasone; D-VMP=daratumumab, bortezomib, melphalan, prednisone; D-VRd=daratumumab, bortezomib, lenalidomide, dexamethasone; HSC=hematopoietic stem cell collection; IRRs=infusion-related reactions; IV=intravenous; MM=multiple myeloma; mo=month; N/A=not applicable; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; q2w=once every 2 weeks; q4w=once every 4 weeks; qw=every week; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; TTR=time to response; VGPR=very good partial response; wks=weeks

8 Statistical and Clinical Evaluation

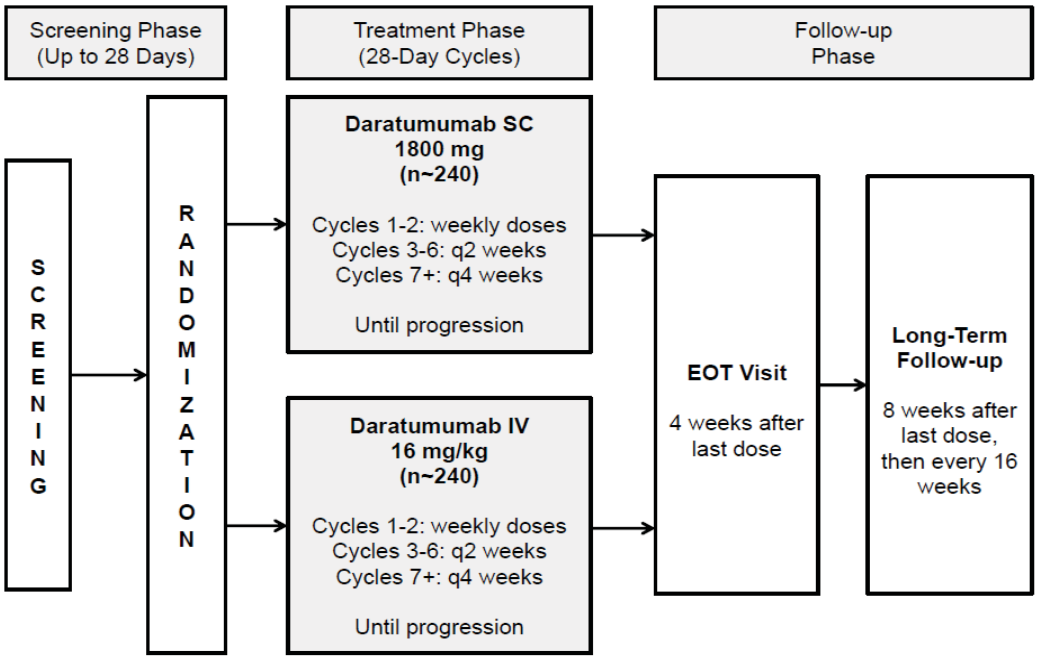
8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Key Monotherapy Study MMY3012

The Applicant's Position:

Trial Design: Phase 3, randomized, open-label, active-controlled, multicenter study to demonstrate that the efficacy and PK of daratumumab monotherapy administered subcutaneously (daratumumab SC) were non-inferior to the active control (daratumumab monotherapy administered by IV infusion [daratumumab IV]). The study included adults with multiple myeloma who had received ≥3 prior lines of therapy including a PI and an IMiD or whose disease was refractory to both a PI and an IMiD (same population as approved for DARZALEX IV monotherapy). The design was typical for non-inferiority studies (FDA Noninferiority Clinical Trial guidance, November 2016). The planned total sample size was approximately 480 subjects. The data cutoff for the primary analysis occurred on 08 January 2019, approximately 6 months after the 480th subject was randomized. A diagram of the study design is presented in Figure 6, and the Time and Events Schedules in the study protocol.

Figure 6: Schematic Overview of the Study Design for Study MMY3012



EOT=end-of-treatment; SC=subcutaneous

Choice of Control: The active comparator was daratumumab IV (approved route of

administration for this patient population). Daratumumab is proposed to be used interchangeably as daratumumab SC 1800 mg or daratumumab IV 16 mg/kg. Therefore, daratumumab IV was selected as the active control.

Key Inclusion/Exclusion Criteria: Study entry criteria were appropriate for the study population and consistent with historical studies of daratumumab IV. Key eligibility criteria: ≥18 years of age; documented multiple myeloma with measurable disease; evidence of response to ≥1 prior treatment regimen, relapsed or refractory disease, received ≥3 prior lines of therapy including a PI and an IMiD or refractory to both a PI and an IMiD; and an ECOG Performance Status score of 0, 1, or 2.

Stratification and Randomization: Subjects were randomized 1:1 to daratumumab SC or daratumumab IV. Eligible subjects were stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines vs. >4 prior lines), and type of myeloma (IgG vs. non-IgG).

Dosing and Compliance: Subjects in the daratumumab SC group received a flat dose of daratumumab SC 1800 mg (daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL), delivered by SC injection in the abdomen. Subjects in the daratumumab IV group received 16 mg/kg daratumumab as per the approved label. The dosing schedule for both treatment groups was weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, then every 4 weeks thereafter. Study drug (daratumumab IV or daratumumab SC) was administered by qualified site staff, who were responsible for recording administration details in the electronic case report form.

Treatment and Follow-up Phases: Subjects received treatment (28-days/cycle) until disease progression or the occurrence of unacceptable treatment-related toxicity. Subjects were to be followed for safety and efficacy as per the Time and Events Schedule per protocol. After study drug discontinuation, subjects had an End-of-Treatment Visit within 4 and 8 weeks after the last dose, then were followed for survival, subsequent anticancer treatment, response to subsequent anticancer treatment, and date of progression. An Independent Data Monitoring Committee (IDMC) was commissioned for the study to review safety.

Completer: A subject was considered to have completed the study if he or she died before the end of the study, was lost to follow-up, or withdrew consent before the end of the study.

Administrative Structure: The administrative structure of the study is described in Appendix 4 of the CSR and includes a list of investigators (with affiliations), subinvestigators, and other important staff, as well as the name and affiliation of the IDMC Chairman.

Study Endpoints: The co-primary efficacy endpoint for this study was ORR, defined as the proportion of subjects who achieved a partial response (PR) or better according to the

International Myeloma Working Group (IMWG) response criteria using computerized algorithm. The co-primary PK endpoint was maximum C_{trough}, defined as the concentration of daratumumab predose on Cycle 3 Day 1. These endpoints are appropriate for demonstrating non-inferiority (FDA Noninferiority Clinical Trial guidance, November 2016); both endpoints must be met to demonstrate non-inferiority. Major secondary efficacy endpoints included rate of IRRs, PFS, very good partial response (VGPR) or better response rate, and overall survival (OS). Other secondary endpoints included best M-protein response, rate of CR or better, time to next therapy, time to response, and duration of response. PRO assessments were also completed using the modified-Cancer Therapy Satisfaction Questionnaire (CTSQ) to measure subject satisfaction with therapy.

Statistical Analysis Plan and Amendments: The final, approved, Statistical Analysis Plan (version 3.0) was issued on 12 February 2019 and submitted to the Agency on 15 February 2019 (IND 125541, SN 0467) prior to final database lock on 18 February 2019. The SAP incorporated all feedback from the FDA.

The Intent-to-Treat (ITT) population was used for the analysis of ORR, which included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. The PK-evaluable population was used for the analysis of maximum C_{trough}, which included all subjects who received all 8 weekly full doses of daratumumab IV or daratumumab SC in Cycle 1 and Cycle 2 and provided a predose PK sample on Cycle 3 Day 1 within the sampling window of 8 hours prior to the start of dose administration.

Non-inferiority of daratumumab SC relative to daratumumab IV was claimed in this study if both co-primary endpoints ORR and maximum C_{trough} met their criteria as below:

- ORR: lower bound of 95% CI for the relative risk (SC/IV) was ≥60%
- Maximum C_{trough}: lower bound of 90% CI for ratio (SC/IV) of geometric mean of maximum C_{trough} was ≥80%

Protocol Amendments: The original protocol was dated 23 May 2017 and amended twice globally and 2 additional times (for Japan and Russia). Details of each amendment are included in the protocol. None of the modifications were thought to have an impact on the integrity of the study or interpretations of the results.

The FDA's Assessment:
Regarding the choice of control for Study MMY3012, the Applicant stated that daratumumab is proposed to be used interchangeably as daratumumab SC or daratumumab IV; however, the study was not specifically designed to test interchangeability (i.e., the study did not include a switch between products). Otherwise, FDA agrees with the description of Study MMY3012. See Appendix 18.5.1 for the full eligibility criteria used in the trial.

8.1.2 Supportive Monotherapy Phase 1/1b Studies

The Applicant's Position:
Study MMY1004: Phase 1b, open-label, nonrandomized, multicenter dose escalation study to evaluate the PK, safety, and antitumor activity of SC delivery of daratumumab to subjects with relapsed or refractory multiple myeloma. The study population included subjects who received at least 2 prior lines of therapy (including at least 1 IMiD and at least 1 PI). The study included 2 parts. Part 1 was conducted to select an appropriate SC therapeutic dose for daratumumab SC using a mix-and-deliver (Dara-MD) formulation prepared on site to be evaluated in Part 2. An intermediate SC formulation of daratumumab was used in Part 1; therefore, data from Part 1 was not included in the submission. Part 2 was conducted to evaluate the final clinical and commercial formulation of daratumumab SC and to confirm the dose level selected from Part 1 based on the PK, safety, and antitumor activity.

Study MMY1008: Phase 1, open-label, nonrandomized, multicenter study to evaluate the tolerability and safety of SC delivery of the final formulation to Japanese subjects with relapsed or refractory multiple myeloma. The study population included subjects with relapsed or refractory multiple myeloma who received at least 2 prior lines of therapy and who had no further established treatment options. Prior lines of therapy included at least 1 IMiD and 1 PI.

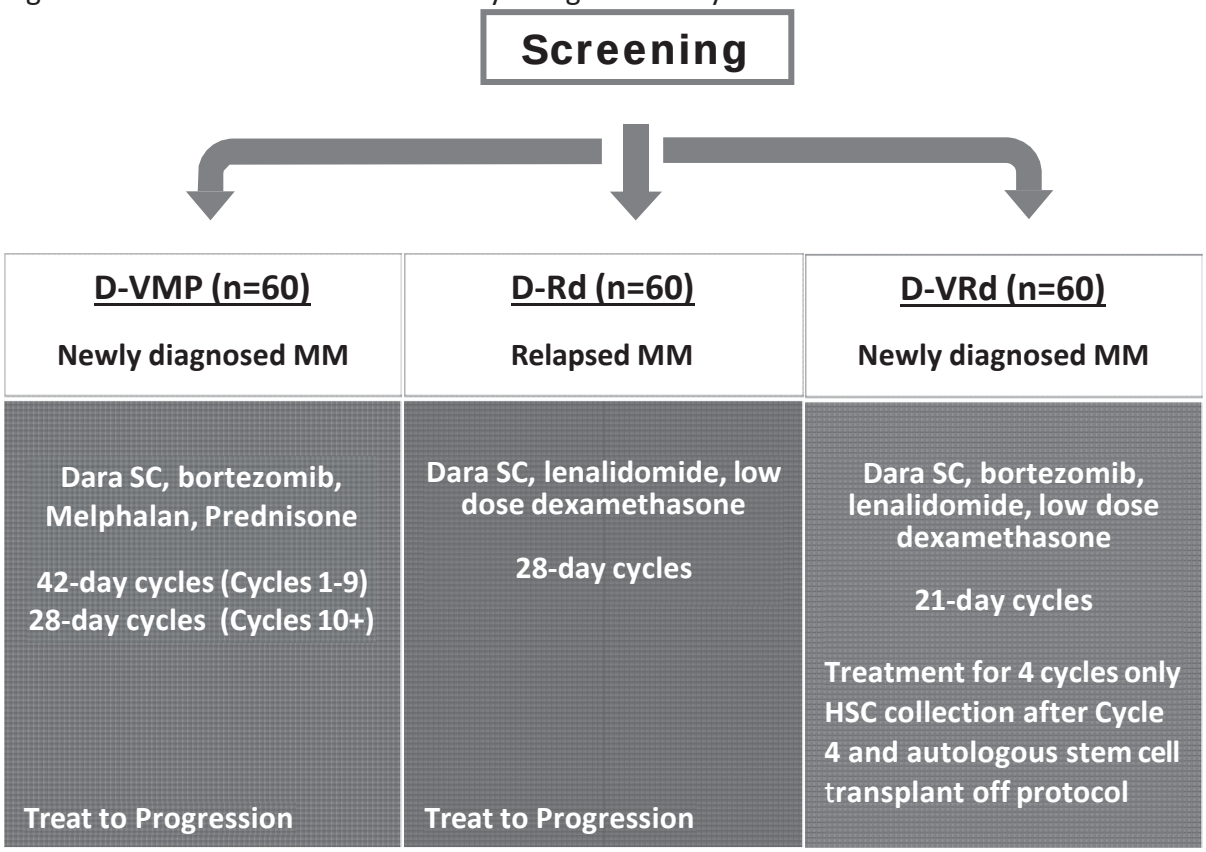
8.1.3 Key Combination Therapy Study MMY2040

The Applicant's Position:
Trial Design: Phase 2, open-label, multicenter study to investigate the efficacy, PK, and safety of daratumumab SC in combination with established multiple myeloma regimens: in combination with VMP in subjects with newly diagnosed multiple myeloma who are ineligible for ASCT; or in combination with Rd in subjects with relapsed or refractory multiple myeloma or VRd (bortezomib, lenalidomide, and dexamethasone) in subjects with newly diagnosed multiple myeloma who are eligible for ASCT. A new cohort of SC daratumumab in combination with carfilzomib and dexamethasone (D-Kd) was added per protocol Amendment 2. However, the primary analysis was focused the D-VMP, D-Rd, and D-VRd (daratumumab SC, bortezomib, lenalidomide, and dexamethasone) cohorts. The D-VMP, D-Rd, and D-VRd regimens were selected for the following reasons:

- To evaluate 3 classes of myeloma drugs, (IMiDs, PIs, alkylators) and their combinations
- To evaluate daratumumab in combination with standard regimens in the 3 major segments of the multiple myeloma disease spectrum (newly diagnosed patients with multiple myeloma who are eligible for ASCT, newly diagnosed patients with multiple myeloma who are ineligible for ASCT, and relapsed multiple myeloma)
- To evaluate 3 different daratumumab starting dose schedules approved in daratumumab IV product label (6 weekly, 8 weekly, and 9 weekly doses)

A diagram of the study design is presented in Figure 7. The Time and Events Schedules are provided in the protocol.

Figure 7: Schematic Overview of Study Design for Study MMY2040



Key Inclusion/Exclusion Criteria: Key eligibility criteria: ≥18 years of age, a multiple myeloma diagnosis according to the IMWG diagnostic criteria, and an ECOG performance status score of 0, 1, or 2. Subjects in the D-VMP cohort were newly diagnosed or previously untreated and were not considered a candidate for high-dose ASCT. Subjects in the D-Rd cohort had relapsed or refractory disease, achieved a response of PR or better to at least 1 prior treatment regimen, and progressed from or were refractory to their last line of treatment. Subjects in the D-VRd cohort were newly diagnosed and eligible/planned for high-dose therapy and ASCT.

Stratification and Enrollment: Each subject was assigned into the treatment group for which he or she was eligible.

Dosing and Compliance: The study drug (daratumumab SC) and the components of the backbone regimens were dispensed by qualified site staff, and the details of each administration were to be recorded in the eCRF. For the combinations included in this study, the dosing

schedules for daratumumab SC were consistent with the approved dosing schedules for daratumumab IV (see clinical study report for details on treatment schedules for D-VMP, D-Rd, and D-VRd cohorts). Subjects were to be provided with a diary to record compliance for melphalan, lenalidomide, prednisone, and dexamethasone.

Treatment and Follow-up Phases: Subjects in the D-VMP cohort were to receive treatment on a 42-day cycle for Cycles 1 to 9 and 28-day cycles for Cycles 10+. Subjects in the D-Rd cohort were to receive treatment on a 28-day cycle. Subjects in the D-VMP and D-Rd cohorts were to continue study treatment until disease progression or unacceptable toxicity. Subjects in the D-VRd cohort were to receive treatment for 4 cycles only (21-day cycles) as induction therapy prior to hematopoietic stem cell collection occurred, which occurred off study. Subjects were followed up for safety and efficacy as per the Time and Events Schedule in the MMY2040 protocol. Unless a subject withdrew consent for study participation or was lost to follow-up, post-treatment visits were scheduled at 30 days and 8 weeks after the final dose of study drug.

Completer: A subject was considered to have completed the study if he or she completed all protocol-specified procedures before the end of the study, was lost to follow-up, or withdrew consent before the end of the study, or transitioned to commercial daratumumab SC.

Administrative Structure: The administrative structure of the study is described in Appendix 4 of the CSR and includes a list of investigators (with affiliations), subinvestigators, and other important staff.

Study Endpoints: The primary efficacy endpoint for the D-VMP and D-Rd cohorts was ORR (PR or better). The primary endpoint for the D-VRd cohort was response rate of VGPR or better. Key secondary endpoints included rate of VGPR or better (D-VMP and D-Rd cohort) and ORR (D-VRd cohort), PK, and immunogenicity. Other secondary endpoints included rate of complete response (CR) or better.

Statistical Analysis Plan and Amendments: The final, approved, Statistical Analysis Plan (version 2.0) was issued on 20 March 2019 prior to final database lock on 29 March 2019. Analyses for the primary endpoint were based on computerized algorithm using the IMWG response criteria. No formal comparisons between the treatment cohorts were performed. The statistical analysis plan was revised to remove duration of response from the efficacy analyses for all treatment cohorts. For the D-VMP cohort, 60 subjects were required to test the null hypothesis that the ORR is at most 70%, against the alternative hypothesis that the ORR is at least 90% with a 1 sided alpha of 0.05 and at least 98% power. For the D-Rd cohort, 60 subjects were required to test the null hypothesis that the ORR is at most 75% against the alternative hypothesis that the ORR is at least 90% with a 1-sided alpha of 0.05 and at least 90% power. For the D-VRd cohort, 60 subjects were needed to be able to achieve a power of at least 93% to test the null hypothesis that the response rate of VGPR or better is at most 50%, against the alternative hypothesis that the VGPR or better is at least 70% with a 1 sided alpha of 0.05.

Protocol Amendments: The original protocol was dated 20 December 2017 and amended globally 3 times. Details of each amendment are included in the protocol; key changes are summarized in the CSR.

The FDA's Assessment:
The design of MMY2040 included single-arm cohorts to assess daratumumab SC in combination with other anti-myeloma agents. D-VRd is not an approved regimen for daratumumab IV. Otherwise, FDA agrees with the description of MMY2040. See Appendix 18.5.2 for the full eligibility criteria.

The FDA's assessment of clinical efficacy was based on data from the two studies (MMY3012 and MMY2040). Study MMY3012 was intended to assess the non-inferiority of monotherapy of daratumumab SC over daratumumab IV via one of the co-primary endpoints ORR and the secondary efficacy endpoints. The other primary endpoint of Study MMY3012, maximum C_{trough}, was a PK primary endpoint that is assessed under the Clinical Pharmacology section. The treatment effect, ORR for daratumumab IV, was estimated as 29.2% (95% CI: 20.8%, 38.9%) using data from Study MMY2002, including 106 subjects with relapsed or refractory MM who had received at least 3 prior therapies and who were treated with daratumumab IV 16 mg/kg. Non-inferiority of daratumumab SC to IV was defined as 60% retention of the lower bound, 20.8%. With this NI margin and the assumption that the true ORR is the same for both groups, a sample size of 480 (240 per arm) would demonstrate the non-inferiority of daratumumab SC vs. IV with a power of 80% and a 1-sided alpha of 0.025.

Study MMY2040 was intended to assess the effectiveness of combination of daratumumab SC with standard multiple myeloma treatments. FDA recommended the Applicant report the 95% CI for the primary endpoint and key secondary endpoints. FDA also recommended the Applicant to report duration of response (DoR) along with its corresponding ORR, the primary endpoint, given there is adequate follow-up time for evaluation of DoR. FDA acknowledged the Applicant's proposal to not report the DoR corresponding to the primary endpoint ORR due to immaturity of the data at this time of the primary analysis. The Applicant will report DoR when the data is mature in an addendum to the primary analysis. FDA requested the Applicant provide justification regarding how they determined that the DoR data is not mature enough to report in the primary analysis and the timeline to submit the CSR addendum which will include the DoR analysis. Note that FDA assessed effectiveness of two combination regimens, D-VMP and D-Rd. See Section 8.1.6 for the rationale to exclude the D-VRd cohort.

8.1.4 Study Results

The Applicant's Position:
Key Monotherapy Study MMY3012
Note: References to Attachments in this Section are to attachments in the MMY3012 CSR.

Compliance with Good Clinical Practices

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Financial Disclosure

For Study 3012, there were no clinical investigators who disclosed any financial interests or arrangements.

Patient Disposition

The first subject signed informed consent on 31 October 2017 and the clinical cutoff for the primary analysis was 08 January 2019. At the time of the clinical cutoff date, 263 and 259 subjects were randomly assigned to the daratumumab SC and daratumumab IV groups, respectively; ITT population). Four subjects did not receive study drug. At the data cutoff, approximately 57% of subjects in both treatment groups had discontinued study drug (Table 8). Reasons for this were similar between treatment groups and most commonly due to PD (approximately 44% of subjects in both treatment groups). A low and similar proportion of subjects in both treatment groups discontinued due to TEAEs (6.9% and 8.1%, respectively).

Table 8: 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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Protocol Violations/Deviations

A few subjects (3.8%) had major protocol deviations (Table 9); none of these affected subject safety or data integrity. Further details are provided in the CSR.

Table 9: Summary of Subjects with Major Protocol Deviations – Intent-to-treat Analysis Set (Study 54767414MMY3012)

	Dara IV	Dara SC	Total
Analysis set: intent-to-treat	259	263	522
Total number of subjects with major protocol deviations	7 (2.7%)	13 (4.9%)	20 (3.8%)
Type of major protocol deviations			
Developed withdrawal criteria but not withdrawn	1 (0.4%)	0	1 (0.2%)
Entered but did not satisfy criteria	0	1 (0.4%)	1 (0.2%)
Received a disallowed concomitant treatment	1 (0.4%)	0	1 (0.2%)
Received wrong treatment or incorrect dose	5 (1.9%)	5 (1.9%)	10 (1.9%)
Other	0	7 (2.7%)	7 (1.3%)

Note: Dara IV=daratumumab intravenous; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: Of the major protocol deviations related to receiving wrong treatment or incorrect dose, 9 were related to postdose medications required by the protocol, and 1 was related to a subject receiving daratumumab SC while experiencing an AE of Grade 3 cryptococcal meningitis. None of these major protocol deviations involved a subject receiving the incorrect study drug or an incorrect dose of study drug.
Note: Percentages are calculated with the number of subjects in each group as the denominators.
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Table of Demographic Characteristics

Treatment groups were similar in terms of demographics characteristics (Table 10).

Table 10: 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%)
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%)
	Dara IV	Dara SC	Total
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.

[TSIDEM01 RTF] [JNJ-54767414\MMY3012\DBR_CSR\RE_CSR\PROD\TSIDEM01.SAS] 05MAR2019, 16:41

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The study population was representative of the general multiple myeloma patient population. Treatment groups were similar in terms of baseline disease characteristics, except that the daratumumab SC group had a higher proportion of subjects with high cytogenetic risk (daratumumab SC: 26.3%; daratumumab IV: 17.3%) (Table 11).

Table 11: 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)
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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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Daratumumab was administered by qualified healthcare professionals and administrations were recorded in the eCRFs for each subject. The median duration of treatment (daratumumab SC: 4.75 months; daratumumab IV: 5.36 months) and median number of cycles completed (6 cycles for both) were similar between treatment groups (CSR Table 10 and Attachment TSIEXP01).

All subjects received the required predose medications (analgesics, antihistamines, corticosteroids) at ≥1 visit (Attachment TSICM02). A few subjects in each treatment group (daratumumab SC: 3; daratumumab IV: 5) did not receive any of the required postdose medications during the study (e.g., corticosteroids for the 2 days following the first 3 doses of study drug) Attachment TSICM03). Concomitant medications were taken by 512/518 subjects during the study (Attachment TSICM01). Except for corticosteroids for systemic use (daratumumab SC: 19.2%; daratumumab IV: 31.0%), the most frequently used concomitant medications by pharmacologic class (≥25% in either treatment group) were similar between treatment groups and included direct acting antivirals, other analgesics and antipyretics, opioids, sulfonamides and trimethoprim, drugs for peptic ulcer and gastro-oesophageal reflux disease, drugs affecting bone structure and mineralization, antigout preparations, beta-blocking agents, and antithrombotic agents.

A similar proportion of subjects in both treatment groups received subsequent anti-myeloma therapies (Attachment TSISAT01), consistent with the similar incidence of PD (CSR Table 3). PIs (bortezomib, ixazomib, and carfilzomib), IMiDs (thalidomide, lenalidomide, and pomalidomide), the alkylating agent cyclophosphamide, and corticosteroids for systemic use (since they are components of a variety of combination regimens) were the most common subsequent therapies.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of the disposition for MMY3012. The rates of major protocol deviations as defined by the Applicant were small (3.8% overall) and balanced between arms. The median age of patients enrolled in the trial (67) was slightly lower than the median age at diagnosis of 69 for patients with MM in the U.S. and there was a severe underrepresentation of Black patients (2.7% overall) compared to the U.S. population of patients with MM. However, available data do not indicate that the underrepresentation of Blacks should limit the applicability of the trial results. Otherwise, FDA agrees that the demographic characteristics were similar between arms. FDA agrees with the Applicant's presentation and assessment of baseline disease characteristics.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Overall Response Rate (Co-primary Endpoint)

Efficacy data from Study MMY3012 demonstrate that daratumumab SC is non-inferior to daratumumab IV in terms of ORR. ORR was 41.1% and 37.1% for the daratumumab SC and daratumumab IV groups, respectively (relative risk: 1.11; 95% CI: 0.89, 1.37; Table 12). The lower bound of the 95% CI (0.89) indicated 89% retention of ORR with 97.5% confidence, thus, meeting the non-inferiority criteria of 60% retention of the effect size for the co-primary endpoint of ORR.

All sensitivity analyses supported the findings of the co-primary endpoint. ORR was comparable between treatment groups across all clinically relevant subgroups analyzed (Figure 8). ORR in all

body-weight subgroups was consistent with ORR in the overall ITT Analysis Set for the corresponding treatment group, and these data suggest that subjects in the highest body weight group (>85 kg) have adequate daratumumab exposure following SC administration of the drug to achieve consistent ORR.

The FDA's Assessment:
The FDA agrees with the Applicant's results presented in Table 12 and that Study MMY3012 statistically demonstrated efficacy non-inferiority of daratumumab SC over daratumumab IV based on the protocol prespecified NI margin of 60%.

The FDA agrees with the Applicant's subgroup analyses presented in Figure 8 and notes that the p-values are not adjusted for multiplicity. Therefore, all results should be considered exploratory.

Cycle 3 Day 1 Ctrough (PK Co-primary endpoint):

For the other co-primary PK endpoint (Ctrough, Cycle 3 Day 1 predose), the average (SD) maximum C_{trough} (Cycle 3 Day 1 predose) was numerically higher for daratumumab SC [593 (306) µg/mL, N=149] than daratumumab IV [522 (226) µg/mL, N=146], with a geometric means ratio for maximum Ctrough of 107.93% (90% CI: 95.74%, 121.67%; Mod2.7.2/Tab11). The lower bound of 90% CI exceeded the non-inferiority criterion of 80%, demonstrating that daratumumab SC was non inferior to daratumumab IV.

The FDA's Assessment:
The results of the PK co-primary endpoint are presented in the Clinical Pharmacology review section.

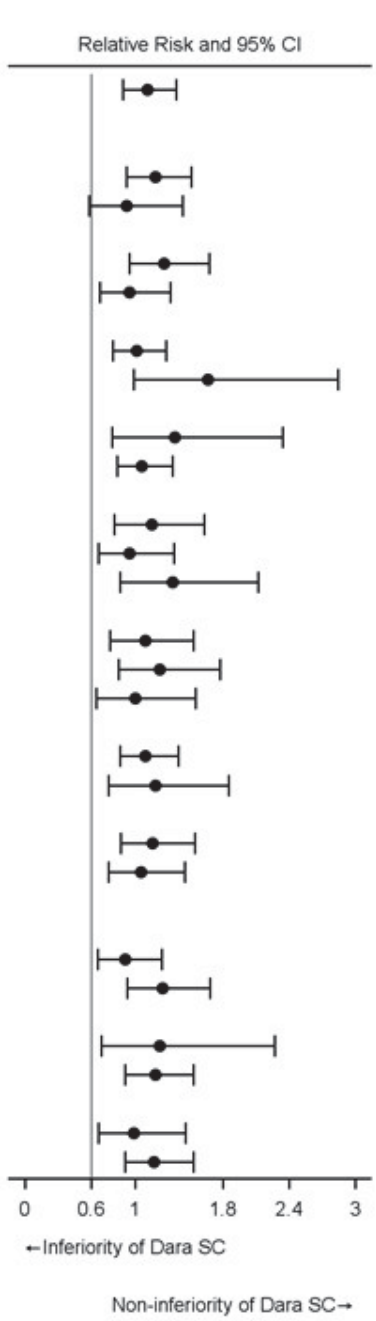
Table 12: Summary of Best Overall Response Based on Computerized Algorithm – Intent-to-treat Analysis Set (Study 54767414MMY3012)

	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.

Source: MMY3012 CSR, Table 17

Figure 8: Forest Plot of Subgroup Analyses on Overall Response Rate Based on Computerized Algorithm – Intent- to-treat Analysis Set (Study 54767414MMY3012)



	Dara IV n/N(%)	Dara SC n/N(%)	Relative Risk (95% CI)
Overall response	96/259 (37.1%)	108/263 (41.1%)	1.11 (0.89, 1.37)
Subgroups			
Age			
<75 years	70/200 (35.0%)	89/216 (41.2%)	1.18 (0.92, 1.51)
>=75 years	26/59 (44.1%)	19/47 (40.4%)	0.92 (0.58, 1.43)
Sex			
Male	54/149 (36.2%)	62/136 (45.6%)	1.26 (0.95, 1.67)
Female	42/110 (38.2%)	46/127 (36.2%)	0.95 (0.68, 1.32)
Race			
White	81/201 (40.3%)	84/207 (40.6%)	1.01 (0.80, 1.28)
Other	15/58 (25.9%)	24/56 (42.9%)	1.66 (0.99, 2.84)
Region			
Asia/Pacific	16/52 (30.8%)	18/43 (41.9%)	1.36 (0.79, 2.34)
Other	80/207 (38.6%)	90/220 (40.9%)	1.06 (0.84, 1.34)
Weight			
<=65 kg	35/92 (38.0%)	41/94 (43.6%)	1.15 (0.81, 1.63)
>65 kg to 85 kg	41/105 (39.0%)	38/102 (37.3%)	0.95 (0.67, 1.35)
>85 kg	20/61 (32.8%)	29/66 (43.9%)	1.34 (0.86, 2.12)
ISS staging			
I	39/94 (41.5%)	37/82 (45.1%)	1.09 (0.77, 1.53)
II	31/89 (34.8%)	43/101 (42.6%)	1.22 (0.85, 1.77)
III	26/76 (34.2%)	27/79 (34.2%)	1.00 (0.65, 1.55)
Number of prior lines of therapy			
<=4	72/175 (41.1%)	78/174 (44.8%)	1.09 (0.86, 1.39)
>4	24/84 (28.6%)	30/89 (33.7%)	1.18 (0.76, 1.85)
Type of myeloma			
IgG	53/150 (35.3%)	65/159 (40.9%)	1.16 (0.87, 1.54)
Non-IgG	43/109 (39.4%)	43/104 (41.3%)	1.05 (0.76, 1.45)
Baseline renal function (GFR, mL/min/1.73m2)			
<=60 mL/min/1.73m2	45/96 (46.9%)	43/101 (42.6%)	0.91 (0.66, 1.24)
>60 mL/min/1.73m2	51/159 (32.1%)	65/162 (40.1%)	1.25 (0.93, 1.68)
Cytogenetic risk			
High risk	11/35 (31.4%)	20/52 (38.5%)	1.22 (0.69, 2.27)
Standard risk	64/167 (38.3%)	66/146 (45.2%)	1.18 (0.91, 1.53)
ECOG performance score			
0	36/88 (40.9%)	26/64 (40.6%)	0.99 (0.67, 1.46)
>=1	60/171 (35.1%)	82/199 (41.2%)	1.17 (0.91, 1.53)

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.

Source: MMY3012 CSR, Figure 7

Data Quality and Integrity

The FDA's Assessment:
The statistical reviewer was able to perform all analyses using the submitted data and found the quality of data adequate.

Efficacy Results – Secondary and Other Relevant Endpoints

Results for other secondary efficacy endpoints in Study MMY3012 were similar between the daratumumab SC and daratumumab IV groups. With a median overall follow-up of 7.46 months, PFS was comparable between treatment groups (HR=0.99 [95% CI: 0.78, 1.26]; p=0.9258). Most PFS events were attributed to disease progression (88.7% of subjects in both treatment groups), most commonly due to increases in M-protein. Overall survival data were not yet mature. The median was not estimable in the daratumumab SC group and 13 months in the daratumumab IV group. A similar 6-month survival rate was observed (daratumumab SC: 87.5%; daratumumab IV: 83.0%) in both treatment groups; HR for OS was 0.90 (95% CI: 0.59, 1.35); p=0.6032. Approximately 18% of subjects in the study had died in both treatment groups as of the data cutoff.

The FDA's Assessment:
The other key secondary endpoint, the rate of VGPR or better for daratumumab SC and daratumumab IV were 19% and 17%, respectively (RR = 1.16; 95% CI 0.73, 1.85).

Of note, the key secondary endpoints (PFS, rate of VGPR or better, and OS, in order) did not meet the pre-specified testing for superiority.

Dose/Dose Response

Dose/Dose Response was not assessed in the study.

Durability of Response

Median duration of response was not reached in either treatment group (MMY3012 CSR).

Persistence of Effect

The persistence of efficacy is indicated by the durability of the response and prolongation of PFS observed across the daratumumab IV studies. Given that the non-inferiority criteria for daratumumab SC compared with daratumumab IV were met, persistence of the SC administration is expected to be comparable to IV administration.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The median time to a response (PR or better) was rapid, occurring approximately by the first month of treatment in both treatment groups. Median time to VGPR or better (daratumumab SC: 1.9 months; daratumumab IV: 1.1 months) and to CR or better (5.6 and 3.8 months, respectively) did not differ to a clinically meaningful extent between treatment groups (Mod2.7.3/Table 8). Overall, results from the modified-CTSQ demonstrated that subjects receiving daratumumab SC had a more positive perception of their cancer therapy and greater satisfaction with therapy compared with subjects receiving daratumumab IV (range of mean scores for the Satisfaction with Therapy domain: daratumumab SC: 76.9 to 88.5; daratumumab IV: 70.5 to 79.8). The mean Satisfaction With Therapy scores were generally consistent over time for both treatment groups.

The FDA's Assessment:
The COA endpoint was not included in the hierarchical testing order and was not adjusted for multiplicity. In addition, the hypothesis and analysis were not pre-specified in the statistical analysis plan. The results should be considered exploratory. No efficacy conclusions can be made based on the results of these endpoints.

Additional Analyses Conducted on the Individual Trial: Not applicable.

Supportive Monotherapy Phase 1/1b Studies
Study MMY1004, a 2-part, open-label, nonrandomized Phase 1b study, was conducted to evaluate the PK, safety, and antitumor activity of SC delivery of daratumumab with rHuPH20. Part 1 (dose ranging) evaluated the PK and safety of 2 doses of daratumumab (1200 mg and 1800 mg) in a mix and-deliver (MD) SC formulation of daratumumab and rHuPH20, prepared at the site. The daratumumab MD 1800 mg dose provided similar or higher daratumumab exposure compared with the IV 16 mg/kg dose and was therefore selected for further investigation. Part 2 of the Study MMY1004 evaluated the final, co-formulated preparation of daratumumab and rHuPH20 for SC administration (daratumumab SC). This is the same investigational product that was dosed in Studies MMY1008, MMY3012, and MMY2040, and is identical to the proposed commercial formulation.

The results from Study MMY1008 demonstrated that daratumumab SC in Japanese subjects with relapsed or refractory multiple myeloma had similar PK as the Study MMY3012 population, was safe and well-tolerated, and no new safety signals were reported. The study also showed that the daratumumab SC 1800 mg dose had a favorable efficacy profile in this population (ORR [sCR+CR+VGPR+PR] of 66.7%).

Combination Therapy Study MMY2040
Note: References to Attachments in this Section are to attachments in the MMY2040 CSR.

Compliance with Good Clinical Practices

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable

regulatory requirements. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Financial Disclosure

For Study 2040, financial interests or arrangements for 3 clinical investigators have been disclosed (details are provided at the end of this document).

The FDA's Assessment:
Among the 3 investigators with disclosable financial interests/arrangements, 2 had significant payments of other sorts and 1 had significant equity interest. These issues are not anticipated to affect the integrity of the trial.

Patient Disposition: The first subject consent was signed on 02 May 2018 and the clinical cutoff date was 04 March 2019. As of the clinical cutoff:

- **D-VMP:** most subjects (92.5%) remain on treatment. Five subjects (7.5%) discontinued treatment (2 subjects due to an AE, 2 subjects due to PD, and 1 subject died).
- **D-Rd:** most subjects (90.8%) remain on treatment. Five subjects (7.7%) discontinued treatment (4 subjects due an AE and 1 subject due to PD).
- **D-VRd:** 97.0% of subjects have completed treatment; no subjects remain on treatment. Two subjects (3.0%) discontinued treatment (1 subject due to an AE and 1 subject due to PD).

Table of Demographic Characteristics

A summary of demographics characteristics for the 3 treatment cohorts in Study MMY2040 are provided in Table 13.

Table 13: 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)

	D-VRd	D-VMP	D-Rd
Median	174.00	160.00	170.00
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.

[TSIDEM01 RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TSIDEM01.SAS] 29MAR2019, 18:10

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics for the 3 treatment cohorts are summarized in Table 14.

Table 14: 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

	D-VRd	D-VMP	D-Rd
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%)
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

	D-VRd	D-VMP	D-Rd
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.

[TSIDEM02.RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TSIDEM02.SAS] 29MAR2019, 18:10

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Daratumumab was administered by qualified healthcare professionals and administrations were recorded in the eCRFs for each subject. 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 (Mod5.3.5.2/MMY2040/Sec4.9). All subjects in the study received concomitant medications during treatment (Attachment TSICM01).

Predose medications (i.e., anti-pyretic analgesics, antihistamines, and corticosteroids), that were administered to all subjects in each treatment cohort were intended to prevent or lessen the severity of IRRs. The high frequency of concomitant medication use is consistent with subjects with underlying multiple myeloma and additionally, due to the subject population with median age ≥59 years with co-morbid conditions. The most frequently used concomitant medications administered during the study across all treatment cohorts were:

- Antivirals for systemic use (D-VMP: 94.0%; D-Rd cohort: 83.1%; D-VRd: 92.5%)
- Antibacterials for systemic use (D-VMP: 92.5%; D-Rd cohort: 84.6%; D-VRd: 83.6%)
- Analgesics (D-VMP: 88.1%; D-Rd cohort: 92.3%; D-VRd: 79.1%)

As of the clinical cutoff, 2 subjects each in the D-VMP cohort and D-Rd cohorts (~3.0%), and 20 subjects (29.9%) in the D-VRd cohort have received subsequent anti-myeloma therapies. Twelve subjects in the D-VRd cohort have reported receiving ASCT. This lower than expected number is due to the limited 8-week follow-up in this study (Attachment TSISAT01).

The FDA's Assessment:
FDA agrees with the Applicant's presentation of the patient disposition, demographics, and baseline disease characteristics for MMY2040. The median ages of patients in each combination cohort are consistent with the patient populations intended for each regimen. Similar to MMY3012, there is an underrepresentation of Blacks, but otherwise, the demographic characteristics are representative of the U.S. population of patients with MM.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Response data from Study MMY2040 demonstrate that the combination of daratumumab SC with standard multiple myeloma treatments was highly effective (Table 15).

The primary endpoints for all 3 cohorts were met (Mod5.3.5.2/MMY2040/Sec6.2):

- D-VMP: ORR was 88.1% (90% CI: 79.5%, 93.9%).
- D-Rd: ORR was 90.8% (90% CI: 82.6%, 95.9%).
- D-VRd: The rate of VGPR or better was 71.6% (90% CI: 61.2%, 80.6%).

Table 15: 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 %	n (%)	90% CI for %	n (%)	90% CI for %
Analysis set: all treated	67		67		65	
Best overall response						
Stringent complete response (sCR)	6 (9.0%)	(4.0%, 16.9%)	5 (7.5%)	(3.0%, 15.1%)	4 (6.2%)	(2.1%, 13.5%)
Complete response (CR)	5 (7.5%)	(3.0%, 15.1%)	7 (10.4%)	(5.0%, 18.7%)	8 (12.3%)	(6.3%, 21.1%)
Very good partial response (VGPR)	37 (55.2%)	(44.5%, 65.6%)	31 (46.3%)	(35.8%, 57.0%)	30 (46.2%)	(35.5%, 57.1%)
Partial response (PR)	17 (25.4%)	(16.9%, 35.6%)	16 (23.9%)	(15.6%, 34.0%)	17 (26.2%)	(17.4%, 36.6%)
Minimal response (MR)	0	(NE, NE)	0	(NE, NE)	3 (4.6%)	(1.3%, 11.5%)
Stable disease (SD)	1 (1.5%)	(0.1%, 6.9%)	6 (9.0%)	(4.0%, 16.9%)	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%)	59 (88.1%)	(79.5%, 93.9%)	59 (90.8%)	(82.6%, 95.9%)
CR or better (sCR + CR)	11 (16.4%)	(9.5%, 25.7%)	12 (17.9%)	(10.7%, 27.4%)	12 (18.5%)	(11.0%, 28.2%)
VGPR or better (sCR + CR + VGPR)	48 (71.6%)	(61.2%, 80.6%)	43 (64.2%)	(53.5%, 73.9%)	42 (64.6%)	(53.7%, 74.5%)

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] 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.

[TEFORR01.RTF] [JNJ-54767414\MMY2040\DBR_CSR\RE_CSR\PROD\TEFORR01.SAS] 29MAR2019, 19:41

The FDA's Assessment:

The FDA did not agree with the analysis based on 90% CI and requested the Applicant to provide 95% confidence interval for the ORRs. Meanwhile, FDA calculated the 95% CIs. Table 16 and Table 17 below summarize FDA's analysis results of response rates with 95% CI by IRC and investigator assessment, respectively.

Table 16: Study 2040 Efficacy Results per IRC-Assessed by FDA

	D-VMP	D-Rd	D-VRd
N	67	65	67
Response, n	59	59	65
sCR	5 (7.5)	4 (6.2)	6 (9.0)
CR	7 (10.4)	8 (12.3)	5 (7.5)
VGPR	31 (46.3)	30 (46.2)	37 (55.2)
PR	16 (23.9)	17 (26.2)	17 (25.4)
ORR (95% CI), %	88.1 (77.8, 94.7)	90.8 (81.0, 96.5)	97.0 (89.6, 99.6)
VGPR or better (95% CI), %	64.2 (51.5, 75.5)	64.6 (51.8, 76.1)	71.6 (59.3, 82.0)

Source: Generated by FDA reviewer using Applicant-provided datasets (adsl, adeff).

Table 17: Study 2040 Efficacy Results per INV-Assessed by FDA

	D-VMP	D-Rd	D-VRd
N	67	65	67
Response, n	57	60	64
sCR	4 (6.0)	4 (6.2)	1 (1.5)
CR	4 (6.0)	5 (7.7)	1 (1.5)
VGPR	33 (49.3)	34 (52.3)	47 (70.1)
PR	16 (23.9)	17 (26.2)	15 (22.4)
ORR (95% CI), %	85.1 (74.3, 92.6)	92.3 (83.0, 97.5)	95.5 (87.5, 99.1)
VGPR or better (95% CI), %	61.2 (48.5, 72.9)	66.2 (53.4, 77.4)	73.1 (60.9, 83.2)

Source: Generated by FDA reviewer using Applicant-provided datasets (adsl, adeff).

Results from Study MMY2040 showed that 1) the lower bound of 95% CIs of the primary endpoints for all 3 cohorts excluded their pre-specified null hypotheses based on IRC-assessed response; however, the D-VRd cohort was excluded (see Section 8.1.6 for details), and 2) ORR and VGPR or

better results based on INV-assessed response were consistent with those according to IRC-assessed response.

Data Quality and Integrity

The FDA's Assessment:
The statistical reviewer was able to perform all analyses using the submitted data and found the quality of data adequate.

Efficacy Results – Secondary and Other Relevant Endpoints

Results from key secondary endpoints support these clinically meaningful efficacy outcomes. VGPR or better for the D-VMP and D-Rd cohorts was 64.2% (90% CI: 53.3%, 73.9%) and 64.6% (90% CI: 53.7%, 74.5%), respectively. The ORR for the D-VRd cohort was 97.0% (90% CI: 90.9%, 99.5%). Complete response or better was observed in 17.9%, 18.5%, and 16.4% of subjects in the D-VMP, D-Rd, and D-VRd cohorts, respectively.

Additional Analyses Conducted on the Individual Trial

Response rates for daratumumab SC subjects in the Study MMY2040 D-VMP and D-Rd cohorts were similar to those observed in the daratumumab IV Studies MMY3007 (D-VMP) and MMY3003 (D-Rd). No clinically meaningful differences were identified between the daratumumab SC and IV treatment groups by body weight subgroups.

- D-VMP: ORR was 85.1% (CI: 76.0%, 91.7%) and 87.3% (CI: 84.0%, 90.1%) for Study MMY2040 (SC) subjects and MMY3007 (IV) subjects using 6 months cutoff, respectively. In MMY3007, ORR was 90.9% after a median follow-up of 16.5 months
- D-Rd: ORR was 90.8% (CI: 82.6%, 95.9%) and 88.7% (CI: 85.1%, 91.7%) for Study MMY2040 (SC) subjects and MMY3003 (IV) subjects using 6 months cutoff, respectively. In MMY3003, ORR was 91.3% after a median follow-up of 13.5 months.

The FDA's Assessment:
FDA calculated the 95% CIs of secondary efficacy endpoints for Study MMY2040 as shown in Table 16 and Table 17. Results from the secondary endpoints were consistent with those from the primary endpoint. Note that the duration of response (DoR) corresponding to the primary endpoint ORR was not reported due to immaturity of the data at the time of the primary analysis. The Applicant will report DoR in an addendum to the primary analysis when the data matures.

8.1.5 Assessment of Efficacy Across Trials

The Applicant's Position:
Assessment of efficacy of daratumumab SC was supported by 4 studies (MMY3012, MMY2040, MMY1004, MMY1008). Data from Study MMY2040 were compared with historical studies with

daratumumab IV. Study MMY3012 demonstrated that daratumumab SC was non-inferior to daratumumab IV in terms of ORR and maximum Ctrough (Cycle 3 Day 1 predose). Response rates for daratumumab SC in combination with standard background therapies were comparable to those observed in daratumumab IV studies (MMY3003, MMY3007). No clinically meaningful differences were identified between the daratumumab SC and IV treatment groups in sub-populations, including by body weight. The totality of the data confirms that daratumumab SC 1800 mg is therapeutically consistent with the daratumumab IV 16 mg/kg formulation.

Subpopulations

Although efficacy analysis by body weight was not planned for Study MMY2040, ORR data by body weight subgroups are presented to provide a comparison with historical IV studies (MMY3007 and MMY3003). The data show that ORR was generally consistent between daratumumab SC and daratumumab IV within each body weight subgroup, with overlapping 90% CIs. The observed differences in percentages for different combinations may have been due to the small sample size in the SC combinations (Table 18; Table 19).

Table 18: Subgroup Analysis of Overall Response Rate Up to Month 6: D-VMP; Safety Analysis Set (Combination Therapy Studies: MMY3007 and MMY2040)

	MMY 3007 Dara IV + VMP						MMY 2040 Dara SC + VMP					
	≤65 kg		>65 kg to 85 kg		>85 kg		≤65 kg		>65 kg to 85 kg		>85 kg	
	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]
Analysis set: safety	129		172		45		32		25		10	
Best overall response												
Overall response (sCR+CR+VGPR+PR)	112 (86.8%)	(80.9%, 91.4%)	152 (88.4%)	(83.6%, 92.2%)	38 (84.4%)	(72.8%, 92.5%)	30 (93.8%)	(81.6%, 98 9%)	20 (80.0%)	(62.5%, 91.8%)	7 (70.0%)	(39.3%, 91 3%)
CR or better (sCR + CR)	9 (7.0%)	(3.7%, 11 9%)	11 (6.4%)	(3.6%, 10.4%)	6 (13.3%)	(6.0%, 24.6%)	3 (9.4%)	(2.6%, 22 5%)	2 (8.0%)	(1.4%, 23 1%)	0	(NE, NE)
VGPR or better (sCR + CR + VGPR)	73 (56.6%)	(49.0%, 64.0%)	89 (51.7%)	(45.2%, 58.2%)	28 (62.2%)	(48.9%, 74.3%)	20 (62.5%)	(46.4%, 76.7%)	14 (56.0%)	(37.9%, 73.0%)	6 (60.0%)	(30.4%, 85.0%

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); VMP = bortezomib/melphalan/prednisone.
[a] 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.

Source: Modified from Attachment TEFORR01A2

Table 19: Subgroup Analysis of Overall Response Rate Up to Month 6: D-Rd; Safety Analysis Set (Combination Therapy Studies: MMY3003 and MMY2040)

	MMY 3003 Dara IV + Rd						MMY 2040 Dara SC + Rd					
	≤65 kg		>65 kg to 85 kg		>85 kg		≤65 kg		>65 kg to 85 kg		>85 kg	
	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]	n (%)	90% CI for %[a]
Analysis set: safety	94		121		65		9		33		23	
Best overall response												
Overall response (sCR+CR+VGPR+PR)	83 (88.3%)	(81.4%, 93.3%)	106 (87.6%)	(81.6%, 92 2%)	59 (90.8%)	(82.6%, 95.9%)	9 (100.0%)	(71.7%, 100.0%)	29 (87.9%)	(74.4%, 95.8%)	21 (91.3%)	(75.1%, 98.4%)
CR or better (sCR + CR)	14 (14.9%)	(9.2%, 22.3%)	14 (11.6%)	(7.1%, 17.5%)	6 (9.2%)	(4.1%, 17.4%)	1 (11.1%)	(0.6%, 42.9%)	3 (9.1%)	(2.5%, 21.9%)	2 (8.7%)	(1.6%, 24.9%)
VGPR or better (sCR + CR + VGPR)	60 (63.8%)	(54.9%, 72.1%)	74 (61.2%)	(53.3%, 68.6%)	34 (52.3%)	(41.4%, 63.0%)	7 (77.8%)	(45.0%, 95.9%)	16 (48.5%)	(33.3%, 63.9%)	15 (65.2%)	(46.0%, 81.4%)

Note: Dara IV = daratumumab intravenous; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); Rd = lenalidomide/dexamethasone.
[a] 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.
Note: There were 3 subjects in study MMY3003 with missing baseline weight.

Source: Modified from Attachment TEFORR01B2

Additional Efficacy Considerations: Not applicable.

The FDA's Assessment:
Not applicable.

8.1.6 Integrated Assessment of Effectiveness

The Applicant's Position:
Overall, efficacy of the flat dose of daratumumab SC 1800 mg is comparable to the existing daratumumab 16 mg/kg IV formulation. Daratumumab SC also reduces treatment burden for patients due to its considerably shorter duration of administration of 3 to 5 minutes and reduced rate of IRRs, and led to a higher satisfaction with therapy as reported by subjects.

Study MMY3012 demonstrates that daratumumab SC is non-inferior to daratumumab IV in terms of ORR and maximum Ctrough (Cycle 3 Day 1 predose). Response rates for daratumumab SC in combination with standard background therapies were comparable to those observed in daratumumab IV studies (MMY3003, MMY3007). No clinically meaningful differences were identified between the daratumumab SC and IV treatment groups in subpopulations, including by body weight. The totality of the data confirm that daratumumab SC 1800 mg is therapeutically consistent with the daratumumab IV 16 mg/kg formulation.

Daratumumab SC as Monotherapy

Integrated efficacy data were presented from 553 subjects assigned to receive daratumumab SC or IV monotherapy for the treatment of relapsed or refractory multiple myeloma in 3 clinical studies, including the Phase 3 randomized, open-label, multicenter non-inferiority Study MMY3012 that compared daratumumab SC (n=263) to that of currently marketed daratumumab IV (n=259). Efficacy results based on the pooled monotherapy analysis set were consistent with those described for the daratumumab SC group of Study MMY3012 (see Section 8.1.4). Overall, monotherapy studies had an ORR of 42.5% and 37.1% for the daratumumab SC and daratumumab IV groups, respectively. Daratumumab SC showed clinical efficacy consistent with daratumumab IV, with considerably shorter duration of administration, and higher satisfaction with therapy reported by subjects. The flat dosing of daratumumab SC 1800 mg resulted in similar or slightly higher trough concentrations (C_{trough}) compared to daratumumab IV 16 mg/kg throughout the treatment period, and demonstrated non-inferiority based on maximum C_{trough} (Cycle 3 Day 1) between daratumumab SC and daratumumab IV 16 mg/kg. Subgroup analyses showed the 1800 mg flat dose achieved adequate exposure for all body weight subgroups, as the maximum Ctrough (Cycle 3 Day 1) from daratumumab SC is similar or higher than daratumumab IV. Exposure-response analysis for efficacy showed similar efficacy for daratumumab SC across body weights groups.

Daratumumab SC in Combination with Standard Background Therapies

Efficacy data were presented from 199 subjects from Study MMY2040 who received daratumumab SC in combination with standard background therapies (D-VMP: 67 subjects; D-Rd: 65 subjects; D-VRd: 67 subjects). The study demonstrated that daratumumab SC administered in combination with standard multiple myeloma treatments was consistent with daratumumab IV administration:

- In subjects with newly diagnosed multiple myeloma who were transplant ineligible and treated with D-VMP (median treatment duration of 6.5 months), ORR was 88.1% (90% CI: 79.5%, 93.9%).
- In subjects with relapsed or refractory multiple myeloma treated with D-Rd (median treatment

duration of 7.0 months), ORR was 90.8% (90% CI: 82.6%, 95.9%).

- In subjects with newly diagnosed multiple myeloma who were transplant eligible and treated with D-VRd prior to off-study therapy/ASCT (median treatment duration of 2.6 months), a VGPR or better rate of 71.6% (90% CI: 61.2%, 80.6%) was observed.

Overall response rate up to Month 6 for daratumumab SC combination therapy regimens with VMP and Rd in Study MMY2040 were comparable to those for corresponding daratumumab IV infusion combination regimens (i.e., data from MMY3007 with daratumumab IV + VMP; and MMY3003 for daratumumab IV + Rd). Response rates were also consistent with longer follow-up data (Studies MMY3007: 16.5 months; MMY3003: 13.5 months).

The FDA's Assessment:

- Study MMY3012 met the protocol pre-specified non-inferiority margin of daratumumab SC compared to daratumumab IV.
- Study MMY2040 met the protocol pre-specified hypotheses on primary endpoints for all 3 cohorts. (b) (4) .
- FDA does not agree with the Applicant's conclusions that daratumumab SC reduces treatment burden and led to a higher satisfaction with therapy as Study MMY3012 was not designed to evaluate patient preference and this was not rigorously tested.
- Regarding the Applicant's statement that no clinically meaningful differences were identified between the daratumumab SC and IV treatment groups in subpopulations, the numbers of patients in the subgroups are too small to make any definitive conclusions; however, no differences in efficacy were observed between subgroups based on the limited numbers.
- In consideration of the indications for approval, FDA considered the totality of evidence from the available efficacy, safety and PK data from MMY3012 and MMY2040. FDA also considered the prior experience with daratumumab IV.
  - For the D-Rd regimen in newly diagnosed patients who are ineligible for autologous stem cell transplant, safety data from the D-Rd regimen in the RRMM population is available from MMY2040 and there are no specific safety concerns based on the experience with daratumumab IV in this combination regimen.
  - For the D-Vd regimen in patients who have received at least one prior therapy, FDA has no specific safety concerns based on the experience with daratumumab IV in this combination regimen and is able to extrapolate based on the totality of available efficacy, PK and safety data from MMY3012.
  - (b) (4)

8.2 Review of Safety

The Applicant's Position:
Safety data demonstrate that daratumumab SC was well-tolerated in patients with multiple myeloma and led to fewer IRRs compared to the currently available daratumumab IV formulation. No other clinically meaningful differences in the safety profile for daratumumab SC 1800 mg, when given as monotherapy or in combination with standard background therapies, were identified in comparison to daratumumab IV 16 mg/kg, including across pre-specified subgroups for body weight. No new safety concerns were identified for daratumumab SC.

Daratumumab SC as Monotherapy

Integrated safety data were presented from 291 subjects who received daratumumab SC as monotherapy for the treatment of relapsed or refractory multiple myeloma across 3 clinical studies (MMY3012, MMY1004, MMY1008), including the Phase 3 randomized, open-label, multicenter, non-inferiority Study MMY3012 which compared daratumumab SC (n=260) to that of currently marketed daratumumab IV (n=258).

Daratumumab SC was well tolerated and was associated with a significantly reduced incidence of IRRs relative to daratumumab IV. The safety profile of daratumumab administered SC at a flat dose of 1800 mg was otherwise comparable to that of the daratumumab IV 16 mg/kg formulation (median treatment durations of 4.75 and 5.36 months, respectively). Key safety findings from the Phase 3 non-inferiority Study MMY3012 were as follows:

- All TEAEs were balanced between treatment groups (<5% difference in incidence) except for a higher incidence of neutropenia in the daratumumab SC group (daratumumab SC, 19.2%; daratumumab IV, 13.6%) and lower incidence in the daratumumab SC group of dyspnea (daratumumab SC, 5.4%; daratumumab IV, 10.9%) and chills (daratumumab SC, 5.8%; daratumumab IV, 12.4%).
  - The overall incidence of Grade 3 or 4 TEAEs was also balanced between the treatment groups (daratumumab SC, 45.4%; daratumumab IV, 48.8%). Individual Grade 3 or 4 TEAEs were reported at similar rates (<5% difference in incidence) in the daratumumab SC and daratumumab IV groups with the exception of neutropenia (daratumumab SC, 13.1%; daratumumab IV, 7.8%).
- A comparable proportion of subjects in both treatment groups experienced TEAE(s) with a fatal outcome (Grade 5; daratumumab SC: 5.4%; daratumumab IV: 6.6%), TEAEs that were serious (daratumumab SC, 26.2%; daratumumab IV, 29.5%), or TEAEs leading to treatment discontinuation (daratumumab SC, 6.9%; daratumumab IV, 8.1%).
- The proportion of subjects with an IRR was significantly lower in the daratumumab SC group (12.7%) compared with the daratumumab IV group (34.5%) (odds ratio=0.28 [95% CI: 0.18, 0.44]; p<0.0001). Most IRRs were Grade 1 or 2. No Grade 4 or 5 IRRs were reported, and no IRRs in the daratumumab SC group led to treatment discontinuation, dose interruption, or incomplete administration of a dose.
- The incidence of injection-site reactions in the daratumumab SC group was low (6.9%). All

injection-site reactions were Grade 1 or 2 and did not lead to treatment discontinuation.

- Neutropenia was the only Grade 3 or 4 cytopenia TEAEs reported at ≥5% higher incidence in the daratumumab SC group (daratumumab SC, 13.1%; daratumumab IV, 7.8%). One Grade 5 event of febrile neutropenia was reported (in the daratumumab SC group). In both treatment groups, neutropenia was rarely reported as serious (daratumumab SC, 0%; daratumumab IV, 0.4%) or as the reason for treatment discontinuation (daratumumab SC, 0%; daratumumab IV, 0.4%) or modification (daratumumab SC, 1.9%; daratumumab IV, 3.5%), and hematopoietic growth factor use was comparable in the 2 groups (daratumumab SC, 10.4%; daratumumab IV, 11.2%).
  - The higher incidence of neutropenia in the daratumumab SC group was not associated with a higher incidence of TEAEs in the system organ class (SOC) of infections and infestations (all grade: daratumumab SC, 45.8%; daratumumab IV, 45.3%. Grade 3 or 4: daratumumab SC, 10.4%; daratumumab IV, 11.2%).
  - Grade 3 or 4 cytopenia TEAEs of anemia, lymphopenia, and thrombocytopenia were balanced between treatment groups (<5% difference in incidence).
- Most infection TEAEs were manageable and rarely led to treatment discontinuation.
  - Two subjects in each treatment group reported TEAEs of reactivation of hepatitis B. All events were Grade 1 or 2 except for the 1 subject in the daratumumab IV group who had a fatal outcome.
- The incidence of second primary malignancies was low and equal between treatment groups (1.2% in each group). No cases of tumor lysis syndrome (TLS) or intravascular hemolysis were reported in either treatment group.

Safety results, based on data from Study MMY3012 integrated with that from 31 subjects treated with daratumumab SC in supportive Studies MMY1004 and MMY1008, were consistent with those described for the daratumumab SC group of Study MMY3012.

Daratumumab SC in Combination with Standard Background Therapies

Safety data were presented from 199 subjects who received daratumumab SC in combination with standard background therapies for multiple myeloma in the Phase 2 Study MMY2040. This open-label study investigated the efficacy and safety of daratumumab SC in combination with standard background therapies, including bortezomib, melphalan, and prednisone (D-VMP) in subjects with newly diagnosed multiple myeloma who were transplant ineligible (n=67); or lenalidomide and dexamethasone (D-Rd) in subjects with relapsed or refractory multiple myeloma (n=65), and bortezomib, lenalidomide, and dexamethasone (D-VRd) in subjects with newly diagnosed multiple myeloma who were transplant eligible (n=67). Subjects in the D-VMP and D-Rd cohorts were treated until disease progression or intolerability, while subjects in the D-VRd cohort were treated for a maximum of 4 cycles. 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.
Daratumumab SC in combination with all 3 background therapies was well tolerated. No new safety concerns were identified.

- Grade 3 or 4 TEAEs occurred in 68.7% of subjects in the D-VMP cohort, 78.5% in the D-Rd

cohort, and 58.2% in the D-VRd cohort. The most frequently reported Grade 3 or 4 TEAEs (≥10%) were hematologic events, consisting of:
  - D-VMP cohort: thrombocytopenia (34.3%), neutropenia (31.3%), lymphopenia (20.9%), and anemia (11.9%)
  - D-Rd cohort: neutropenia (47.7%) and lymphopenia (12.3%)
  - D-VRd cohort: neutropenia (28.4%), lymphopenia (16.4%), and thrombocytopenia (14.9%)
- In all 3 daratumumab SC combination therapy cohorts, the incidence of discontinuation of treatment due to TEAEs (1.5% to 4.6%) or TEAEs with a fatal outcome (1.5% to 3.0%) was low.
- The rate of IRRs was low and similar across treatment cohorts (4.6% for D-Rd; 9.0% for D-VMP and D-VRd) and most IRRs were associated with the first administration. All but.1 IRR was Grade 1 or 2 in severity, and 1 IRR resulted in discontinuation of daratumumab treatment.
- Injection-site reactions were infrequent in all 3 cohorts (6.0% for D-VMP, 3.1% for D-Rd, 13.4% for D-VRd), were all assessed as Grade 1 or 2, and none resulted in treatment discontinuation.
- There were no TEAE reports of hepatitis B reactivation, TLS, or intravascular hemolysis. One subject had a second primary malignancy of melanoma of the skin.

A comparison of key safety data for daratumumab SC in combination with VMP or Rd in Study MMY2040 with previously submitted data from Phase 3 studies of daratumumab IV in combination with the corresponding regimens (i.e., data from MMY3007 with daratumumab IV + VMP; and MMY3003 for daratumumab IV + Rd) showed a comparable safety profile, with the exception of a substantially lower incidence of IRRs with daratumumab SC combination therapies.

The FDA's Assessment:

FDA's independent analysis demonstrated the safety profile of daratumumab SC monotherapy at the dosing used in Study MMY3012. FDA does not agree with the Applicant's conclusion that there were no other clinically meaningful differences in the safety profile for daratumumab SC 1800 mg, when given as monotherapy or in combination with standard background therapies, in comparison to daratumumab IV 16 mg/kg. FDA analysis, which was consistent with the Applicant's analysis, showed higher rates of neutropenia with daratumumab SC (19.2%) as compared to daratumumab IV (13.6%), including severe (Grade 3-4) neutropenia (13.1% with daratumumab SC as compared to 7.8% with daratumumab IV). FDA also does not agree with the Applicant's statement that no new safety concerns were identified for daratumumab SC. Injection-site reactions were a new, important safety risk identified in studies MMY3012 and MMY2040. Study MMY2040 included small numbers of patients in each cohort, and the duration of follow-up was short; however; the totality of evidence supports safety of daratumumab SC in these combination regimens.

8.2.1 Safety Review Approach

The Applicant's Position:

Safety data from a total of 748 subjects who were treated with study drug across the 4 daratumumab SC clinical studies (Table 20; Section 7.1) are summarized and organized according to treatment administered as monotherapy (n=549) or in combination with standard background therapies (n=199).

Table 20: Subject Data Included in Summary of Clinical Safety

Study	Daratumumab as Monotherapy				Daratumumab as Combination Therapy			
	MMY3012	MMY1004	MMY1008	**Total Subjects**	MMY2040 D-VMP	MMY2040 D-Rd	MMY2040 D-VRd	**Total Subjects**
Daratumumab SC	260	25	6	**291**	67	65	67	**199**
Daratumumab IV	258	--	--	**258**	--	--	--	**--**

Key: D=daratumumab; IV=intravenous; Rd=lenalidomide + low-dose dexamethasone; N=number of subjects; SC=subcutaneous; VMP=bortezomib + melphalan + prednisone

Data from cross-study analyses of Study MMY2040 and previously submitted data from 2 Phase 3, randomized, open-label, active-controlled, registrational studies of daratumumab IV in combination with the corresponding regimens are also included in the integrated safety summary. Specifically, data for the D-VMP and D-Rd cohorts in Study MMY2040 are compared with data from subjects receiving daratumumab IV (16 mg/kg) in combination with the same background regimen from Studies MMY3007 (D-VMP; N=346) or MMY3003 (D-Rd; N=283). To account for differences in treatment duration and follow-up, the comparison of daratumumab SC safety profiles for the D-VMP and D-Rd cohorts of Study MMY2040 with that of historical data involving daratumumab IV-based regimens are based on data collected from the first dose of study treatment up to the end of Month 6 for each subject.

The safety evaluation included the following AEs of clinical interest: IRRs, including cases of anaphylaxis or suspected anaphylaxis (any grade for Study MMY2040); local injection-site reactions, cytopenia AEs (neutropenia, anemia, thrombocytopenia [including hemorrhage]), infections and infestations, second primary malignancies, TLS, intravascular hemolysis, and treatment-emergent interferences for blood typing.

The FDA's Assessment:

FDA's assessment of safety focused primarily on results from the randomized, phase 3 study MMY3012. The safety population from this trial included 260 patients who received daratumumab SC and 258 patients who received daratumumab IV (total = 518). FDA also assessed the safety of daratumumab SC in combination with bortezomib, melphalan, and prednisone (D-VMP) and in combination with lenalidomide and dexamethasone (D-Rd) based on the results of study MMY2040. The safety population from this trial included 67 patients who received D-VMP and 65 patients who received D-Rd. FDA also performed an integrated assessment of safety based on the pooled population of 490 patients who received daratumumab SC in studies MMY3012 (N=260), MMY1004 (N=25), MMY1008 (N=6) and MMY2040 (N=199).

8.2.2 Review of the Safety Database

Overall Exposure

The Applicant's Position:
A total of 291 and 258 subjects received at least 1 dose of monotherapy treatment with daratumumab SC or daratumumab IV, respectively, across Studies MMY3012 (260 and 258 subjects, respectively), MMY1004 (25 subjects, daratumumab SC only), and MMY1008 (6 subjects, daratumumab SC only).

In combination therapy Study MMY2040, all 199 subjects received at least 1 dose of combination therapy treatment (67, 65, and 67 subjects in the D-VMP, D-Rd, and D-VRd cohorts, respectively).

The FDA's Assessment:
FDA confirmed that among the 260 patients who received daratumumab SC in MMY3012, 7% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. Among the 67 patients who received D-VMP in MMY2040, 93% were exposed for 6 months or longer and 19% were exposed for 12 months or longer. Among the 65 patients who received D-Rd in MMY2040, 92% were exposed for 6 months or longer and 20% were exposed for 12 months or longer.

Relevant characteristics of the safety population

The Applicant's Position:
Monotherapy
The demographic and baseline disease characteristics of subjects treated with daratumumab SC in the Pooled Monotherapy Safety analysis set were generally similar to those for the daratumumab IV treatment group of MMY3012, with the exception of more subjects in the pooled daratumumab SC group with a high cytogenic risk at baseline (Table 11).

Combination therapy
By design, all subjects receiving background therapy with VMP or VRd in Study MMY2040 had newly diagnosed multiple myeloma, while those receiving background therapy with Rd had relapsed or refractory disease. The median number of lines of prior systemic therapy in the D-Rd cohort was 1 (range: 1, 5), 53.8% of subjects had received prior therapy with a PI + IMiD, and 30.8% were refractory to the last line of prior therapy (Mod5.3.5.2/MMY2040/Tab10). Baseline demographic and disease characteristics in each of the 3 daratumumab SC combination therapy cohorts of Study MMY2040 are summarized in Table 13 and Table 14.

Comparison to Historic Data with Daratumumab IV
Study inclusion criteria, demographic, and baseline disease characteristics for the D-VMP and D-Rd cohorts of Study MMY2040 were generally consistent with those reported for the D-VMP and D-Rd groups in Studies MMY3007 and MMY3003, with the exception that Study MMY3007 enrolled younger patients (Mod5.3.5.3/ISS/AttTSIDEM01A, AttTSIDEM02A; Mod5.3.5.3/ISS/AttTSIDEM01B, AttTSIDEM02B).

The FDA's Assessment:
FDA agrees that demographics and baseline disease characteristics were similar between the daratumumab SC and daratumumab IV arms in MMY3012, except for the difference in the proportion of patients with standard- (73.7% vs. 82.7%) and high-risk (26.3% vs. 17.3%) cytogenetics. However, differences in cytogenetic risk are not known to be associated with differences in safety with daratumumab. FDA did not independently confirm the demographics or baseline disease characteristics for the pooled daratumumab SC monotherapy population, which includes an additional 31 patients in total from studies MMY1004 and MMY1008.

FDA agrees with the demographics and baseline characteristics for patients in the D-VMP and D-Rd cohorts from MMY2040. FDA notes limitations in drawing cross-study comparisons regarding the Applicant's comparison of historical safety data from studies MMY3007 and MMY3003.

Adequacy of the safety database

The Applicant's Position:
The study populations enrolled in Study MMY3012, supportive monotherapy Studies MMY1004 and MMY1008, and combination therapy Study MMY2040 are representative of the target population to be treated for multiple myeloma and considered adequate for assessment of safety of the daratumumab SC administration.

The FDA's Assessment:
FDA agrees that the safety assessments from the pivotal trial MMY3012 provide adequate primary evidence to support approval of daratumumab SC as monotherapy in patients who have received at least three prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD. FDA also agrees that the safety assessments from MMY2040 for the D-VMP and D-Rd cohorts in combination with the safety and clinical pharmacology assessments from MMY3012 provide adequate evidence to support the approval of daratumumab SC for the following combination regimen indications:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy

The analysis of safety for the combination regimens with daratumumab SC is limited by the MMY2040 trial design, which consists of single arm combination cohorts. Therefore, there is no randomized data to directly compare these regimens with either placebo- or daratumumab IV-containing regimens.

8.2.3 Adequacy of the Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues were identified regarding the data integrity or submission quality that had an effect on the safety review. The clinical sites for Studies MMY3012, MMY2040, MMY1004, and MMY1008 were monitored by the clinical research team following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans, including automated database edit checks and internal data review by data management, clinical program management, and medical reviewers.

The FDA's Assessment:
The quality of the submitted safety data was adequate for substantive primary review.

Categorization of Adverse Event

The Applicant's Position:
The collection of AEs was appropriate across the 4 studies. The protocols for Studies MMY3012, MMY1004, MMY1008, and MMY2040 defined AEs and SAEs, as well as reporting procedures including the time frame for collection of events. Standard methodologies were used to categorize AEs. MedDRA version 21.1 was used and AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. In MMY3012 and MMY2040, administration-related systemic reactions associated with daratumumab SC were categorized as "infusion-related reactions (IRRs)." The description of these events as administration-related systemic reactions is more accurate. Adverse events (AEs) that were considered by the investigator to be an IRR associated with daratumumab, were noted on the eCRF. Similarly, for injection site reactions, AEs that were considered by the investigator to be an injection site reaction associated with daratumumab were noted on the eCRF.

Routine Clinical Tests

The Applicant's Position:
The safety assessment methods and time points described in the study protocols were reasonable for the safety assessment of the multiple myeloma population. Clinical laboratory tests included hematology and serum chemistry (see protocol Time and Events Schedules for more details). The investigator was required per protocol to review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.4 Safety Results

Deaths

The Applicant's Position:
Monotherapy
In the randomized monotherapy Study MMY3012, the proportion of subjects who died within 30 days of the last dose of study drug was low and similar between treatment groups (daratumumab SC: 5.0%; daratumumab IV: 7.0%) (Mod2.7.4/Table 13), as was the proportion of subjects who had a TEAE(s) with outcome of death (daratumumab SC, 5.4%; daratumumab IV, 6.6%) (MMY3012 CSR Table 14). Deaths within 30 days of last dose and TEAEs with an outcome of death for the Pooled Monotherapy Safety analysis set were also similar to those reported for the daratumumab IV group of Study MMY3012 (MMY3012 CSR Tables 13 and 14).

Combination Therapy
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 (i.e., Grade 5 TEAE) (Mod5.3.5.2/MMY2040/Sec7.1.2.1):

- **D-VMP:** 2 deaths (3.0%) (neutropenic sepsis, pneumonia)
- **D-Rd:** 1 death (1.5%) (myocardial infarction)
- **D-VRd:** 1 death (1.5%) (respiratory infection)

Comparison to Historic Data with Daratumumab IV
D-VMP Regimens
Deaths during 30 days of the last dose were reported for 3.0% of subjects in Study MMY2040 and 2.9% of subjects in Study MMY3007. The proportion of subjects who experienced a TEAE with an outcome of death (i.e., Grade 5) was 3.0% and 3.8% for Studies MMY2040 and MMY3007, respectively.

D-Rd Regimens

Deaths during 30 days of the last dose were reported for 1.5% of subjects in Study MMY2040 and 3.2% of subjects in Study MMY3003. The proportion of subjects who experienced a TEAE with an outcome of death (i.e., Grade 5) was 1.5% and 3.2% for Studies MMY2040 and MMY3003, respectively.

The FDA's Assessment:
FDA confirmed that 31 deaths occurred during treatment or within 30 days of the last dose of study treatment in MMY3012 – 13 (5%) deaths in the daratumumab SC arm and 18 (7%) deaths in the daratumumab IV arm. Of these deaths, 4 were attributed to progressive disease (1 in the daratumumab SC arm and 3 in the daratumumab IV arm).

A total of 31 patients had a fatal treatment-emergent adverse event (TEAE) in MMY3012 – 14 (5.4%) in the daratumumab SC arm and 17 (6.6%) in the daratumumab IV arm. Of these 31 patients, fatal TEAEs in 2 patients on the daratumumab SC arm and 1 patient on the daratumumab IV arm occurred >30 days after the last dose of study treatment. One additional patient on the daratumumab IV arm had a fatal TEAE that was not considered treatment-emergent because it occurred in the setting of progressive disease after the patient had transitioned to subsequent therapy.

Fatal TEAEs that occurred in more than 1 patient in the daratumumab SC arm in MMY3012 were: general physical health deterioration (4 patients), septic shock (2 patients), and respiratory failure (2 patients).

FDA agrees with the Applicant's assessment of the number of deaths in Study MMY2040, but notes that the preferred terms for these events included pneumonitis rather than pneumonia (a TEAE of pneumonia preceded pneumonitis in this patient on the D-VMP arm), and respiratory failure rather than respiratory infection (death due to respiratory failure in this patient on the D-VRd arm occurred in the setting of pleural effusion, fluid overload, and suspected cardiac amyloidosis, but no respiratory infection was documented).

Overall, FDA agrees that the rates and causes of deaths and fatal TEAEs were similar between daratumumab SC and daratumumab IV in MMY3012. FDA also agrees that the rates of deaths and fatal TEAEs were similar in the pooled SC monotherapy population (N=291), which includes 25 additional patients from MMY1004, and 6 additional patients from MMY1008. The single arm combination cohort design of MMY2040 limits cross-trial comparisons, however, the rates of deaths and fatal TEAEs were low across all three combination arms.

Serious Adverse Events

The Applicant's Position:
Monotherapy
Serious TEAEs were reported at a similar frequency in the daratumumab SC (26.2%) and daratumumab IV (29.5%) treatment groups of Study MMY3012, as was the frequency of serious

TEAEs considered related to study treatment (daratumumab SC: 6.5%; daratumumab IV: 8.5%) (Mod 2.7.4/Sec2.3.3.1). The incidence of specific TEAE preferred terms reported as serious was low, with pneumonia being the only serious TEAE reported in at least 2% of subjects in either treatment group (daratumumab SC, 2.7%; daratumumab IV, 4.3%). The incidence of serious TEAEs reported in subjects treated with daratumumab SC in the Pooled Monotherapy Safety analysis set (all: 25.4%; related: 5.8%) was similar to that for the daratumumab IV treatment group of MMY3012.

Combination Therapy
The overall incidence and most frequently reported serious TEAEs (≥2%) in each daratumumab SC combination therapy cohort of Study MMY2040 (Mod 2.7.4/Sec2.3.2.2) were pyrexia for D-VMP (7.5%) and D-VRd (6.0%), and pneumonia for D-Rd (6.2%).

Comparison to Historic Data with Daratumumab IV
D-VMP Regimens
The overall incidence of serious TEAEs was similar for Studies MMY2040 (35.8%) and MMY3007 (33.2%). Pyrexia was the most frequent individual serious TEAE through Month 6 in the D-VMP cohort of Study MMY2040 (7.5%) and was reported at a higher rate than in the D-VMP group of Study MMY3007 (1.4%). However, TEAEs in the infection and infestation SOC were reported at a lower rate in the D-VMP cohort of Study MMY2040 (9.0%) than in the D-VMP group of Study MMY3007 (17.6%).

D-Rd Regimens
The overall incidence of serious TEAEs was similar for Studies MMY2040 (35.4%) and MMY3003 (35.0%). Pneumonia was the most common individual serious TEAEs through Month 6 in the D-Rd cohort of Study MMY2040 (4.6%) and Study MMY3003 (4.9%). Neutropenia was the only other individual serious TEAEs reported in >2 subjects in the D-Rd cohort of Study MMY2040 (4.6%) and was reported at a higher rate than in the D-Rd group of Study MMY3003 (0.7%). Of note, the reported rates for serious febrile neutropenia following D-Rd treatment was not higher for Study MMY2040 (1.5%) than for Study MMY3003 (2.8%).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the incidence of serious TEAEs in MMY3012. The overall incidence of serious TEAEs was similar between arms (26.2% for daratumumab SC vs. 29.5% for daratumumab IV) and pneumonia was the only serious TEAE reported in ≥2% of patients.

FDA's analysis of the incidence of serious TEAEs in MMY2040, which includes all TEAEs regardless of relatedness, differs from that reported by the Applicant above but is consistent with the results presented in the Clinical Study Report (CSR) for MMY2040. Serious TEAEs occurred in 37% of patients on the D-VMP arm. Serious TEAEs that occurred in ≥2% of patients on the D-VMP arm were: febrile neutropenia (3%), thrombocytopenia (3%), pyrexia (7.5%), neutropenic sepsis (3%), pneumonia (4.5%), and hypotension (3%). Serious TEAEs occurred in 40% of patients on the D-Rd

arm. Serious TEAEs that occurred in ≥2% of patients on the D-VMP arm were: neutropenia (4.6%), cardiac failure (3.1%), diarrhea (3.1%), pyrexia (3.1%), influenza (4.6%), pneumonia (6%), upper respiratory tract infection (3.1%), and acute kidney injury (3.1%).

FDA does not agree with the Applicant's use of historical data to assess the relative incidence of serious TEAEs with daratumumab SC versus daratumumab IV combination therapies given the limitations of cross trial comparisons.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Adverse Events Leading to Discontinuation of Study Drug

In the randomized monotherapy Study MMY3012, a similar proportion of subjects in both treatment groups experienced TEAEs leading to treatment discontinuation (6.9% and 8.1%, 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). A similar proportion of subjects treated with daratumumab SC had TEAEs leading to treatment discontinuation in the Pooled Monotherapy Safety analysis set (all, 6.2%; Grade 3 or 4, 3.8%).

In the combination therapy Study MMY2040, TEAEs leading to discontinuation of all study treatment was low in all 3 cohorts and occurred in 2 subjects (3.0%) in the D-VMP cohort (pneumonitis and neutropenic sepsis); 3 subjects (4.6%) in the D-Rd cohort (pneumonia [n=2] and myocardial infarction), and 1 subject (1.5%) in the D-VRd cohort (respiratory failure) and comparable with the historic daratumumab IV combination data:

- 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%).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the overall incidence of TEAEs leading to treatment discontinuation in MMY3012 and the assessment of TEAEs leading the discontinuation in at least 1% of patients in either arm. FDA did not independently confirm the incidences of TEAEs leading to discontinuation in the Pooled SC Monotherapy analysis set.

FDA agrees with the Applicant's assessment of the overall incidence of TEAEs leading to treatment discontinuation in MMY2040 and the assessment of the TEAEs leading to discontinuation in patients in the D-VMP and D-Rd cohorts.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In the randomized monotherapy Study MMY3012, TEAEs leading to modification of study treatment (dose delay; dose modification was not permitted) were reported at a similar rate in the daratumumab SC and daratumumab IV groups (Mod2.7.4/Sec2.3.3.2.1). The incidence of TEAEs leading to daratumumab treatment modification in subjects treated with daratumumab SC in the Pooled Monotherapy Safety analysis set was similar to that for the daratumumab IV group of MMY3012.

In the combination therapy Study MMY2040, the overall incidence of TEAEs leading to daratumumab treatment modification in each cohort was: D-VMP, 40.3%; D-Rd, 55.4%; and D-VRd, 23.9% (Mod2.7.4/Sec2.3.3.2.1). In comparison to historical safety data for D-VMP in Study MMY3007 and D-Rd in Study MMY3003 up to Month 6, the incidences of TEAEs leading to daratumumab treatment modification were similar for daratumumab SC and daratumumab IV.

No IRRs in the daratumumab SC group led to treatment discontinuation, dose interruption, or incomplete administration of a dose.

The FDA's Assessment:
The results presented in Module 2.7.4, Section 2.3.3.2.1 referenced above by the Applicant (reported incidence of TEAEs leading to dose modification of 26.5% for daratumumab SC vs. 27.1% for daratumumab IV) only include "TEAEs which led to a modification of daratumumab treatment that were planned prior to the start of the injection or infusion (cycle delay, injection/infusion skipped, injection/infusion delayed within cycle)." FDA Analysis of all TEAEs that led to a dose interruption based on the AEACN variable in the ADAE dataset, showed rates of dose interruption due to TEAEs of 25.8% for daratumumab SC vs. 46.1% for daratumumab IV.

Therefore, FDA does not agree with the Applicant's statement that the rates of TEAEs leading to dose modifications was similar between arms; however, the rate was lower in the daratumumab SC arm. The only TEAE leading to dose interruption that occurred in >5% of patients in the daratumumab SC arm was thrombocytopenia (8.1% in daratumumab SC arm vs. 5% in daratumumab IV arm). FDA did not independently confirm the incidences of TEAEs leading to dose interruption in the pooled SC monotherapy analysis set.

FDA's analysis of infusion reactions in MMY3012 is discussed in Section 8.2.5 below.

FDA agrees with the incidence of TEAEs leading to dose interruption in the D-Rd cohort (55.4%) reported by the Applicant. FDA analysis showed a slightly higher incidence of TEAEs leading to dose interruption in the D-VMP cohort (43.3%) compared to the incidence reported by the Applicant (40.3%). Additional FDA analyses showed that there were no TEAEs leading to dose interruption that occurred in >5% of patients in the D-VMP cohort; TEAEs leading to dose interruption that in >5% of patients in the D-Rd cohort were neutropenia (20%) and dyspnea (6.2%).

Significant Adverse Events

The Applicant's Position:

Grade 3 or 4 Adverse Events

In the randomized monotherapy Study MMY3012, a similar incidence of Grade 3 or 4 TEAEs was reported in the daratumumab SC (45.4%) and daratumumab IV (48.8%) groups (Mod2.7.4/Sec2.2.2.1). The most common Grade 3 or 4 TEAEs were cytopenias. The incidence of Grade 3 or 4 TEAEs was similar between the daratumumab SC and daratumumab IV groups except for neutropenia, which was reported at a higher rate in the daratumumab SC group (see Section 6.1.8.3). The incidence of Grade 3 or 4 TEAEs reported in subjects treated with daratumumab SC in the Pooled Monotherapy Safety analysis set was also similar to that for the daratumumab IV treatment group of MMY3012, with the exception of neutropenia (pooled daratumumab SC, 12.7%; daratumumab IV, 7.8%).

In the combination therapy Study MMY2040, Grade 3 or 4 TEAEs were reported for 68.7% of subjects in the D-VMP cohort, 78.5% of subjects in the D-Rd cohort, and 58.2% of subjects in the D-VRd cohort. Cytopenias were the most common Grade 3 or 4 TEAEs in all 3 cohorts (Mod2.7.4/Sec2.2.2.2). In comparison to historical safety data in Studies MMY3007 and MMY3003 up to Month 6, the incidence of Grade 3 or 4 TEAEs in the Blood and lymphatic system disorders SOC and the incidence of Grade 3 or 4 neutropenia TEAEs were similar for daratumumab SC and daratumumab IV.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the overall incidence of severe (Grade 3-4) TEAEs in MMY3012. Additional FDA analysis showed that the Grade 3-4 TEAEs occurring in >5% of patients in MMY3012 were (SC vs. IV): anemia (13.1% vs. 14%), lymphopenia (5% vs. 6.2%), neutropenia (13.1% vs. 7.8%), thrombocytopenia (13.8% vs. 13.6%), pneumonia (5.4% vs. 6.2%), and hypertension (3.1% vs. 6.2%). FDA did not independently confirm the incidence of severe TEAEs in the pooled SC monotherapy analysis set.

FDA agrees with the Applicant's assessment of the overall incidence of severe (Grade 3-4) TEAEs in MMY2040. Additional FDA analysis showed that the Grade 3-4 TEAEs occurring in >5% of patients in the D-VMP cohort were: anemia (11.9%), leukopenia (6.0%), lymphopenia (20.9%), neutropenia (31.3%), thrombocytopenia (34.3%), and hypertension (6.0%). The Grade 3-4 TEAEs occurring in >5% of patients in the D-Rd cohort were: leukopenia (9.2%), lymphopenia (12.3%), neutropenia (47.7%), thrombocytopenia (6.2%), pneumonia (6.2%), and hyperglycemia (6.2%).

Treatment-Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Adverse drug reactions in monotherapy Study MMY3012 and combination therapy Study MMY2040 were evaluated according to the following points:

- All TEAEs reported in ≥10% subjects in any treatment group/cohort were considered to have

met the ADR threshold (Table 21, Table 23).

- TEAEs were evaluated in the context of a potential plausible biological or pharmacological association with daratumumab or as medically significant events with a high probability that they could be associated with daratumumab.
- All laboratory parameters for Studies MMY3012 and MMY2040 were reviewed. No laboratory parameters had an incidence of Grade 3 or 4 values ≥10% except for hematology parameters.
- Thrombocytopenia, neutropenia, lymphopenia, leukopenia, and anemia were listed in a separate hematology laboratory table based on hematology laboratory parameters regardless of the incidence and difference between groups (Table 22, Table 24).

Consistent with previous daratumumab submissions, some AE terms represent a grouping of MedDRA preferred terms to more accurately reflect the incidence of ADRs.

Based on biological plausibility, injection-site reactions were identified as a new ADR for daratumumab SC that had not been previously observed with daratumumab IV. In the randomized monotherapy Study MMY3012, the incidence of injection-site reaction was 6.9%, which did not meet the 10% threshold for inclusion in the ADR frequency table for this study (Table 21). In the combination therapy Study MMY2040, injection-site reaction was reported in 6.0% of subjects in the D-VMP cohort, 3.1% of subjects in the D-Rd cohort, and 13.4% of subjects in the D-VRd cohort. The preferred term, injection site erythema, a specific injection- site reaction term, also met the 10% threshold for inclusion in the ADR frequency table for this study. Based on the 10% threshold, the following new ADRs were identified for daratumumab SC that had not been previously observed with daratumumab IV in Study MMY2040: pruritus, rash, and insomnia (Table 23).

Table 21: Adverse Drug Reactions (≥ 10% in Any Treatment Group) in Study MMY3012

Body System/Preferred Term	Daratumumab IV			Daratumumab SC		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Analysis set: safety	258			260		
Infusion reactions[a]	89 (34.5%)	14 (5.4%)	0	33 (12.7%)	4 (1.5%)	0
Gastrointestinal disorders						
Diarrhoea	28 (10.9%)	1 (0.4%)	0	39 (15.0%)	2 (0.8%)	0
Nausea	28 (10.9%)	1 (0.4%)	0	21 (8.1%)	1 (0.4%)	0
General disorders and administration site conditions						
Pyrexia	33 (12.8%)	2 (0.8%)	0	34 (13.1%)	0	0
Fatigue	27 (10.5%)	2 (0.8%)	0	28 (10.8%)	2 (0.8%)	0
Chills	32 (12.4%)	2 (0.8%)	0	15 (5.8%)	1 (0.4%)	0
Infections and infestations						
Upper respiratory tract infection[b]	56 (21.7%)	3 (1.2%)	0	63 (24.2%)	2 (0.8%)	0
Musculoskeletal and connective tissue disorders						
Back pain	32 (12.4%)	7 (2.7%)	0	27 (10.4%)	4 (1.5%)	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	37 (14.3%)	0	0	23 (8.8%)	2 (0.8%)	0
Dyspnoea[d]	28 (10.9%)	2 (0.8%)	0	15 (5.8%)	2 (0.8%)	0

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

[a] Includes terms determined by investigators to be related to infusion.

[b] Acute sinusitis, Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection

[c] Cough, Productive cough

[d] Dyspnoea, Dyspnoea exertional

Adverse events are reported using MedDRA version 21.1.

Percentages are calculated with the number of safety subjects in each treatment arm as denominators.

Modified from Mod5.3.5.3/ISS/AttTSFAE40_SCS_3012

Table 22: Treatment-emergent Hematology Laboratory Abnormalities; Safety Analysis Set (Study MMY3012)

	Daratumumab IV			Daratumumab SC		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Analysis set: safety	258			260		
Anemia	100 (38.8%)	41 (15.9%)	0	110 (42.3%)	37 (14.2%)	0
Thrombocytopenia	116 (45.0%)	19 (7.4%)	17 (6.6%)	112 (43.1%)	32 (12.3%)	10 (3.8%)
Leukopenia	147 (57.0%)	29 (11.2%)	6 (2.3%)	170 (65.4%)	47 (18.1%)	2 (0.8%)
Neutropenia	112 (43.4%)	20 (7.8%)	9 (3.5%)	144 (55.4%)	43 (16.5%)	7 (2.7%)
Lymphopenia	144 (55.8%)	70 (27.1%)	23 (8.9%)	153 (58.8%)	72 (27.7%)	21 (8.1%)

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

Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. For each parameter, the percentage of subjects represents those subjects for whom the toxicity grade worsened during treatment compared to baseline; percentages are calculated with the number of safety subjects in each treatment arm. For each subject and each parameter, the worst toxicity grade is selected.

Modified from Mod5.3.5.3/ISS/AttTSFLAB04_SCS_3012

Table 23: Adverse Drug Reactions (≥ 10% in Any Treatment Group) in Study MMY2040

	D-VRd		D-VMP		D-Rd	
Body System/Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Analysis set: safety	67		67		65	
Gastrointestinal disorders						
Constipation	26 (38.8%)	0	23 (34.3%)	0	15 (23.1%)	1 (1.5%)
Diarrhoea	16 (23.9%)	1 (1.5%)	20 (29.9%)	2 (3.0%)	23 (35.4%)	2 (3.1%)
Nausea	12 (17.9%)	1 (1.5%)	24 (35.8%)	0	7 (10.8%)	0
Vomiting	8 (11.9%)	1 (1.5%)	14 (20.9%)	0	5 (7.7%)	0
General disorders and administration site conditions						
Pyrexia	24 (35.8%)	1 (1.5%)	22 (32.8%)	0	14 (21.5%)	1 (1.5%)
Fatigue	19 (28.4%)	3 (4.5%)	9 (13.4%)	0	16 (24.6%)	1 (1.5%)
Oedema peripheral[a]	13 (19.4%)	0	9 (13.4%)	1 (1.5%)	5 (7.7%)	0
Asthenia	10 (14.9%)	0	15 (22.4%)	1 (1.5%)	17 (26.2%)	1 (1.5%)
Injection site erythema	9 (13.4%)	0	5 (7.5%)	0	0	0
Chills	8 (11.9%)	0	3 (4.5%)	0	3 (4.6%)	0
Infections and infestations						
Upper respiratory tract infection[b]	9 (13.4%)	0	21 (31.3%)	0	23 (35.4%)	2 (3.1%)
Pneumonia[c]	4 (6.0%)	2 (3.0%)	6 (9.0%)	3 (4.5%)	7 (10.8%)	5 (7.7%)
Bronchitis[d]	2 (3.0%)	0	8 (11.9%)	0	9 (13.8%)	1 (1.5%)
Metabolism and nutrition disorders						
Decreased appetite	2 (3.0%)	0	10 (14.9%)	1 (1.5%)	4 (6.2%)	0
Hyperglycaemia	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	7 (10.8%)	4 (6.2%)
Musculoskeletal and connective tissue disorders						
Back pain	7 (10.4%)	0	13 (19.4%)	2 (3.0%)	8 (12.3%)	0
Muscle spasms	4 (6.0%)	0	1 (1.5%)	0	18 (27.7%)	1 (1.5%)
Nervous system disorders						
Peripheral sensory neuropathy	28 (41.8%)	2 (3.0%)	23 (34.3%)	1 (1.5%)	9 (13.8%)	1 (1.5%)
Headache	7 (10.4%)	0	4 (6.0%)	0	4 (6.2%)	0
Psychiatric disorders						
Insomnia	12 (17.9%)	0	13 (19.4%)	0	10 (15.4%)	3 (4.6%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea[e]	11 (16.4%)	1 (1.5%)	3 (4.5%)	0	13 (20.0%)	2 (3.1%)
Cough[f]	5 (7.5%)	0	13 (19.4%)	0	7 (10.8%)	0
Skin and subcutaneous tissue disorders						
Rash	9 (13.4%)	0	8 (11.9%)	0	5 (7.7%)	0
Pruritus	4 (6.0%)	1 (1.5%)	7 (10.4%)	0	2 (3.1%)	0
Vascular disorders						
Hypertension	1 (1.5%)	1 (1.5%)	9 (13.4%)	4 (6.0%)	1 (1.5%)	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.

[a] Oedema, Oedema peripheral, Peripheral swelling

[b] Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral pharyngitis

[c] Lung infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial

[d] Bronchitis, Bronchitis viral

[e] Dyspnoea, Dyspnoea exertional

[f] Cough, Productive cough

Adverse events are reported using MedDRA version 21.1.

Percentages are calculated with the number of safety subjects in each treatment arm as denominators.

Table 24: Treatment-emergent Hematology Laboratory Abnormalities; Safety Analysis Set (Study 54767414MMY2040)

	D-VRd			D-VMP			D-Rd		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Analysis set: safety	67			67			65		
Anemia	25 (37.3%)	3 (4.5%)	0	30 (44.8%)	11 (16.4%)	0	27 (41.5%)	4 (6.2%)	0
Thrombocytopenia	50 (74.6%)	7 (10.4%)	3 (4.5%)	62 (92.5%)	16 (23.9%)	9 (13.4%)	56 (86.2%)	4 (6.2%)	2 (3.1%)
Leukopenia	56 (83.6%)	15 (22.4%)	2 (3.0%)	63 (94.0%)	21 (31.3%)	10 (14.9%)	61 (93.8%)	15 (23.1%)	7 (10.8%)
Neutropenia	45 (67.2%)	18 (26 9%)	3 (4.5%)	57 (85.1%)	18 (26.9%)	10 (14.9%)	59 (90.8%)	24 (36.9%)	11 (16.9%)
Lymphopenia	60 (89.6%)	27 (40.3%)	8 (11.9%)	61 (91.0%)	42 (62.7%)	13 (19.4%)	52 (80.0%)	29 (44.6%)	9 (13.8%)

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

Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. For each parameter, the percentage of subjects represents those subjects for whom the toxicity grade worsened during treatment compared to baseline; percentages are calculated with the number of safety subjects in each treatment arm. For each subject and each parameter, the worst toxicity grade is selected.

[TSFLAB04_SCS_2040.RTF] [JNJ-54767414\Z_SMPC\DBR_BLA_SUBQ_2019\RE_BLA_SUBQ_2019\PROD\TSFLAB04_SCS_2040.SAS] 10MAY2019, 18:06

The FDA's Assessment:
FDA agrees with the Applicant's assessment of TEAEs occurring in at least 10% of patients in either arm in MMY3012 in Table 15 with one exception: based on FDA preferred term grouping combining the terms fatigue and asthenia under "fatigue", the percentages of patients with fatigue were 14.6% in the daratumumab SC arm and 15.5% in the daratumumab IV arm. FDA also agrees with the Applicant's assessment and presentation of cytopenias in MMY3012 in Table 16 based on laboratory abnormalities as these events are generally under-reported in adverse event datasets.

The overall incidence of TEAEs was similar between arms in MMY3012 (87.7% in the daratumumab SC arm versus 89.1% in the daratumumab IV arm). The rates of neutropenia were higher in the daratumumab SC arm compared to the daratumumab IV arm (55% vs. 43% based on laboratory shift analysis, 19% vs. 14% based on TEAEs of all grades, and 13% vs. 8% based on Grade 3-4 TEAEs).

All patients in the D-VMP and D-Rd cohorts in MMY2040 had at least one TEAE. FDA agrees with the Applicant's assessment of TEAEs occurring in at least 10% of patients in the D-VMP and D-Rd cohorts in MMY2040 shown in Table 17 with the exception of the incidences of fatigue. FDA analysis combining the preferred terms fatigue and asthenia under "fatigue" showed the incidence of fatigue was 34.3% % in the D-VMP cohort and 49.2% in the D-Rd cohort. FDA agrees that pruritis, rash and insomnia were not previously observed in ≥10% of patients treated with daratumumab IV in the ACYCLONE and POLLUX trials. FDA agrees with the Applicant's assessment of cytopenias in MMY2040 in Table 18.

FDA's analysis of infusion reactions and injection site reactions is discussed in Section 8.2.5 below. Injection site reactions are a new, but not unexpected adverse reaction associated with daratumumab SC.

Laboratory Findings

The Applicant's Position:
Hematology
In the randomized monotherapy Study MMY3012, the worst toxicity grades observed during treatment for hematology parameters were balanced between treatment groups except for a higher incidence of Grade 3 toxicity for neutrophils in the daratumumab SC group (daratumumab SC: 17.4%; daratumumab IV: 8.4%) (MMY3012 CSR, Section 8.2.1.1.1), which was consistent with TEAEs reporting for neutropenia. Hematology laboratory results for the Pooled Monotherapy Safety analysis set were highly consistent with those reported for Study MMY3012 alone (Mod2.7.4/Sec3.1.1). In the combination therapy Study MMY2040, the pattern of hematology laboratory abnormalities across the cohorts in Study MMY2040 was consistent with the reported distribution of cytopenia TEAEs for this study. Results for the comparisons to historical safety data for hematology laboratory abnormalities (Mod2.7.4/Sec3.1.2) were as follows:

D-VMP: A similar proportion of subjects in Studies MMY2040 and MMY3007 had a worst toxicity of Grade 3 for neutrophil decrease (26.9% and 29.3%, respectively), hemoglobin decrease (16.4% and 17.7%, respectively), white blood cell decrease (28.4% and 31.9%, respectively), and platelet decrease (23.9% and 22.0%, respectively), while the proportion with a worst toxicity Grade 3 for lymphocyte decrease was higher in Study MMY2040 than in Study MMY3007 (59.7% and 42.3%, respectively). While the proportion of subjects with a worst toxicity of Grade 4 were low, rates were higher for Study MMY2040 than for Study MMY3007 for white blood cell decrease (14.9% and 5.2%, respectively), platelet decrease (13.4% and 8.1%, respectively), and lymphocyte decrease (19.4% and 10.4%, respectively).

D-Rd: A similar proportion of subjects in Studies MMY2040 and MMY3003 had a worst toxicity of Grade 3 for neutrophil decrease (35.4% and 34.0%, respectively), hemoglobin decrease (6.2% and 11.0%, respectively), platelet decrease (4.6% and 7.8%, respectively), and lymphocyte decrease (44.6% and 41.1%, respectively), while the proportion with a worst toxicity Grade 3 for white blood cell decrease was lower in Study MMY2040 than in Study MMY3003 (23.1% and 34.0%, respectively). The incidence of a worst toxicity of Grade 4 decrease for each hematology parameter was similar in Study MMY2040 and Study MMY3003.

Clinical Chemistry

In the randomized monotherapy Study MMY3012, Grade 3 or 4 abnormal chemistry values were uncommon for daratumumab SC and daratumumab IV, with only Grade 3 low sodium (6.7% vs 4.9%, respectively) and Grade 3 high glucose (5.1% vs 3.7%, respectively) having incidence ≥5% in either group (Mod5.3.5.1/MMY3012/Tab38). The worst toxicity grades for biochemistry laboratory parameters observed during monotherapy treatment in the Pooled Monotherapy Safety analysis set were highly consistent with those reported for Study MMY3012 alone (Mod2.7.4/Sec3.2.1). No subject in the pooled daratumumab SC group had treatment-emergent, Grade 4 elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin. Results for hepatic laboratory parameters were consistent with those observed for the daratumumab IV group in Study MMY3012. No subject in Study MMY3012 met the criteria for drug-induced liver injury.

Biochemistry laboratory value shifts from baseline to worst postbaseline severity of Grade 3 or 4 were rare (<10% of subjects) in both treatment groups.

In the combination therapy Study MMY2040, treatment-emergent Grade 3 or 4 biochemistry laboratory abnormalities were infrequent (<5%) in all treatment cohorts except for Grade 3 low sodium and Grade 3 high creatinine in the D-VMP cohort (11.9% and 6.0%, respectively) (Mod2.7.4/Sec3.2.2). 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.

The FDA's Assessment:

FDA agrees that the worst toxicity grades observed during treatment in MMY3012 for

hematology parameters were balanced between treatment groups for decreased lymphocytes, decreased platelets, and decreased hemoglobin. There were differences in the incidence of decreased leukocytes between arms (65% in daratumumab SC vs. 57% in daratumumab IV for all grades and 19% vs. 14% for Grades 3-4) and decreased neutrophils between arms (55% for daratumumab SC vs. 43% for daratumumab IV for all grades, and 19% vs. 11% for Grades 3-4). The differences in rates of neutropenia, including severe (Grade 3-4) neutropenia between daratumumab SC and daratumumab IV, which were also reflected in the captured rates of neutropenia in the AE dataset, are discussed further in Section 8.2.5 below.

FDA reviewed but did not independently confirm the laboratory results in the pooled SC monotherapy analysis set or the clinical chemistry lab shift data. FDA agrees with the Applicant's assessment of the clinical chemistry data presented above. Given the longer duration of follow-up represented in the 4-month Safety Update (4MSU) for MMY2040, FDA reviewed the hematology lab shift data from the update and recommended the updated data be included in the USPI.

FDA does not agree with the Applicant's use of historical data to assess the relative incidence of hematology laboratory abnormalities for daratumumab SC vs. daratumumab IV combination therapies given the limitations of cross trial comparisons.

Vital Signs

The Applicant's Position:
A review of vital sign data in subjects treated with daratumumab SC either as monotherapy in Study MMY3012 or in combination with standard background therapies for multiple myeloma in Study MMY2040 did not identify any safety signal (Mod5.3.5.1/MMY3012/Sec8.2.2; Mod5.3.5.2/MMY2040/Sec7.2.2).

The FDA's Assessment:
FDA agrees with the Applicant's assessment that no safety signals were identified based on vital sign data in MMY3012. FDA did not independently confirm the vital sign findings for MMY2040. FDA findings from MMY3012 are as follows:

- Potentially clinically significant post-baseline systolic blood pressure (SBP) elevations, defined as SBP ≥ 160 mmHg, were observed in 46 (17.7%) patients on the daratumumab SC arm and 68 (26.4%) patients on the daratumumab IV arm. Potentially clinically significant post-baseline diastolic blood pressure (DBP) increases, defined as DBP ≥100 mmHg, were observed in 15 (5.8%) patients on the daratumumab SC arm and 28 (10.9%) patients on the daratumumab IV arm. Hypertension was reported as an adverse event in 13 (5%) patients on the daratumumab SC arm and 22 (8.5%) patients on the daratumumab IV arm. Grade 3 hypertension was reported in 8 (3.1%) patients on the daratumumab SC arm and 16 (6.2%) patients on the daratumumab IV arm.
- Potentially clinically significant post-baseline SBP decreases, defined as SBP < 90 mmHg, were observed in 16 (6.2%) patients on the daratumumab SC arm and 23 (8.9%) patients on

the daratumumab IV arm. Hypotension reported as an adverse event in 5 (1.9%) patients on the daratumumab SC arm and 10 (3.9%) patients on the daratumumab IV arm. Grade 3 hypotension was reported in 1 (0.4%) patient on the daratumumab SC arm and 1 (0.4%) patient on the daratumumab IV arm.

- Potentially clinically significant post-baseline heart rate (HR) increases, defined as HR >120 bpm, were observed in 9 (3.5%) patients on the daratumumab SC arm and 8 (3.1%) patients on the daratumumab IV arm.
- Potentially clinically significant post-baseline heart rate (HR) decreases, defined as HR <50 bpm, were observed in 7 (2.7%) patients on the daratumumab SC arm and 12 (4.7%) patients on the daratumumab IV arm.

Electrocardiograms (ECGs)

The Applicant's Position:
No clinically relevant ECG abnormalities were reported among the 4 studies.

The FDA's Assessment:
The FDA Clinical Pharmacology review team assessed the ECG data for this study and stated that "FDA concurs with the Applicant's position that daratumumab IV has no clinically meaningful effect on electrocardiographic (ECG) parameters; therefore, it is acceptable to not perform additional QT analyses for daratumumab SC 1800 mg as the range of concentrations for daratumumab SC 1800 mg was within that observed previously for daratumumab IV 16 mg/kg."

QT

The Applicant's Position:
Immunoglobulin G1 (IgG1) antibodies are too large to directly access the human Ether-à-go-go-Related Gene (hERG) potassium channel and cause QT prolongation. Daratumumab is not expected to affect cardiovascular function. There was no increase in cardiovascular toxicities in randomized clinical trials.

The FDA's Assessment:
Refer to the FDA assessment under ECG.

Immunogenicity

The Applicant's Position:
The incidence of anti-daratumumab antibodies was low across the pooled immunogenicity-evaluable populations from all 4 studies included in this submission: 0.2% (1/426) in the overall pooled SC treatment group (Studies MMY1004 Part 2, MMY1009, MMY3012 SC group, and MMY2040), 0.4% (1/236) in the pooled SC monotherapy group (Studies MMY3012 SC group, MMY1004 Part 2 and MMY1008) and 0.5% (1/204) in the IV group (Study MMY3012 IV group).

Only 1 subject was positive for neutralizing antibodies in the pooled monotherapy daratumumab SC group (n=236), and none in the pooled SC combination therapy group (n=190) and daratumumab IV group (n=204) (Mod2.7.2/Table 26).

Daratumumab exposure was comparable between antibody negative subjects and those with anti-daratumumab antibodies or neutralizing antibodies.(Mod2.7.2/Sec4.1).

At the time of the clinical data cutoff, 27 of 420 subjects (6.4%) evaluable for immunogenicity were positive for anti-rHuPH20 antibodies: 16 subjects in the monotherapy group and 11 subjects in the combination therapy group (Mod2.7.2/Table 27). There were several subjects with treatment-emergent peak titers of 5 (N=16), 10 (N=4), 20 (N=3), and 80 (N=2); and 1 subject each with a peak titer of 320 and 2560. None of the anti-rHuPH20 antibodies were classified as neutralizing. The incidence of baseline and treatment-emergent anti-rHuPH20 antibodies was low and 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. (Mod2.7.2/Sec4.2).

The FDA's Assessment:
FDA's assessment of immunogenicity performed by the Clinical Pharmacology review team is discussed in Section 6.2.1.

8.2.5 Analysis of Submission Specific Safety Issues

The Applicant's Position:
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. Although a higher incidence of neutropenia was noted following daratumumab SC monotherapy, particularly among subjects with a low body weight (i.e., ≤65 kg), this was not associated with clinically meaningful safety sequelae. Relative to historical data, an increase in neutropenia was not observed among low body weight subjects when daratumumab SC was administered in combination with VMP or Rd. No new clinically relevant safety concerns were identified for daratumumab SC given as monotherapy or in combination with standard background therapies, and daratumumab SC was associated with a lower rate of IRRs compared to daratumumab IV.

Infusion-related Reactions

The proportion of subjects with an IRR (a key secondary study endpoint for Study MMY3012) with daratumumab SC monotherapy was significantly lower in the daratumumab SC group (12.7%) compared with the daratumumab IV group (34.5%) (odds ratio=0.28 [95% confidence interval: 0.18, 0.44]; p<0.0001). Most IRRs occurred following the first injection and were Grade 1 or 2. No Grade 4 or 5 IRRs were reported, and no IRRs in the daratumumab SC group led to treatment discontinuation, dose interruption, or incomplete administration of a dose.

The FDA's Assessment:
IRRs are more accurately classified as systemic administration-related reactions because daratumumab SC is injected rather than infused. However, in the pivotal trial, AEs deemed by the investigator as being part of an administration-related systemic reaction were captured as an IRR regardless of the route of administration. FDA agrees with the Applicant's assessment of the overall incidence of IRRs in MMY3012 and conclusion that the rates are lower in the daratumumab SC arm. In FDA's analysis of the pooled SC monotherapy population (N=490), 10.6% of patients had an IRR, including 4.5% with a Grade 2 reaction, and 1.4% with a Grade 3 reaction. Reactions to the first injection occurred in 10.2% of patients, reactions to the second injection occurred in 0.2% of patients, and reactions to subsequent injections occurred in 0.8% of patients. The median time to onset was 3.7 hours (range 9 minutes to 3.5 days). The majority (87%) of reactions that occurred happened within 24 hours of administration, and delayed reactions (beyond 24 hours) occurred in 0.4% of patients. FDA agrees with the applicant's assessment that most IRRs were Grade 1 or 2, no Grade 4 or 5 IRRs were reported, and no IRRs led to dose modifications. Systemic administration-related reactions will be included in the Warnings and Precautions section of the USPI with recommendations for management and pre-medications and post-medications.

Local Injection-site Reactions

In monotherapy Study MMY3012, the incidence of injection-site reactions with daratumumab SC was low (6.9%). All injection-site reactions were Grade 1 or 2 and did not lead to treatment discontinuation. In Study MMY2040, injection-site reactions were reported in 6.0% of subjects in the D-VMP cohort, 3.1% of subjects in the D-Rd cohort, and 13.4% of subjects in the D-VRd cohort (Mod5.3.5.2/MMY2040/Tab33).

The FDA's Assessment:
Localized reactions at the site of daratumumab SC administration were captured as injection-site reactions. FDA agrees with the Applicant's assessment of the frequency of injection-site reactions in MMY3012 and MMY2040. Additional FDA analysis of the Pooled SC monotherapy population (N=490), showed an overall incidence of 8%, with the majority of reactions being Grade 1 in severity. Grade 2 reactions occurred in 0.6% of patients. The median time to onset based on available data (there was a substantial amount of missing data for the timing of onset in MMY2040), was 5 minutes (range 0 minutes to 4.7 days). FDA analysis of the AEs characterized as injection-site reactions is shown in Table 25.

Table 25: Injection-Site Reactions in Pooled SC monotherapy Population (N=490)

Preferred Term*	Grade 1	Grade 2	All Grades
Injection site bruising	5	0	1%
Injection site discoloration	1	0	0.2%
Injection site erythema	19	1	4.1%

Injection site hematoma	3	0	0.6%
Injection site hemorrhage	4	0	0.8%
Injection site induration	3	0	0.6%
Injection site pain	1	0	0.2%
Injection site pruritus	2	1	0.6%
Injection site rash	4	0	0.8%
Injection site swelling	1	0	0.2%
Injection site urticaria	0	1	0.2%

*Grouped terms: injection site erythema + erythema; injection site hematoma + hematoma + subcutaneous hematoma; injection site bruising + ecchymosis + contusion; injection site rash + rash; injection site hemorrhage + hemorrhage subcutaneous.
Source: FDA reviewer's independent analysis

FDA agrees with the Applicant's assessment that the frequency of injection-site reactions was low, and that all reactions were Grade 1 or 2 and did not result in permanent discontinuation. Injection-site reactions will be included in the Warnings and Precautions section because they are unique to daratumumab SC.

Cytopenia Adverse Events

In the monotherapy Study MMY3012, neutropenia was the only Grade 3 or 4 cytopenia TEAEs reported at ≥5% higher incidence in the daratumumab SC group (daratumumab SC, 13.1%; daratumumab IV, 7.8%). One Grade 5 event of febrile neutropenia was reported (in the daratumumab SC group). In both treatment groups, neutropenia was rarely reported as serious (daratumumab SC, 0%; daratumumab IV, 0.4%) or as the reason for treatment discontinuation (daratumumab SC, 0%; daratumumab IV, 0.4%) or daratumumab treatment modification (daratumumab SC, 1.9%; daratumumab IV, 3.5%), and hematopoietic growth factor use was comparable in the 2 groups (daratumumab SC, 10.4%; daratumumab IV, 11.2%). The higher incidence of neutropenia in the daratumumab SC group was not associated with a higher incidence of TEAEs in the SOC of infections and infestations (all grade: daratumumab SC, 45.8%; daratumumab IV, 45.3%. Grade 3 or 4: daratumumab SC, 10.4%; daratumumab IV, 11.2%). Grade 3 or 4 cytopenia TEAEs of anemia, lymphopenia, and thrombocytopenia were balanced between treatment groups (<5% difference in incidence).

In the combination therapy Study MMY2040, Grade 3 or 4 neutropenia was reported as a TEAE in 31.3%, 47.7%, and 28.4% of subjects in the D-VMP, D-Rd, and D-VRd cohorts, respectively (Mod2.7.4/Sec2.4.3.1.2). Febrile neutropenia was reported at a low rate in all 3 daratumumab SC cohorts (3.1% to 4.5%), and no subject had study treatment discontinued as a result of this TEAE. In comparison to historical safety data for D-VMP in Study MMY3007 and D-Rd in Study MMY3003 up to Month 6, the incidence of Grade 3 or 4 neutropenia TEAEs (D-VMP, 35.0%; D-

Rd, 48.4%) was similar for daratumumab SC and daratumumab IV. Neutropenia did not lead to treatment discontinuation for the daratumumab SC or daratumumab IV combination cohorts in these studies.

The FDA's Assessment:
FDA agrees with the Applicant's assessment that the rates of cytopenias were balanced between arms in MMY3012, except for neutropenia. In addition to a 5.3% higher incidence of severe (Grade 3-4) neutropenia in the daratumumab SC arm compared to the daratumumab IV arm, there was a 5.6% higher incidence in neutropenia of all grades (19.2% for daratumumab SC vs. 13.6% for daratumumab IV). Furthermore, given that TEAE reporting commonly results in an underrepresentation of laboratory abnormalities, FDA notes that the incidence of neutropenia of any grade based on laboratory shift analysis was 55% vs. 43% (daratumumab SC vs. daratumumab IV), and the incidence of Grade 3-4 neutropenia was 19% vs. 11% (daratumumab SC vs. daratumumab IV).

FDA agrees with the Applicant's assessment of the rates and outcomes of neutropenia and febrile neutropenia reported as TEAEs in MMY2040.

Infections and Infestations

In the randomized monotherapy Study MMY3012, infection and infestation TEAEs were reported at similar overall rates for the daratumumab SC (45.8%) and daratumumab IV (45.3%) groups. The incidence of Grade 3 or 4 TEAEs was similar for the daratumumab SC (10.4%) and daratumumab IV (11.2%) groups. Pneumonia was the only Grade 3 or 4 infection TEAE reported in ≥2% of subjects in the daratumumab SC (2.7%) or daratumumab IV (3.9%) groups. 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 group and 10/117 subjects in the daratumumab IV group). Most infections were manageable and rarely led to treatment discontinuation (daratumumab SC, 1.2%; daratumumab IV, 3.5%). The overall frequency of infection TEAEs among subject treated with daratumumab SC for the Pooled Monotherapy Safety analysis set was also similar to that for the daratumumab IV treatment group of Study MMY3012.

In the combination therapy Study MMY2040, the overall incidence of Grade 3 or 4 infection and infestation TEAEs in each cohort was low: D-VMP, 11.9%; D-Rd, 23.1%; D-VRd, 7.5%. The most common infection or infestation in each cohort was pneumonia (4.5%, 6.2%, and 3.0%, respectively). Treatment was discontinued for an infection or infestation for 2 subjects each in the D-VMP and D-Rd cohorts, and no subject in the D-VRd cohort. In comparison to historical safety data for D-VMP in Study MMY3007, the incidences were lower for daratumumab SC than for daratumumab IV for Grade 3 or 4 infection or infestation TEAEs (10.4% vs 16.2%) and for Grade 3 or 4 pneumonia (3.0% vs 7.8%). In comparison to historical safety data for D-Rd in Study MMY3003 up to Month 6, the incidences for Grade 3 or 4 infection or infestation TEAEs and for

Grade 3 or 4 pneumonia were similar for daratumumab SC and daratumumab IV.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the overall rates of TEAEs, severe (Grade 3-4) TEAEs, fatal TEAEs, and TEAEs leading to treatment discontinuation within the Infections and Infestations system organ class. FDA agrees that pneumonia was the only TEAE that had an incidence ≥2% in either arm; however, FDA analysis based on grouping of related preferred terms showed the incidence of pneumonia as 5.4% vs. 5.0% (daratumumab SC vs. daratumumab IV). FDA analysis using grouped related terms and infections of all grades showed that only pneumonia (8.1% for daratumumab SC vs. 10.5% for daratumumab IV) and upper respiratory tract infections (22.7% for daratumumab SC vs. 20.2% for daratumumab IV) occurred in ≥5% of patients. FDA did not independently confirm rates of infection TEAEs in the pooled SC monotherapy population.

FDA agrees with the Applicant's assessment of the incidence of Grade 3-4 infections and the numbers of patients discontinuing treatment due to an infection. FDA analysis showed that, overall, an infection of any grade occurred in 72.3% of patients in the D-Rd cohort and 68.7% of patients in the D-VMP cohort. FDA analysis using grouping of related preferred terms showed an incidence of Grade 3-4 pneumonia of 9.2% (higher than reported by the Applicant above) in the DR-d cohort and 4.5% in the D-VMP cohort (consistent with Applicant's analysis). Additional FDA analysis of infections of all grades showed that the following TEAEs occurred with an incidence ≥5% in either cohort: bronchitis (D-Rd: 13.8%, D-VMP: 11.9%), herpes zoster (D-Rd: 1.5%, D-VMP: 7.5%), pneumonia (D-Rd: 12.3%, D-VMP: 9%), upper respiratory tract infection (D-Rd: 35.4%, D-VMP: 31.3%), and urinary tract infection (D-Rd: 6.2%, D-VMP: 7.5%). FDA does not agree with the Applicant's use of historical data to assess the relative incidence of serious TEAEs with daratumumab SC versus daratumumab IV combination therapies given the limitations of cross trial comparisons.

Second Primary Malignancies

In the randomized monotherapy Study MMY3012, the incidence of second primary malignancy was low and equal (1.2%) for the daratumumab SC and daratumumab IV groups. No events of second primary malignancy in this study were hematologic in nature and no single malignancy predominated. The incidence of second primary malignancy with daratumumab SC in the Pooled Monotherapy Safety analysis set (1.4%) was also similar to that reported for daratumumab IV in Study MMY3012. In the combination therapy Study MMY2040, 1 subject (in the D-Rd cohort) had a second primary malignancy of melanoma to the chin, which resolved following surgery.

Tumor Lysis Syndrome

No cases of TLS were reported in subjects exposed to daratumumab SC in Studies MMY3012, MMY1008, MMY1004 (Part 2), or MMY2040.

Intravascular Hemolysis

No cases of intravascular hemolysis were reported in subjects exposed to daratumumab SC in Studies MMY3012, MMY1008, MMY1004 (Part 2), or MMY2040.

Treatment-emergent Interferences for Blood Typing

No subject exposed to daratumumab SC had treatment-emergent interference for blood typing reported in Studies MMY3012, MMY1008, MMY1004 (Part 2), or MMY2040.

The FDA's Assessment:
FDA agrees with the Applicant's assessments regarding second primary malignancies, tumor lysis syndrome, intravascular hemolysis, and interferences for blood typing.

8.2.6 Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Applicant's Position:
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. No new clinically relevant safety concerns were identified for daratumumab SC given as monotherapy or in combination with standard background therapies, and daratumumab SC was associated with a lower rate of IRRs compared to daratumumab IV. Although a higher incidence of neutropenia was noted following daratumumab SC monotherapy, particularly among subjects with a low body weight (i.e., ≤65 kg), this was not associated with clinically meaningful safety sequelae. Relative to historical data, an increase in neutropenia was not observed among low body weight subjects when daratumumab SC was administered in combination with VMP or Rd. Further, in Study 3012, there were 2 items of the modified-CTSQ that assessed subject perception of tolerability:

1. When subjects were asked: "How often did you feel that cancer therapy was worth taking even with the side effects", mean values were consistent over time for daratumumab SC and daratumumab IV treatment groups, and ranged between 4 (most of the time) and 5 (always) (Attachment TPROCHG02).
2. When subjects were asked "Were side effects of cancer therapy as you expected", subjects in the daratumumab SC group responded more positively through Cycle 10 (Attachment TPROCHG07).

Together with the data summarized in the Summary of Clinical Efficacy (Mod2.7.3), these results support a positive benefit/risk assessment for daratumumab SC for the treatment of multiple myeloma.

The FDA's Assessment:
FDA does not agree with the Applicant's statement that no new clinically relevant safety concerns were identified for daratumumab SC. Injection-site reactions were a new safety

concern for daratumumab SC consistent with the route of administration. Although the higher incidence of neutropenia observed with daratumumab SC did not appear to result in a higher incidence of infections, neutropenia, especially, severe (Grade 3-4) neutropenia is a concern due to the increased risk it poses for infection.

Regarding the Applicant's assessment of patient perception of tolerability using the 2 items from the modified-CTSQ, this COA analysis was not pre-specified in the statistical analysis plan or in terms of the statistical testing hierarchy and should be considered exploratory. The vague wording of the questions (i.e., the questions do not directly address patient preference) poses a challenge for the interpretation of the results in the context of this trial and patient population. In addition, the clinical meaningfulness of the threshold for mean change in scores for these items selected by the Applicant is unclear. Furthermore, the design of MMY3012 was not appropriate to evaluate patient preference (e.g., it did not include switching between products), and it was an open-label trial. Therefore, conclusions regarding patient preference and benefit-risk cannot be made based on the results of the modified-CTSQ instrument and FDA does not agree with the Applicant's statement in Section 8.1.4 that the results from the modified-CTSQ demonstrate that patients receiving daratumumab SC had a more positive perception of and greater satisfaction with their therapy compared with patients who received daratumumab IV.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:
Although a higher incidence of neutropenia was noted following daratumumab SC monotherapy, particularly among subjects with a low body weight (i.e., ≤65 kg), this was not associated with clinically meaningful safety sequelae.

The FDA's Assessment:
As detailed in the FDA Clinical Pharmacology review, there was a higher incidence of neutropenia , including Grade 3-4 neutropenia, in the daratumumab SC arm compared to the daratumumab IV arm in MMY3012. However, the number of patients in the low BW subgroup was too small to make a definitive conclusion regarding the risk of neutropenia in this subgroup. The FDA Clinical Pharmacology review team found that the range of daratumumab SC exposures (maximum C_{trough}) across subgroups based on body weight was within the range of exposures for daratumumab IV and concluded that the totality of data supports a flat dose of daratumumab 1800 mg SC across all body weight groups. However, given the increased incidence of neutropenia with daratumumab SC, and the incidence of neutropenia, including severe neutropenia, with daratumumab IV in the D-Pd regimen, the current data do not support approval of the D-Pd regimen for daratumumab SC.

In MMY3012, there was a higher incidence of neutropenia of all grades and severe (Grade 3-4) neutropenia in patients age 65 to <75 and patients age ≥75 in the daratumumab SC arm, compared to patients in the daratumumab IV arm, whereas rates of neutropenia between arms

was similar for patients age 18 to 64 (Table 26). However, the number of patients in the age ≥75 subgroup was too small to make any definitive conclusions about the safety of daratumumab SC in this subgroup. The numbers of patients age 65 and above in the D-VMP and D-Rd cohorts of MMY2040 were not sufficient to determine whether there were any differences in safety in this subgroup.

Table 26: Incidence of Neutropenia by Age in MMY3012

Age	Dara SC (All Grades) n (%)	Dara SC (Grades 3-4) n (%)	Dara IV (All Grades) n (%)	Dara IV (Grades 3-4) n (%)
18-64	21 (17.8)	14 (11.9)	17 (17.2)	7 (7.1)
65-74	17 (17.9)	12 (12.6)	12 (12)	8 (8)
75+	12 (25.5)	8 (17)	6 (10.2)	5 (8.5)

Source: FDA reviewer's independent analysis

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:
This section is not applicable.

The FDA's Assessment:
FDA agrees that this section is not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
No carcinogenicity or genotoxicity studies have been conducted with daratumumab.

The FDA's Assessment:
FDA concurs that no carcinogenicity or genotoxicity studies have been conducted.

Human Reproduction and Pregnancy

The Applicant's Position:
There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus. To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of daratumumab treatment.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The USPI will include a Warning and Precaution for embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
The safety and efficacy of daratumumab SC has not been established in pediatric patients.

The FDA's Assessment:
FDA agrees that no studies have been conducted in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There has been no experience of overdosage in clinical studies with daratumumab SC. Daratumumab SC is provided as a single vial for administration by a health care professional. Thus, the risk of overdose with daratumumab SC is negligible. There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

Daratumumab SC, like daratumumab IV, is administered in a controlled setting by healthcare providers. There is no known drug abuse potential with daratumumab. No clinical studies of the withdrawal or rebound effects of daratumumab have been conducted. Treatment is to be continued until disease progression.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
Daratumumab SC has not been authorized for use in any country worldwide. Postmarketing safety information is available for daratumumab IV and from a commercially available rHuPH20 formulation, Hylenex®. The following adverse reactions have been identified during post-approval use of daratumumab IV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Section 6.3 of the USPI will include anaphylactic reaction. Section 6.3 of the USPI will also include pancreatitis based on the addition of pancreatitis as a new adverse drug reaction for DARZALEX (sBLA 761036/S-027).

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
The surveillance of spontaneous cases of AEs reported with the use of daratumumab IV indicates that the safety profile of the drug in postmarketed use is consistent with what is known about the drugs overall established safety profile from clinical studies with daratumumab SC.

The FDA's Assessment:
FDA agrees with the Applicant that the safety profile of daratumumab SC in the postmarket setting is expected to be consistent with the safety profile of daratumumab SC observed in the pivotal and supportive clinical trials.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:
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 IV 16 mg/kg. Although a higher incidence of neutropenia was noted following daratumumab SC monotherapy, particularly among subjects with a low body weight (i.e., ≤65 kg), this was not associated with clinically meaningful safety sequelae. Relative to historical data, an increase in neutropenia was not observed among low body weight subjects when daratumumab SC was administered in combination with VMP or Rd. No new clinically relevant safety concerns were identified for daratumumab SC given as monotherapy or in combination with standard background therapies, and daratumumab SC was associated with a lower rate of IRRs compared to daratumumab IV.

The incidence of anti-daratumumab antibodies in all studies has been very low, and generally not associated with any impact on PK or safety. Further, the baseline and treatment-emergent incidences of anti-rHuPH20 antibodies were consistent with reported literature (Rosengren 2015; Rosengren 2018). Together with the data summarized in the Summary of Clinical Efficacy, these results support a positive benefit/risk assessment for daratumumab SC for the treatment of multiple myeloma.

The FDA's Assessment:
FDA does not agree with the Applicant's conclusion that an increase in neutropenia was not observed among patients with low BW in MMY2040 because the number of patients in the low BW subgroups in the D-Rd and D-VMP cohorts was too small to draw any conclusions. FDA also does not agree with the Applicant's assessment that no new clinically relevant safety concerns

were identified for daratumumab SC. Injection-site reactions are a new and clinically relevant safety concern for daratumumab SC.

FDA's independent analysis of safety has been presented above in Sections 8.2.4 and 8.2.5. A summary is presented below.

FDA's integrated assessment of the safety of daratumumab SC as monotherapy and in combination (D-Rd and D-VMP) focused primarily on the analysis of safety data from the pivotal study MMY3012, with supportive data from MMY2040.

Safety analyses of MMY3012 were based on a clinical database lock of 18 February 2019. The safety population for MMY3012 consisted of 518 patients with RRMM who received either daratumumab SC (N=260) or daratumumab IV (N=258). The incidence of fatal TEAEs (daratumumab SC: 5.4%, daratumumab IV: 6.6%) and serious TEAEs (daratumumab SC: 26.2%, daratumumab IV: 29.5%) was similar between arms. Pneumonia was the only serious TEAE that occurred in ≥2% of patients. TEAEs leading to permanent discontinuation of study treatment occurred in 6.9% of patients on the daratumumab SC arm and 8.1% of patients on the daratumumab IV arm. TEAEs leading to discontinuation of ≥1% of patients in either arm were: thrombocytopenia (daratumumab SC: 0.8%, daratumumab IV: 1.9%), anemia (0.8% vs. 1.2%), and septic shock (0.8% vs. 1.2%). Severe (Grade 3-4) TEAEs occurred in 45.4% of patients on the daratumumab SC arm and 48.8% of patients on the daratumumab IV arm. The incidence of specific Grade 3-4 TEAEs was similar between arms, except for neutropenia, which was higher in the daratumumab SC arm (13.1%) compared to the daratumumab IV arm (7.8%). The incidence of TEAEs was similar between arms in MMY3012 (daratumumab SC: 87.7%, daratumumab IV: 89.1%). The only TEAE with ≥20% incidence in the daratumumab SC arm was upper respiratory tract infection. Injection-site reactions were a new, important safety risk identified for daratumumab SC; however, the frequency of injection site reactions was low (6.9%) and all events were Grade 1-2 in severity.

Safety analyses of MMY2040 were based on a clinical database lock of 20 March 2019. The safety population for the D-Rd cohort of MMY2040 consisted of 65 patients with RRMM who received daratumumab SC in combination with lenalidomide and dexamethasone. The safety population for the D-VMP cohort of MMY2040 consisted of 67 patients with NDMM who were considered transplant-ineligible, who received daratumumab SC in combination with bortezomib, melphalan, and prednisone. Analyses were not presented for the D-VRd cohort as the Applicant did not request this indication and it is not an approved regimen for daratumumab IV. There were 2 fatal TEAEs (3%) in the D-VMP cohort (pneumonitis and neutropenic sepsis) and 1 (1.5%) in the D-Rd cohort (myocardial infarction). Serious TEAEs occurred in 37% of patients on the D-VMP arm and 40% of patients on the D-Rd arm. Pyrexia (7.5%) was the only serious TEAE that occurred in ≥5% of patients on the D-VMP arm. Serious TEAEs occurred in 40% of patients on the D-Rd arm. Pneumonia (6%) was the only serious TEAEs that occurred in ≥5% of patients on the D-VMP arm. Rates of treatment discontinuation due to TEAEs were low in both cohorts (D-VMP: 3%, D-Rd: 4.6%). Grade 3-4 TEAEs were reported for 68.7% of patients in the D-VMP cohort and 78.5% of

patients in the D-Rd cohort. Grade 3-4 TEAEs occurring in >10% of patients in the D-VMP cohort were: anemia (11.9%), lymphopenia (20.9%), neutropenia (31.3%), and thrombocytopenia (34.3%). The Grade 3-4 TEAEs occurring in >10% of patients in the D-Rd cohort were: lymphopenia (12.3%) and neutropenia (47.7%). The most common TEAEs (≥20%) with D-VMP were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain. The most common TEAEs (≥20%) with D-Rd were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia and dyspnea.

FDA notes that safety data with daratumumab SC is not available for the following indications requested by the Applicant:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- in combination with pomalidomide and dexamethasone (b) (4)

FDA considered the totality of evidence from the available safety and PK data from MMY3012 and MMY2040. For the D-Rd regimen in newly diagnosed patients who are ineligible for autologous stem cell transplant, additional safety data from the RRMM population is available from MMY2040. (b) (4)

Given the limited duration of follow-up for MMY2040 at the time the Applicant submitted the BLA, FDA recommended that the results from the 4-month Safety Update (4MSU) be included in the UPSI for the D-Rd and D-VMP regimens. For MMY3012, the 4MSU did not represent substantially increased exposure to daratumumab SC and daratumumab IV compared to the original submission. For MMY2040, the 4MSU represented approximately 4 additional months of exposure to the daratumumab SC-containing regimens. FDA reviewed the data from the 4MSU and determined that although there was an increase in the incidence of certain TEAEs, there was no change in the trend or overall safety profile, and the benefit-risk profile for the indications FDA is approving remains unchanged. For MMY3012, the original data will be included in the USPI and for MMY2040, the 4MSU data will be included in the USPI.

Routine risk minimization activities (i.e., risk communication through prescribing information, labeling, and packaging) are considered sufficient to manage the key risks associated with the use of daratumumab SC in the proposed indications for approval.

8.3 Summary and Conclusions

8.3.1 Statistical Issues

The FDA's Assessment:
The submitted clinical data from MMY3012 show that daratumumab SC was non-inferior to daratumumab IV based on the protocol pre-specified non-inferiority margin. The submitted clinical data from MMY2040 show that the two cohorts (D-VMP and D-Rd), for which the Applicant requested indications, met the protocol pre-specified hypotheses on their primary endpoints. The FDA reviewers verified the analyses results and conducted sensitivity and subgroup analyses to assess whether the results were robust, all of which were consistent with the prespecified analyses.

(b) (4)

There are no pending statistical issues.

8.3.2 Conclusions and Recommendations

The FDA's Assessment:
Based on the favorable benefit-risk profile of daratumumab SC, the clinical and statistical reviewers recommend approval of:

DARZALEX FASPRO for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

X Haiyan Chen, PhD	X Yu-te Wu, PhD
Primary Statistical Reviewer	Statistical Team Leader
X Andrea Baines, MD, PhD	X Bindu Kanapuru, MD
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Not applicable.

10 Pediatrics

The Applicant's Position:

Daratumumab is indicated for adults with multiple myeloma.

(b) (4)

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The Applicant's Position:
This is a new USPI for a new formulation of daratumumab. The Indications and Usage, Contraindications, and Drug Interactions sections of the daratumumab SC USPI are similar to the current daratumumab IV USPI. All other sections contain partially/completely new information.

The FDA's Assessment:
The table below summarizes changes to the proposed prescribing information (PI) made by the FDA. See the final approved prescribing information for DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use accompanying the approval letter for more information.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Full Prescribing Information		
Indications and Usage	(b) (4)	Removed the indications and usage for (b) (4)
Dosage and Administration, Recommended Dosage and Recommended Concomitant Medications	Included information about pre- and post-medications and route of administration in the same subsection of the recommended dosage. … Outlined pre- and post-medications to minimize the risk of hypersensitivity.	Created a separate subsection to identify important dosing information as recommended in the Dosage and Administration guidance, which states that in unusual circumstances, certain dosing-related information may be so important for practitioners that it should precede the basic dosing information ordinarily placed at the beginning of this section. (b) (4) Revised terminology from "infusion reactions" to "administration-related

		reactions" because hypersensitivity reactions were observed following the administration of this product and this product is administered as short injection.
Dosage and Administration, Preparation and Storage	… …	Added headings and reorganized based on feedback provided in the HF labeling comprehension study, in which participants stated that they overlooked the compatibility of the syringe material. Added information that the vial has a peel-off labeling that should be attached to the syringe after the product is withdrawn from the vial.
Warnings and Precautions, Infusion Reactions	Include a description of infusion reactions.	Revised terminology to administration-related reactions. Included injection site reactions, because adverse reactions that do not meet the definition of serious adverse reaction but are otherwise clinically significant because they have implications for prescribing decisions or patients management should also be included in Warnings and Precautions, as stated in the Guidance Document: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format
Warnings and Precautions, Neutropenia	…	Added the rates of neutropenia with low body weight because these patients had a higher grade 3-4 neutropenia.
Warnings and Precautions	…	Added Embryo-Fetal Toxicity, because DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density.
Clinical Trials Experience	Organized the information by study.	Reorganized the information by indications and usages. For the COLUMBA trial, used the safety data from July 2019 submission (b) (4)

	Included headings to describe infusion reactions, injection site reactions and herpes zoster reactivation across trials.	Described the incidence rates for these reactions for each individual trial or cohort with the description of the adverse reactions for a given trial or cohort.
Use in Specific Populations, Pregnancy	(b) (4)	Revised the risk summary statement and animal data, because DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density based on data from studies using CD38 knockout animal models. Added a reference to labeling for lenalidomide, since lenalidomide is contraindicated in pregnant women.
Use in Specific Populations, Lactation	…	Added a reference to labeling for lenalidomide, because of the potential for serious adverse reactions in breastfed child with lenalidomide.
Use in Specific Populations, Females and Males of Reproductive Potential	…	Added risk summary statement and reference to labeling for lenalidomide regarding pregnancy testing and contraception.
Use in Specific Populations, Geriatric Use	Included specific statements on geriatric use for DARZALEX FASPRO as a single agent.	Added specific statements on geriatric use for DARZALEX FASPRO as part of a combination therapy.
Clinical Pharmacology, Mechanism of Action	Included mechanism of action for daratumumab.	Added mechanism of action for hyaluronidase.
Clinical Studies	Organized information by study.	Reorganized information by indications and usages.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:
A risk evaluation and mitigation strategy has never been required for daratumumab IV. Considering no new safety concerns have been identified with daratumumab SC, no additional risk minimization measures beyond product labeling is needed. The proposed risk minimization measures in the USPI are considered sufficient by the Applicant.

The FDA's Assessment:
Not applicable.

13 Postmarketing Requirements and Commitments

The FDA's Assessment:
No PMRs or PMCs are being issued.

14 Division Director (OCP)

X Brian Booth, PhD

15 Division Director (OB)

X Thomas Gwise, PhD

16 Division Director (Clinical)

X Nicole Gormley, MD

17 Office Director (or designated signatory authority)

X Nicole Gormley, MD

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

18 Appendices

18.1 References

The Applicant's References:

1. Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet. 2012;51:119-135.
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4. Clinical Study Report 54767414MMY1001. An open-label, multicenter, phase 1b study of JNJ-54767414 (HuMax® CD38) (anti-CD38 monoclonal antibody) in combination with backbone regimens for the treatment of subjects with multiple myeloma. Janssen Research & Development, LLC (14 June 2018).
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6. Clinical Study Report 54767414MMY1004 (12-month update CSR). 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. Janssen Research & Development, LLC (19 June 2019).
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10. Clinical Study Report 54767414MMY2040. A multicenter phase 2 study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens. Janssen Research & Development, LLC (14 June 2019).

11. Clinical Study Report 54767414MMY3003. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma. Janssen Research & Development, LLC (27 July 2016). Previously submitted to IND 100638 on 12 August 2016, Serial No. 0471.
12. Clinical Study Report 54767414MMY3004. Phase 3 study comparing daratumumab, bortezomib, and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma. Janssen Research & Development, LLC (27 July 2016). Previously submitted to IND 100638 on 12 August 2016, Serial No. 0471.
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18.2 Financial Disclosure

The Applicant's Position:
As agreed to in FDA's Preliminary Meeting Comments for the 18 December 2018 Type B pre-BLA meeting, Studies MMY3012, MMY2040, and MMY1004 were considered as covered by clinical studies for Financial Disclosure for Clinical Investigators. In accordance with 21 CFR 54.4, all investigators were assessed for equity interest, significant payments, proprietary interest, and other compensation. Among the 765 clinical investigators for MMY3012, 284 clinical investigators for MMY2040, and 163 clinical investigators for MMY1004, certification was provided for 100% of investigators. No investigators from MMY3012 had financial arrangements or interest to disclose. Three of 284 investigators for MMY2040 and 2 of 163 investigators for MMY1004 had financial arrangements or interest to disclose. These disclosures are summarized in the tables below.

Covered Clinical Study (Name and/or Number):* 54767414MMY3012

Was a list of clinical investigators provided:	Yes ☒	No ☐(Request list from Applicant)
Total number of investigators identified: 765		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant) N/A

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) N/A

*The table above should be filled by the Applicant and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* 54767414MMY2040

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 284		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes☐	No☒ (Request explanation from Applicant) N/A

*The table above should be filled by the Applicant and confirmed/edited by the FDA

Covered Clinical Study (Name and/or Number):* 54767414MMY1004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 163		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) N/A

*The table above should be filled by the Applicant and confirmed/edited by the FDA.

18.3 OCP Appendices (Technical documents supporting OCP recommendations)

18.3.1 Pharmacometrics Review

18.3.1.1 Applicant's PPK and Exposure-Response Analysis

Report Title: Population Pharmacokinetics and Exposure-response Analysis Report for Subcutaneously Administered Daratumumab in Multiple Myeloma Subjects (J&J Report Number: **JNJ-54767414**), 11 June 2019

Applicant's PPK Analysis

Objectives:

- To evaluate the influence of covariates on daratumumab PK
- To evaluate if the proposed daratumumab SC dose of 1800 mg provides adequate systemic exposure relative to a 16 mg/kg daratumumab intravenous (IV) dose in all subjects, and across all body weights.

Methods:

The PPK analysis included data from an integrated analysis of 3 monotherapy studies (Table 27 and Figure 9). Serum concentration-time data were used for nonlinear mixed-effects modeling (NONMEM®) (ICON plc, Version 7.2). The first-order conditional estimation with interaction estimation method was used. The daratumumab SC model was based on a previous PPK model for daratumumab IV except for the absorption. PK profiles after daratumumab SC 1800 mg administration were simulated using estimated individual PK parameters and were compared with the PK profile after daratumumab IV 16 mg/kg. To compare the effects of covariates on exposure to daratumumab, subgroup analyses were conducted on predicted exposure metrics.

Body weight, age, sex, race, baseline creatinine clearance, baseline albumin, alanine aminotransferase, alkaline phosphatase, and hepatic dysfunction categories using the National Cancer Institute criteria (based on aspartate aminotransferase and total bilirubin) were the intrinsic factors explored as covariates in the PPK analysis. Type of myeloma at baseline (immunoglobulin G [IgG] versus non-IgG) was also investigated, as production of IgG in subjects with multiple myeloma may affect the clearance of daratumumab. Exposure to daratumumab was compared between subgroups for baseline disease status (ie, number of prior lines of therapy, refractory status, and Eastern Cooperative Oncology Group [ECOG] performance status at baseline).

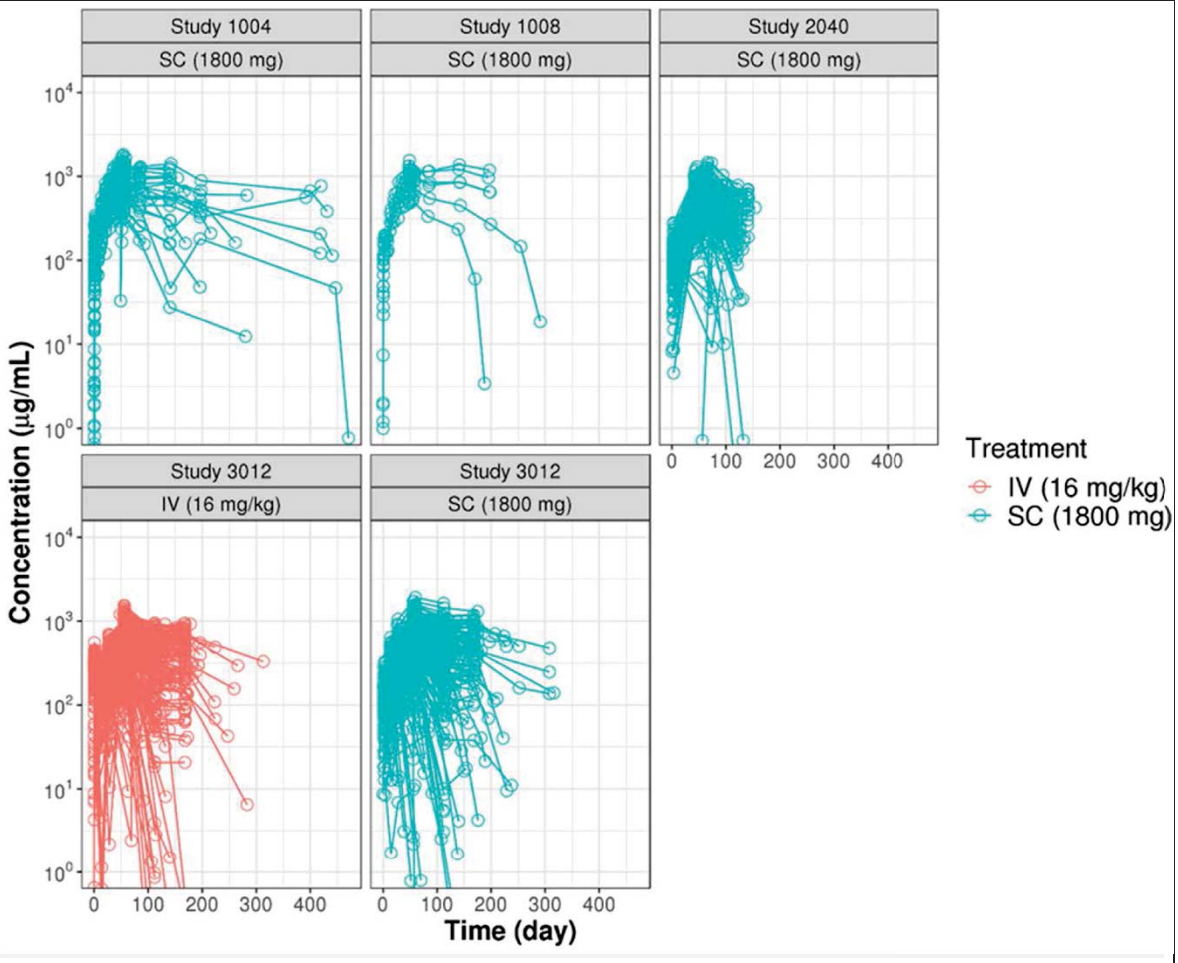
Table 27: Summary of daratumumab PK data in patients with multiple myeloma

Study*	Subjects N	Dose and PK Sample	Study Phase
MMY1004	78	Sparse for 1200 and 1800 mg	Phase 1b Safety and PK
MMY1008	6	Sparse for 1800 mg	Phase 1 Safety and PK
MMY1002	SC 257 & IV 255	Sparse for 1800 mg or 16 mg/kg	Phase 3
MMY2040	199	Sparse for 1800 mg	Phase 2

* MMY2040 is combination study and the other three studies are monotherapy studies.

Source: Table 1 of applicant's population pharmacokinetics report

Figure 9: Daratumumab Serum Concentrations Versus Time Profiles in Studies MMY1004 Part 2, MMY1008, MMY2040, and MMY3012 Stratified by Study and Route of Administration on a Semi-logarithmic Scale



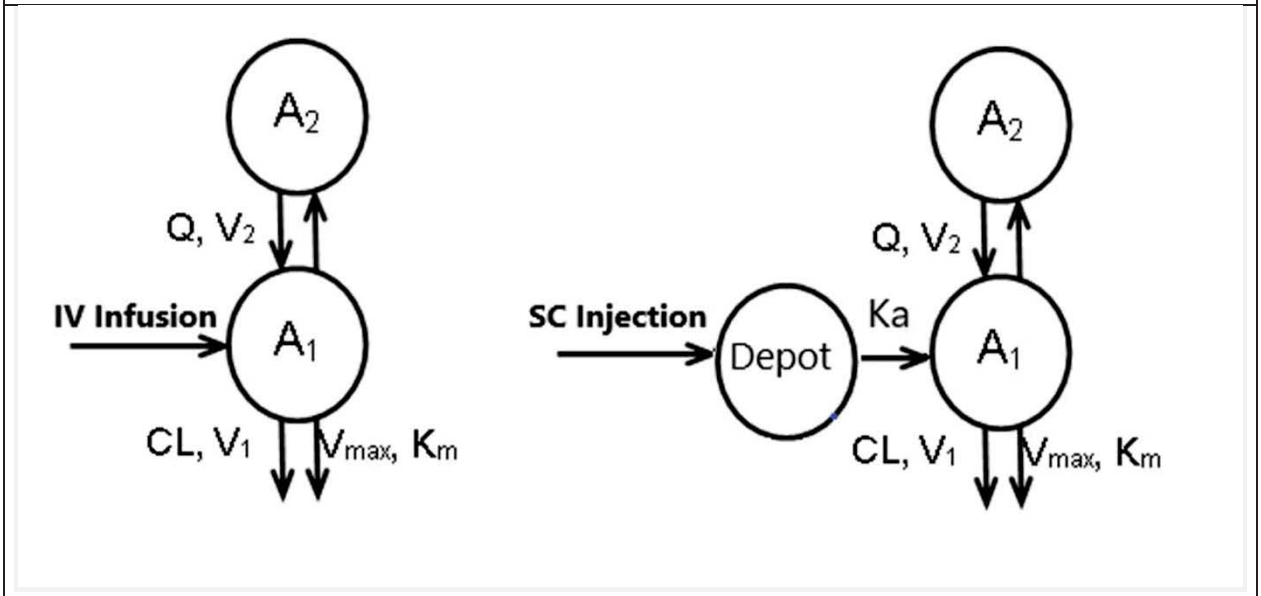
Source: Figures 3 of applicant's population pharmacokinetics report

Results:

Parameter Estimates

The PPK analysis was based on 5159 PK samples from 742 subjects; 487 subjects received daratumumab SC 1800 mg (monotherapy: N=288, combination therapy: N=199), and 255 subjects received daratumumab IV 16 mg/kg. Three subjects were excluded from the PPK analysis because they had no measurable concentrations of daratumumab. The observed concentration-time data of daratumumab were adequately described by a 2-compartment PPK model with parallel linear and nonlinear Michaelis-Menten elimination pathways. The absorption of the SC formulation was modeled with a first-order absorption process. The model was parameterized in terms of bioavailability and first-order absorption for SC administration, nonspecific linear clearance, volume of distribution in the central compartment, intercompartmental clearance, volume of distribution in the peripheral compartment, maximum velocity of the saturable target-mediated drug disposition (TMDD) clearance process (V_{max}), and daratumumab concentrations associated with half V_{max} for both SC and IV administrations (**Figure 10**).

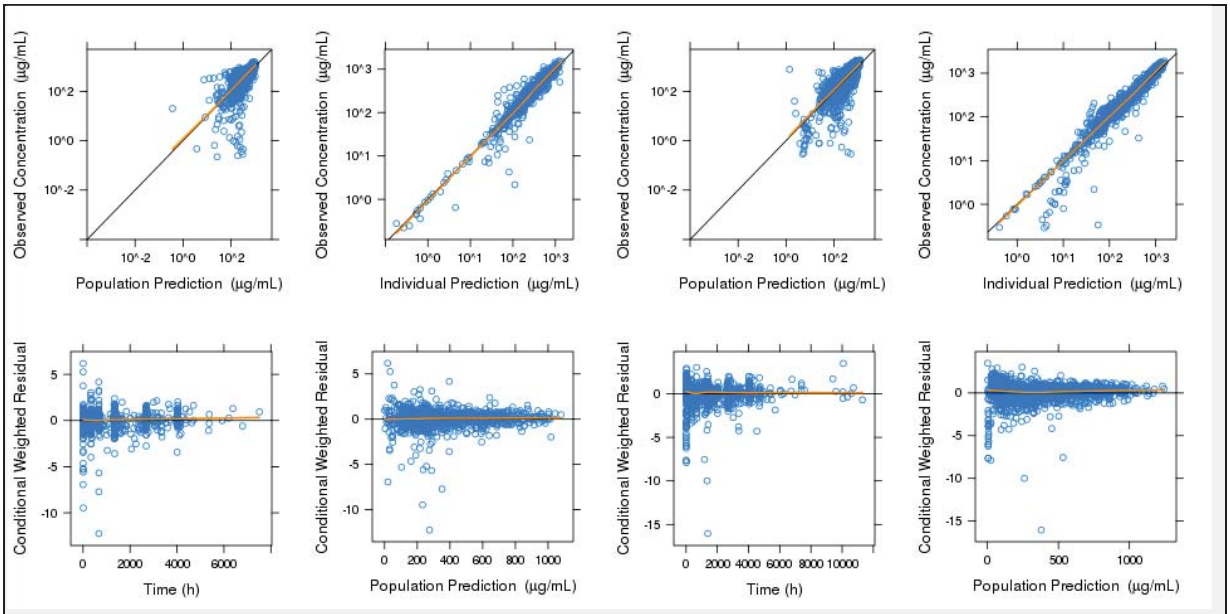
Figure 10: Diagrammatic representation of the final population PK model



Source: Figure 2 of applicant's population pharmacokinetics report

Goodness-of-fit plots are presented in Figure 11.

Figure 11: Goodness-of-fit Plots for the Final PPK Model for Subjects Administered with Daratumumab IV and SC for Monotherapy (Left 4 Panels for IV and Right 4 Panels for SC)



Abbreviations: IV=intravenous; PPK=population pharmacokinetics; SC=subcutaneous.

Key: Orange line represents the lowess smoother. Black line represents the line of identity for observed concentrations versus population prediction and individual prediction plots. For residual plots, black line represents horizontal line crossing the y axis at value of zero.

Source: Attachment 3 of applicant's population pharmacokinetics report

Model parameter estimates are listed in Table 29. The estimated bioavailability for the SC formulation is approximately 0.69, which is consistent with other monoclonal antibodies subcutaneously co-administered with rHuPH20 (Gibiansky 2015, Quartino 2016). The estimated linear clearance was very close to the clearance of nonspecific endogenous IgG in the literature (Ryman 2017), and the volume of distribution of central compartment approached to plasma volume; both were related to body weight, as expected for monoclonal antibodies. The model-derived geometric mean (coefficient of variation%) half-life associated with linear elimination was 20.4 (22.4%) days based on post hoc PK estimates for monotherapy, and 23 to 27 days for combination therapies. Apparent steady state seems to be reached approximately 5 months after start of dosing at the recommended dosing regimen ie, once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter.

Table 28: 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.

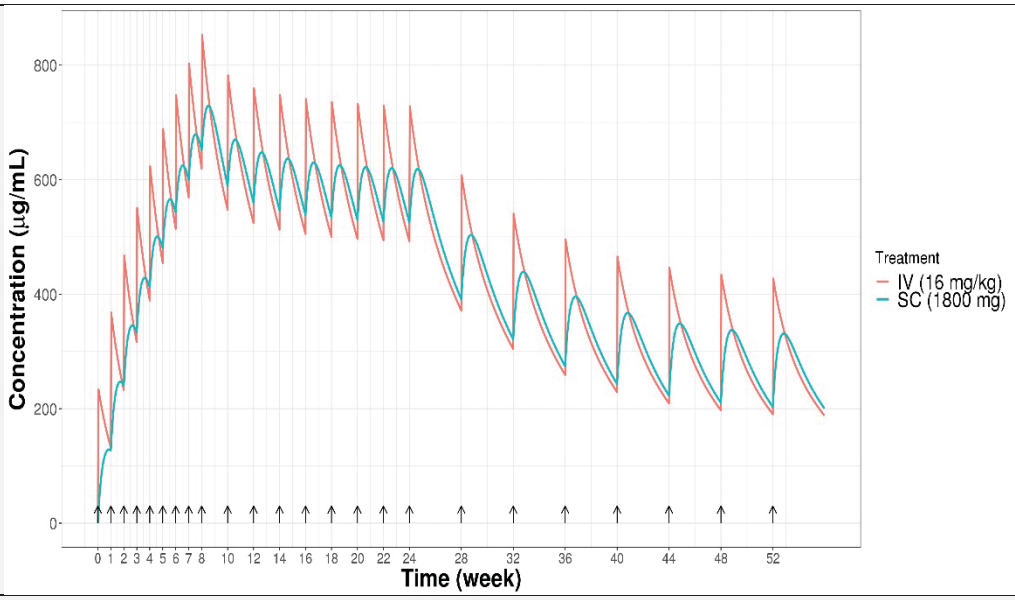
Note: Objective function value=-1759.836. Conditional number=42.8. Conditional number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate. For IIV, RSE% is given for %CV and is an approximate value.

Source: Table 5 of applicant's population pharmacokinetics report

Simulated PK Profiles

Based on the PK simulations, the recommended daratumumab SC 1800 mg dose provided smaller peak-to-trough fluctuations, lower maximum concentrations (C_{max}) and higher trough concentrations (C_{trough}) throughout the dosing schedule compared with daratumumab IV 16 mg/kg for any dosing schedule. For monotherapy, the mean peak-to-trough ratio at Cycle 3 Day 1 for daratumumab SC 1800 mg was 1.2 compared with 1.7 for daratumumab IV 16 mg/kg (Figure 12).

Figure 12: Typical Pharmacokinetics Profile of Daratumumab After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration as per the Approved Dose Schedule



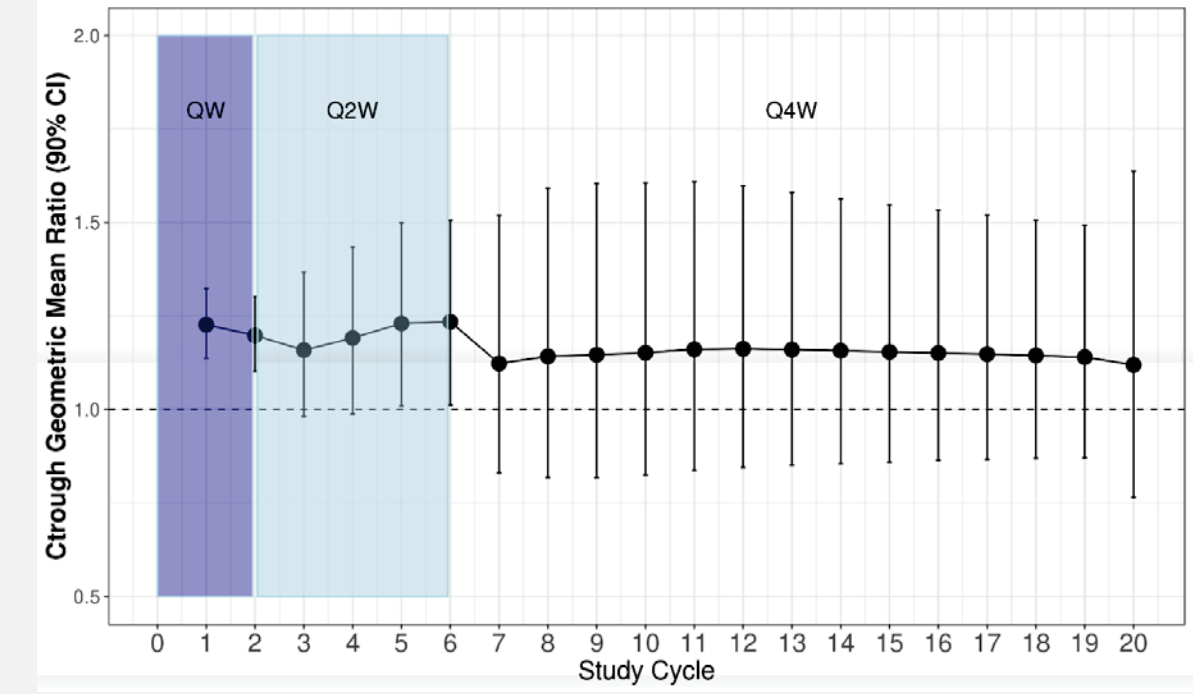
Key: Black arrows represent dose events.

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).

Source: Executive Summary of applicant's population pharmacokinetics report

The geometric mean ratio for daratumumab SC/daratumumab IV C_{trough} over each cycle showed that daratumumab SC 1800 mg resulted in consistently similar or slightly higher C_{trough} than daratumumab IV 16 mg/kg throughout the treatment period (Figure 13).

Figure 13: Daratumumab SC/Daratumumab IV C_{trough} Geometric Mean Ratio Over Time for Monotherapy



Abbreviations: CI=confidence interval; C_{trough}=predicted trough concentration; IV=intravenous; QW=once weekly; Q2W=once every 2 weeks; Q4W=once every 4 weeks; SC=subcutaneous.

Key: Dotted line represent ratio of 1; point and bar represent geometric mean ratio and CI.

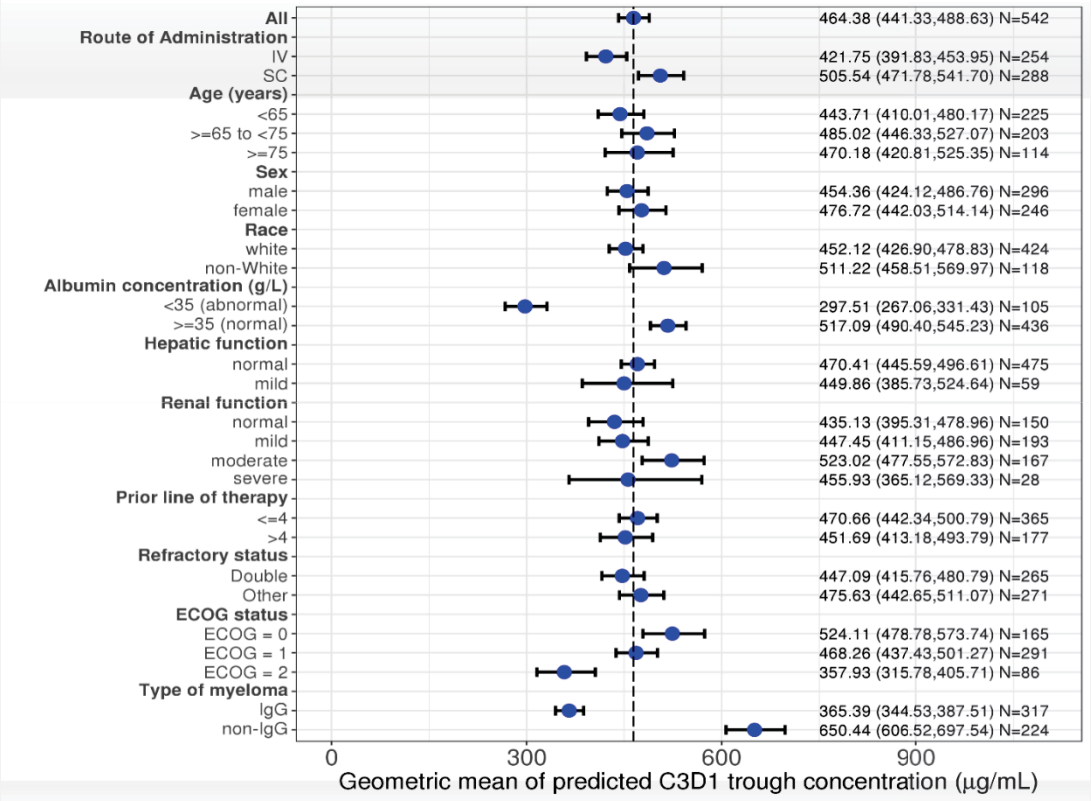
Source: Executive Summary of applicant's population pharmacokinetics report

The simulated trough concentrations following 6 weekly doses of daratumumab SC 1800 mg for combination therapies (daratumumab SC, bortezomib, melphalan, and prednisone [D-VMP], daratumumab SC, lenalidomide, and dexamethasone [DRd], daratumumab SC, bortezomib, lenalidomide, and dexamethasone [D-VRd]), were similar to monotherapy.

Effect of Covariates

The effects of the investigated intrinsic factors (ie, age, sex, race, region, renal impairment, hepatic impairment, and ECOG status) on exposure had no clinically relevant impact. Consistent with the findings from previous IV studies (Mod5.3.5.1/MMY3012, PopPK 2015), although subjects with IgG myeloma had lower exposure, the overall response rate (ORR) for IgG and non-IgG subjects were similar in both daratumumab SC and IV arms (Mod2.7.3/Fig3). Similarly, although subjects with lower baseline albumin concentrations (<35 g/L) appear to have lower exposure, the ORR for subjects with lower (<35 g/L) and higher (≥35 g/L) baseline albumin concentrations were similar in daratumumab SC arm (40% versus 42%, respectively). Subjects with lower baseline albumin concentrations appear to have lower ORR in daratumumab IV arm (25% versus 40%, respectively); however, the rate of serious treatment-emergent adverse events (TEAEs) seems also higher (44% in <35 g/L versus 26% in ≥35 g/L, respectively). Therefore, no dose adjustment is recommended based on any of these factors (Figure 14).

Figure 14: Forest Plot of Subgroup Analyses on the Predicted Cycle 3 Day 1 Trough Concentrations for Monotherapy



Abbreviations: C3D1=Cycle 3 Day 1; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; IV=intravenous; N=maximum number of subjects with data; SC=subcutaneous.

Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of the geometric mean of all subjects. Numbers represent geometric mean value, confidence interval, and number of subjects in the comparison groups.

Source: Figure 7 of applicant's population pharmacokinetics report

Immunogenicity response was not evaluated as a covariate in the PPK model development because only 2 subjects (0.4%) developed antibodies to daratumumab in this PPK analysis dataset.

Applicant's Exposure-Response Analysis

Objectives:

- To corroborate and supplement the evidence of efficacy and safety of daratumumab after daratumumab SC administration co-formulated with rHuPH20
- To confirm the selected SC dose as 1800 mg. Because all subjects received either daratumumab SC 1800 mg or daratumumab IV 16 mg/kg, there is limited exposure variation for

daratumumab and, therefore, only exploratory and graphic E-R analyses were performed for selected efficacy endpoints and adverse events (AEs).

Data and Methods

The E-R analysis for daratumumab monotherapy was based on data from 2 Phase 1 studies (MMY1004 Part 2, MMY1008) and a Phase 3 study (MMY3012); the E-R analysis for combination therapies was based on a Phase 2 study (MMY2040). The relationship between exposure and the primary efficacy endpoint, ORR, was investigated using logistic regression implemented in R.

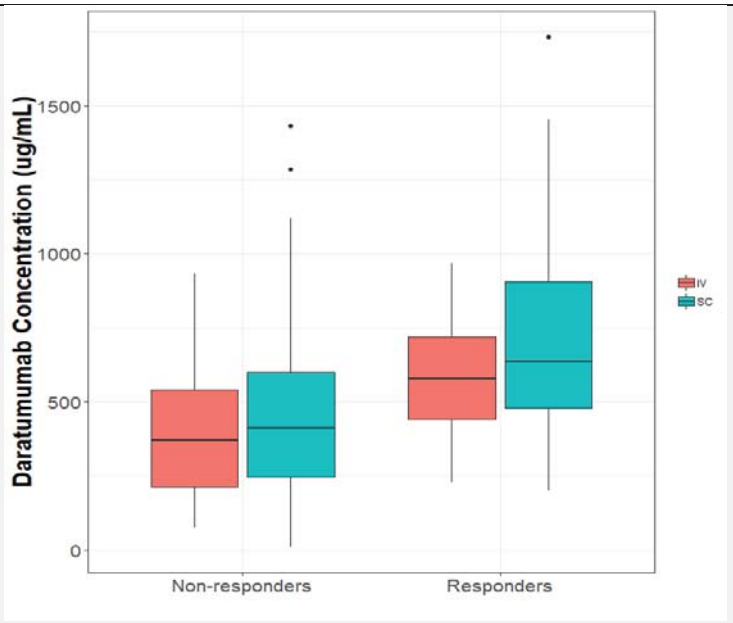
The E-R relationship for safety was explored for selected AEs, including overall serious AEs (SAEs), overall Grade 3 or higher TEAEs, and neutropenia. Both the peak daratumumab concentrations after the first dose and the overall peak concentrations were investigated for their potential relationship with the other AEs using logistic regression.

Results

Exposure-Efficacy Relationship

Daratumumab SC produced higher trough concentrations in both responders and non-responders, and slightly higher ORRs compared with the approved daratumumab IV. These results suggest that sufficient exposure is reached by daratumumab SC at 1800 mg compared with daratumumab IV at 16 mg/kg. Examination of relationship between ORR and maximum trough concentrations suggested a similar exposure-efficacy relationship between daratumumab SC and daratumumab IV (Figure 15).

Figure 15: Box Plot for Daratumumab Maximum Trough Concentrations for Non-responders and Responders After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg for Monotherapy



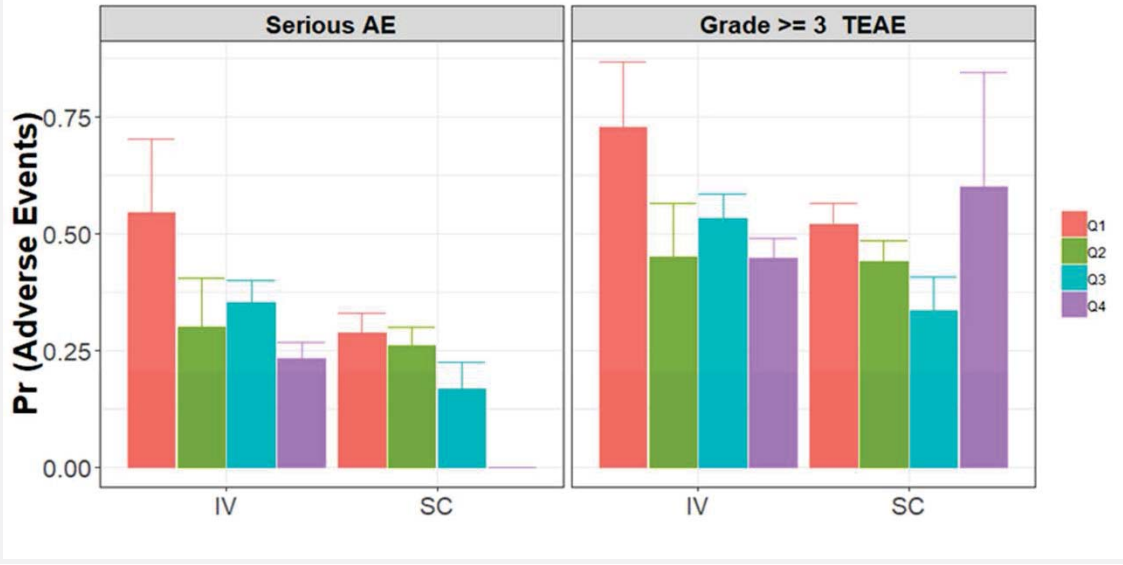
Source: Executive Summary of applicant's population pharmacokinetics report

In the settings of combination therapies, a high ORR was observed consistently across the studied concentrations range, indicating that maximum efficacy in terms of ORR was attained for daratumumab SC 1800 mg. 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.

Exposure-Safety Relationship

No relationship was observed between exposure and safety endpoints (SAEs and Grade 3 or higher TEAEs) using the peak concentrations after the first dose. Dose interruptions, modifications, or discontinuation caused by AEs might lead to the lower overall peak concentrations in those subjects following multiple doses. Therefore, to mitigate the impact from dose interruption, modification or discontinuation, peak concentrations (C_{max}) after first dose was performed (Figure 16).

Figure 16: 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).

Source: Executive Summary of applicant's population pharmacokinetics report

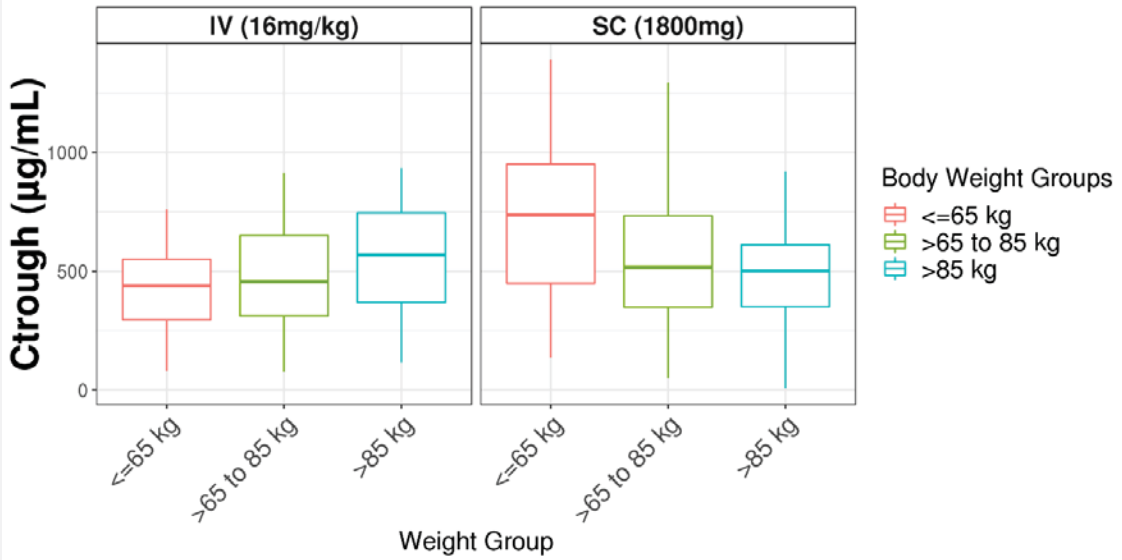
For combination of daratumumab SC with bortezomib, lenalidomide, and dexamethasone (VRd), VMP, and lenalidomide-dexamethasone (Rd), no E-R relationship for safety was observed after combination therapies. Comparisons with historical IV data from Studies MMY3003 (DRd) and MMY3007 (D-VMP) indicate similar incidence of SAEs and Grade 3 or higher TEAEs for daratumumab SC subjects across the exposure range.

Applicant's Analysis of Body Weight Effect on PK, Efficacy and Safety

Body Weight Effect on PK

The mean simulated concentrations of daratumumab after 8 weekly doses for the lower body weight subgroup (≤65 kg) were approximately 67% higher in the daratumumab SC group than in the daratumumab IV group. The mean simulated concentrations of daratumumab after 8 weekly doses in the higher body weight group (>85 kg) were approximately 14% lower in the daratumumab SC group than in the daratumumab IV group. The mean concentrations of daratumumab in the middle body weight group (>65 to 85 kg) were comparable between treatment groups. The spread of trough concentrations across body weight groups was similar to previously observed data from daratumumab IV 16 mg/kg (Cycle 3 Day 1 trough concentration [Ctrough]: 36 to 1764 µg/mL; MMY2002 CSR, TPKCONC01) (Figure 17).

Figure 17: Boxplot of the Simulated Daratumumab Trough Concentrations After 8 Weekly Doses in Weight Groups After Daratumumab SC 1800 mg Administration for Monotherapy



Source: Executive Summary of applicant's population pharmacokinetics report

The simulated peak concentrations (Cmax after Cycle 3 Day 1 dose) for lower body weight subgroup (≤65 kg) for monotherapy daratumumab SC 1800 mg were comparable to the simulated Cmax in the higher body weight subgroup (>85 kg) for daratumumab IV 16 mg/kg, but in general, the Cmax values for the overall population were lower for daratumumab SC.

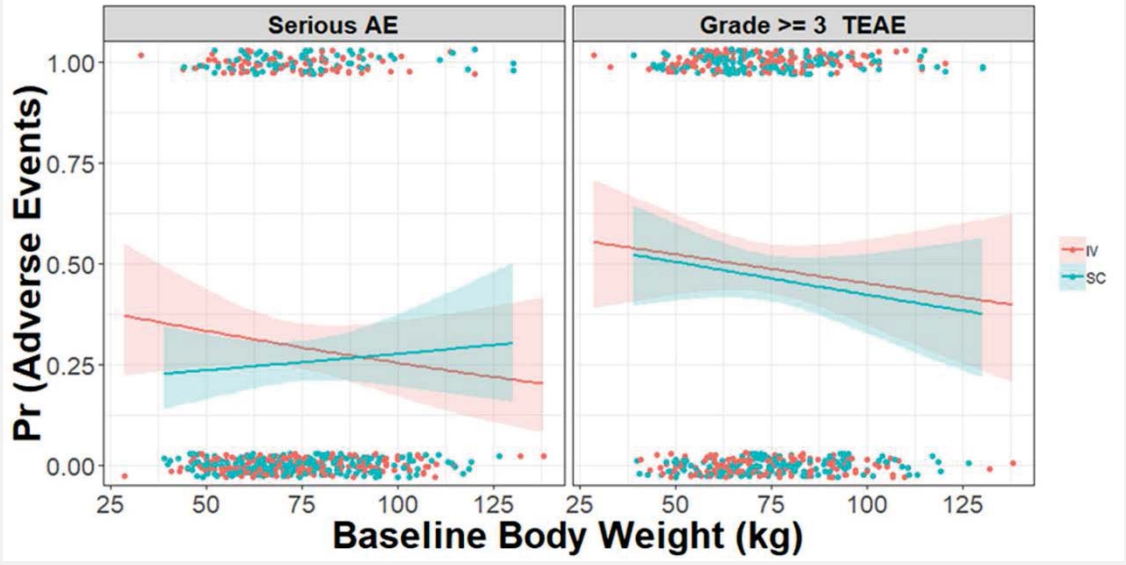
Body Weight Effect on Efficacy

Clinical analysis demonstrated consistent efficacy of the drug in all body weight subgroups (Mod5.3.5.1/MMY3012/Sec9). Specifically, in the high body weight subgroup (>85 kg), ORR in the daratumumab SC arm (43.9%, 95% confidence interval [CI]: 31.7%, 56.7%) was similar to the ORR in the daratumumab IV arm in the same subgroup (32.8%, 95% CI: 21.3%, 46.0%) (Mod5.3.5.1/MMY3012/Tab41).

Body Weight Effect on Safety

Consistent with other mAbs dosed subcutaneously as flat dose, daratumumab SC produced slightly higher concentrations at lower body weights than daratumumab IV, but the rate of SAEs and Grade 3 or higher TEAEs was generally comparable between daratumumab SC and IV treatments. No E-R relationship for safety was observed after either monotherapy or combination therapies (Figure 18).

Figure 18: Rate of SAE, and Grade 3 or Higher TEAE in Relation to Baseline Body Weight After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Dose Regimen for Monotherapy



Abbreviations: AE=adverse events; IV=intravenous; Pr=probability; SAE=serious adverse event; SC=subcutaneous; TEAE=treatment-emergent adverse event.

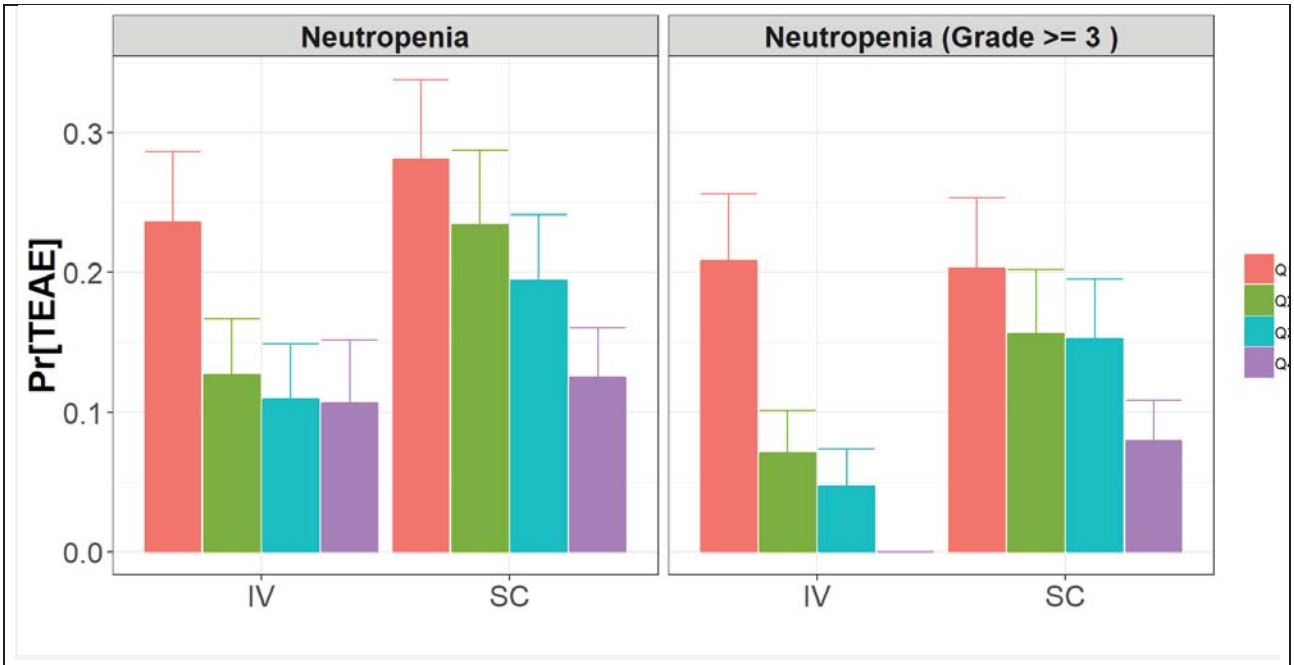
Key: The lines represent the predicted mean curves and the shaded regions are the 95% confidence intervals. Dots represent the observed rate of SAE and TEAE.

Source: Executive Summary of applicant's population pharmacokinetics report

Neutropenia

In monotherapy studies, the event rate of neutropenia (any grades 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. 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 C_{max} 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.
Although slightly higher neutropenia was 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 19: Rate of Neutropenia (any Grades and Grade 3 or Higher) in Relation to Daratumumab Maximum Trough Concentration (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 maximum trough concentrations are: Q1 (9.25 to 320 µg/mL), Q2 (320 to 493 µg/mL), Q3 (493 to 674 µg/mL), and Q4 (674 to 1,730 µg/mL).

Source: Attachment 22 of applicant's population pharmacokinetics report

Conclusions and Dose Justification

1. The PPK and E-R analyses support the selected daratumumab SC 1800 mg with rHuPH20 co-formulation dose regimen for the treatment of multiple myeloma:

- The daratumumab SC 1800 mg with rHuPH20 co-formulation dose regimen consistently produced (1) lower peak-to-trough fluctuations, (2) similar or slightly higher trough levels over time, and (3) lower peak concentrations compared with the approved IV 16 mg/kg dose regimen (mean peak-to-trough ratio at Cycle 3 Day 1 for daratumumab SC 1800 mg was 1.2 compared with 1.7 for daratumumab IV 16 mg/kg). These suggest sufficient concentrations have been attained by daratumumab SC 1800 mg dose regimen.
- A similar PK-efficacy relationship was observed between daratumumab SC and daratumumab IV regimens. The slightly higher trough concentrations in subjects who received SC dose regimen compared to those in subjects who received IV dose regimen resulted in comparable efficacy.
- The range of exposures across all daratumumab SC studies fell within the exposure range observed in the daratumumab IV program.

- The simulated trough concentrations following 6 weekly doses of daratumumab SC 1800 mg for combination therapies (D-VMP, DRd, and D-VRd), were similar to monotherapy.

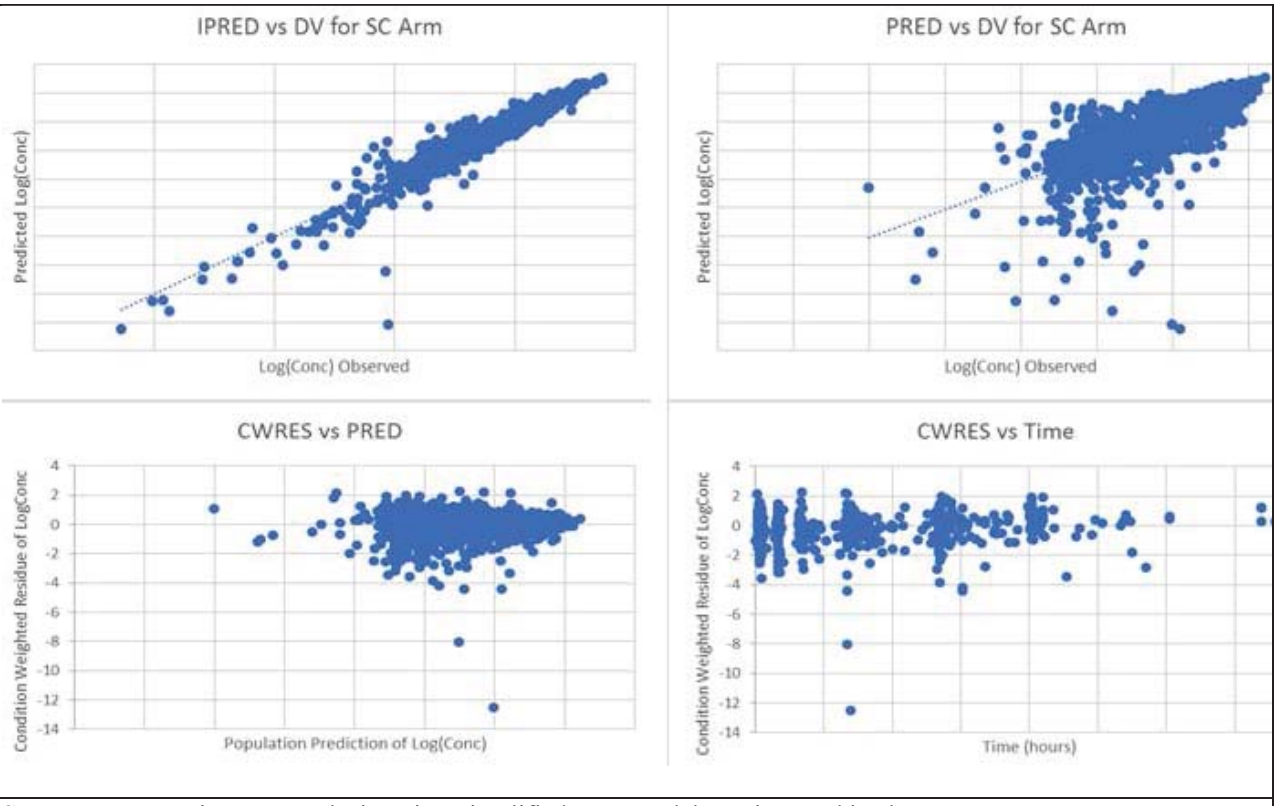
2. The PPK and E-R analyses also support the flat daratumumab SC 1800 mg with rHuPH20 co-formulation dose strategy for patients with multiple myeloma:

- Body weight had a significant effect on both linear clearance and central volume of distribution, but not on nonlinear clearance after daratumumab SC administration, which is consistent with previous PPK models after daratumumab IV administration.
- Overall, consistent exposure was observed across the body weight ranges. As expected, slightly higher concentrations were observed for subjects with lower body weights.
- Clinical analysis suggests that similar efficacy in terms of ORR was observed across the body weight ranges after the flat SC dose regimen.
- There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs and neutropenia). Slightly higher daratumumab concentrations at lower body weights after SC administration did not cause a clinically relevant effect on the safety profile.
- The observed concentration-time data of daratumumab after SC administration were well described by a 2-compartment PPK model with a first-order absorption and parallel linear and nonlinear Michaelis-Menten eliminations.

3. None of the investigated factors (ie, age, sex, race, region, renal impairment, hepatic impairment, baseline albumin, ECOG status, and type of myeloma) had clinically relevant effects. Therefore, no dose adjustment is recommended based on these factors.

FDA Reviewer's Comments on Applicant's PPK and ER Analysis: *Two items may not be appropriate in the PPK model for daratumumab SC data, resulting in the bias shown in the IPRED vs DV plot (**Figure 11**) for both SC and IV data. First, the following three equations were used to estimate bioavailability of SC daratumumab: FP=THETA(10)/(1-THETA(10)), LPF=LOG(FP)+ETA(6), BIO=EXP(LPF)/(1+EXP(LPF)), and F1 = BIO, where ETA(6) was fixed as 0, i.e., the IIV for F1 was fixed as 0. This may not be appropriate for the SC data. In addition, the Michaelis-Menten model may not be applicable to daratumumab SC PK data considering relatively flatter PK profile than the IV dose. When the Michaelis-Menten component was removed from the PPK model and let IIV for F1 is estimated, the simplified model converged faster and the GOF plots improved significantly (**Figure 20** vs **Figure 11**).*

Figure 20: Goodness-of-fit Plots for Daratumumab SC Arm Based on the Simplified PPK Model



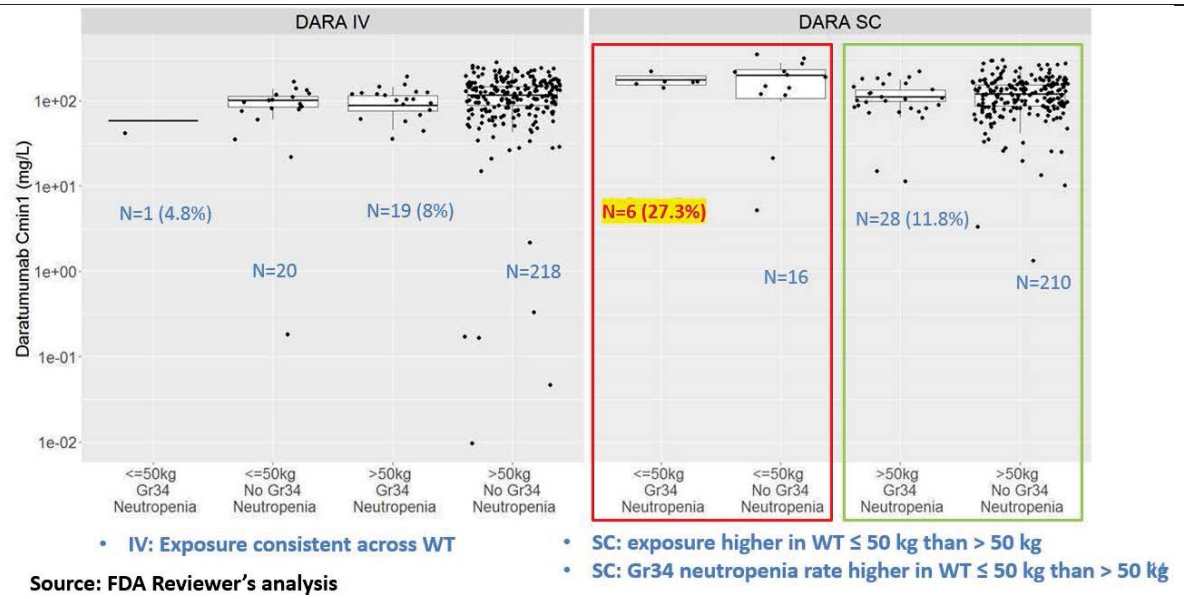
Source: FDA Reviewer's Analysis Using Simplified PPK Model as Discussed in above Comment

*A negative exposure-response relationship for safety was identified for Study 3012 (**Figure 18** and **Figure 19**) particularly the SC arm. The post-hoc exposure from the simplified PPK model could not reverse the negative ER slope, and this cannot be interpreted appropriately from ER perspective for daratumumab safety. In this case, body-weight based dose-response analysis could be more relevant for efficacy and safety of SC arm because 16 mg/kg IV dose produced consistent daratumumab serum concentration across different body weights of MM patients.*

18.3.1.2 FDA Reviewer's Analysis

As shown in Figure 18 and Figure 19, there was a negative ER relationship for safety. On the other hand, body-weight based AE rate analysis suggested a positive ER relationship; the Grade 3 or 4 neutropenia rate of SC arm is about 6 times higher than IV arm in ≤50 kg patients due to higher daratumumab exposure (Figure 21).

Figure 21: Body Weight Effect on Grade 3 or 4 Neutropenia Rate of Study 3012



Note: Daratumumab trough concentration for the 1st dose (Cmin1) was simulated based on applicant's final PPK model. Grade 3 or 4 data are from adae.xpt and body weight data are from adsl.xpt

To further investigate this phenomenon, the FDA Office of Clinical Pharmacology sent an information request to the applicant with the following text: "Reference is made to daratumumab BLA 761145. FDA has concerns with the increased incidence of Grade 3/4 neutropenia observed in the Dara SC arm (13.1%, 34/260) as compared to that in the Dara IV arm (7.8%; 20/258) in the pivotal study MMY3012. The differences were primarily driven by the higher incidence of Grade 3/4 neutropenia in the lower body weight (BW) subgroups (≤ 65 kg), with 20.4% for SC arm vs 8.7% for IV arm. The incidence of overall infections, Grade 3 or 4 infections, treatment discontinuations due to neutropenia or febrile neutropenia, and serious TEAEs related to neutropenia were all similar between the IV and SC arms in this BW subgroup, however, this does not address our concerns. FDA found that patients with BW ≤ 50 kg, the incidence of Grade 3/4 neutropenia was several-fold higher in the Dara SC arm than IV arm, and the observed mean maximum trough concentration of SC arm was 80% higher than IV arm. Provide justifications for why or why not, a dose adjustment for the lower BW subgroups to mitigate the safety risk is needed."

The following are the Applicant's response to the information request: **"**The Sponsor acknowledges the higher incidence of Grade 3/4 neutropenia observed in the daratumumab SC arm compared to the daratumumab IV arm in subjects with bodyweight (BW) ≤50 kg. Per the Agency's request, justification of the flat-dose and additional analyses exploring the basis of this observed difference are provided here. Also included in this response are further analyses of this group's PK data. There are two critical points of note:

1. An imbalance in pre-existing neutropenia in low BW (≤50 kg) subjects likely accounts for the observed difference in Grade 3/4 neutropenia seen in low BW subjects between the two arms, 45.5% of subjects in the daratumumab SC arm had pretreatment Grade 2 or higher neutropenia compared with 19% in the daratumumab IV arm.
2. Daratumumab exposure does not appear to be associated with treatment emergent Grade 3/4 neutropenia."

Objective: The FDA reviewer's analysis aimed to evaluate whether:

- Pre-existing neutropenia in low BW (≤50 kg) subjects accounted for the observed difference in Grade 3/4 neutropenia
- There was a positive dose-response slope for Grade 3 or 4 neutropenia in patients of SC arm
- There was a need of daratumumab SC dose reduction from 1800 mg to 1200 mg for BW ≤50 kg patients

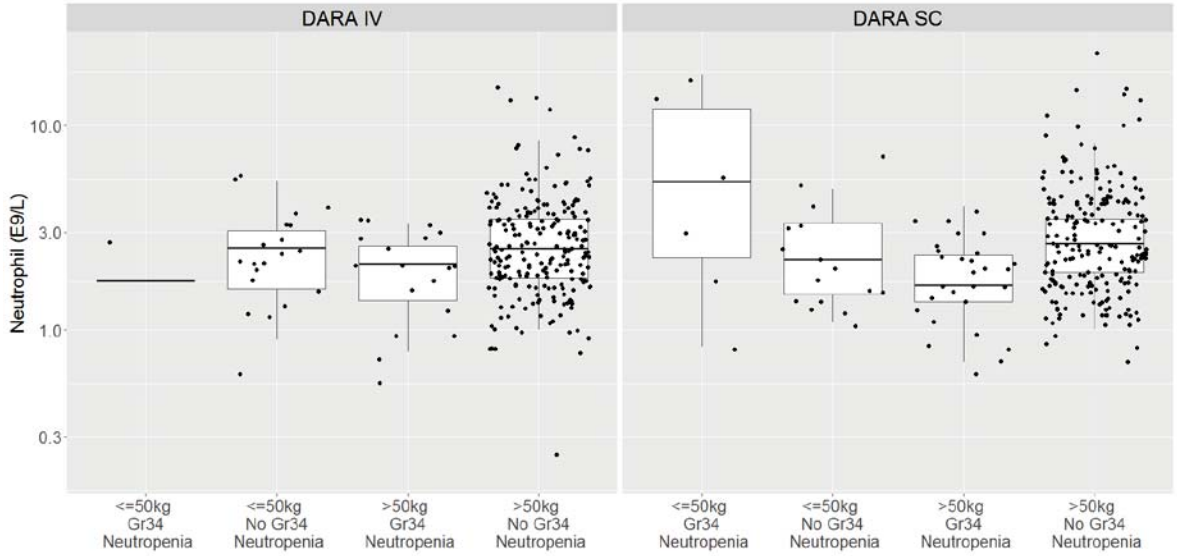
Methods:

PPK simulations were conducted by NONMEM v 7.3. (ICON Development Solutions). Data manipulation and analysis was conducted by R (CRAN - R Project). The applicant's datasets for pivotal Study 3012 were used for the analysis.

Results and Discussion:

Pre-existing neutropenia in low BW (≤50 kg) subjects does not account for the observed difference in Grade 3/4 neutropenia. As shown in Figure 22, baseline neutrophil counts were plotted against Grade 3 or 4 neutropenia responder and non-responder by body weight. Representing BW ≤50 kg Grade 3 or 4 neutropenia patients, the first box of the right panel is higher than the other three boxes. This counters the applicant's statement: "pre-existing neutropenia in low BW (≤50 kg) subjects likely accounts for the observed difference in Grade 3/4 neutropenia seen in low BW subjects between the two arms, 45.5% of subjects in the daratumumab SC arm had pretreatment Grade 2 or higher neutropenia compared with 19% in the daratumumab IV arm".

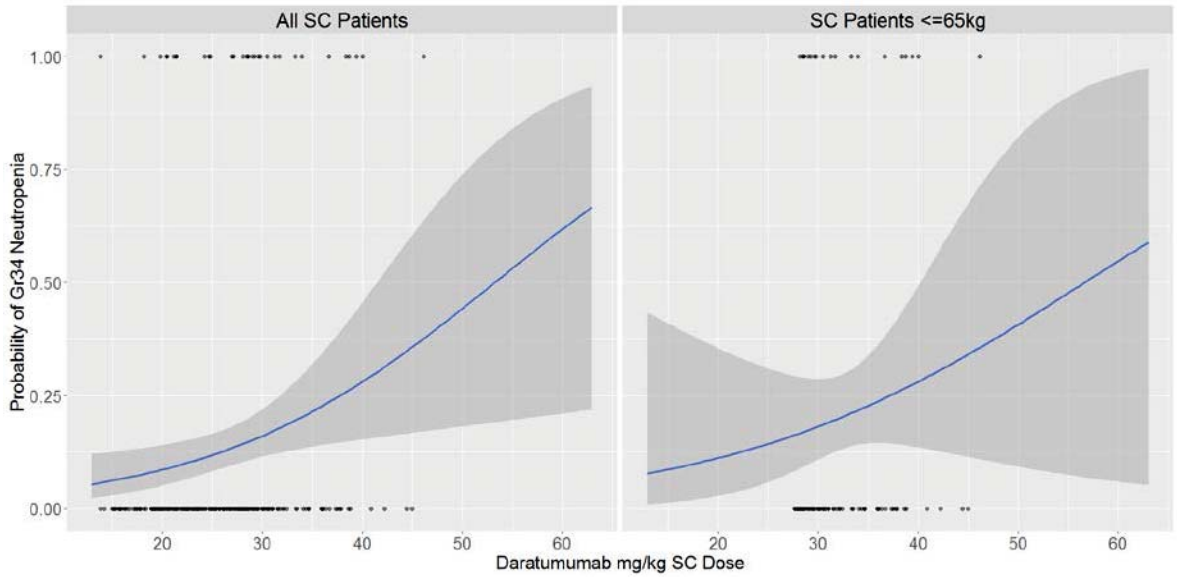
Figure 22: Baseline Neutrophil Count vs. Patient Category Where the Count Was Not Lower in Patients with Grade 3 or 4 Neutropenia and with BW≤ 50 kg of SC Arm (first box of right panel)



Source: FDA reviewer's analysis based on adsl.xpt, lb.xpt, and adeas.xpt

While a negative exposure-response relationship appeared for Grade 3 or 4 neutropenia by the univariate analysis, there is a positive dose-response slope identified for Grade 3 or 4 neutropenia in all patients of SC arm (left panel of Figure 23). As sensitivity analysis, the plot for BW≤65 kg demonstrates the same trend (right panel of Figure 23).

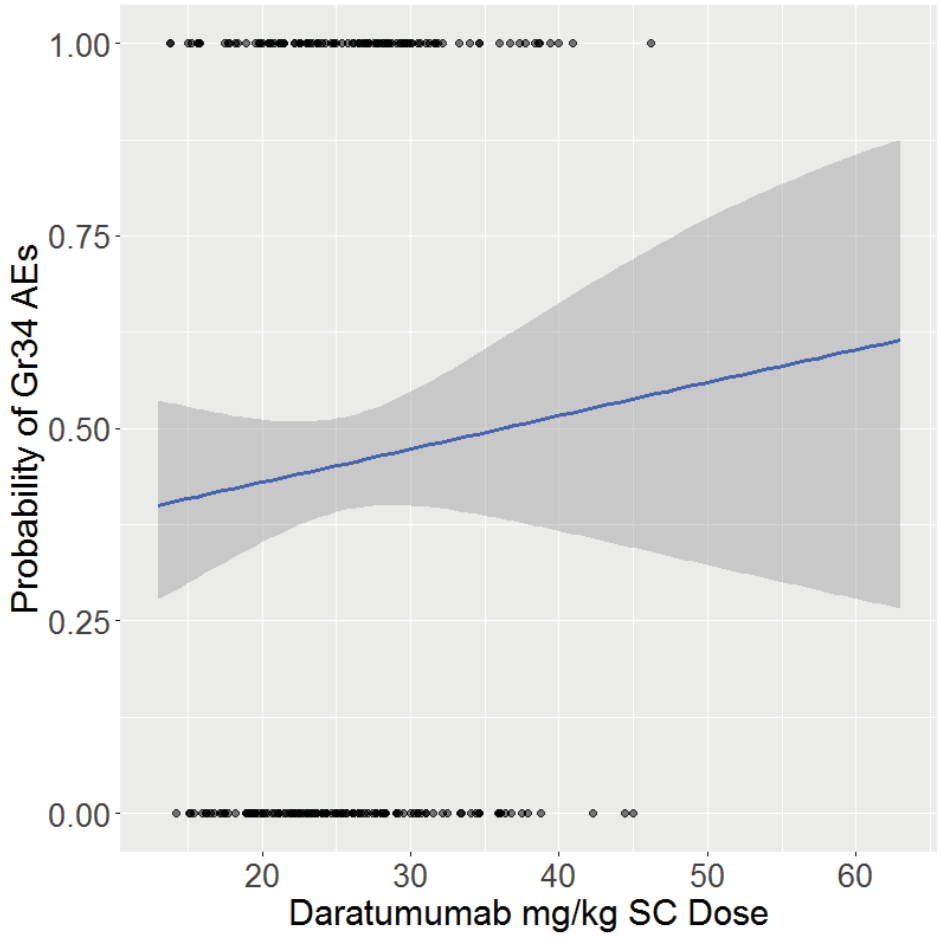
Figure 23: Grade 3 or 4 Neutropenia vs. Per kg Dose of SC Arm



Source: FDA reviewer's analysis based on adsl.xpt and adeas.xpt

There is also a positive dose-response slope identified for general Grade 3 or 4 AEs in patients of SC arm (Figure 24).

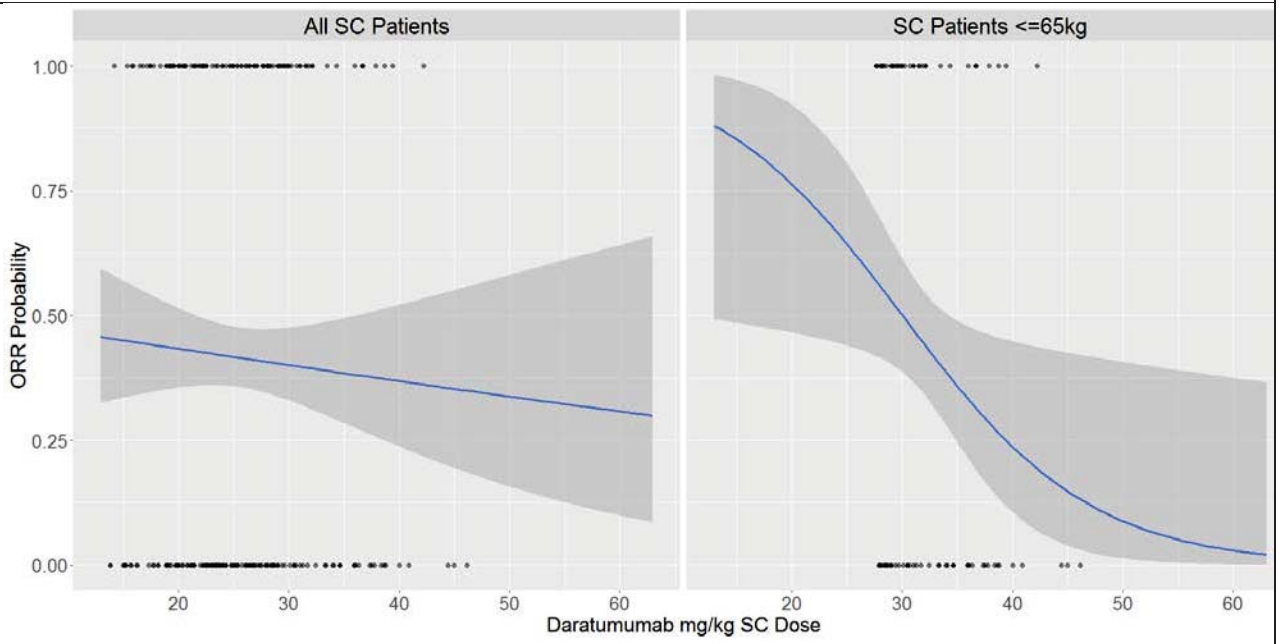
Figure 24: Grade 3 or 4 AEs vs. Per kg Dose of SC Arm



Source: FDA reviewer's analysis based on adsl.xpt and adeas.xpt

In addition, there is an apparent negative dose-response relationship identified for primary efficacy of SC arm as shown in the left panel of Figure 25. As sensitivity analysis, the plot for BW≤65 kg demonstrates the same trend as shown in the right panel of Figure 25. The logistic regression parameters for primary efficacy endpoint ORR are listed in Table 29 under Figure 25.

Figure 25: ORR vs. SC Dose Per kg Body Weight of SC Arm



Source: FDA reviewer's analysis based on adsl.xpt and adeff.xpt

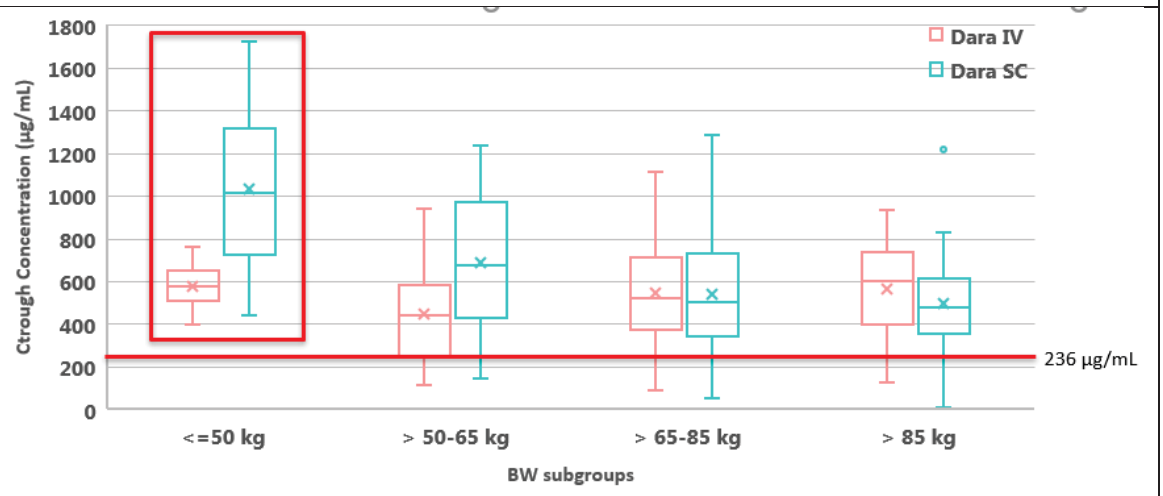
Table 29: Logistic Regression Parameters for Primary Efficacy Endpoint ORR

	Intercept	Slope for mg/kg dose	Slope for prior therapy lines >4	Slope for Non-IgG patients
All data				
ORR ~	0.004973	-0.013574		
	0.14147	-0.01241	-0.51417	
	0.07496	-0.01176	-0.52434	0.12832
Data for BW≤65 kg				
ORR ~	3.5179	-0.1171		
	3.6470	-0.1142	-0.6492	
	3.4516	-0.1099	-0.6602	0.1421

Source: FDA reviewer's analysis based on adsl.xpt, and adeff.xpt

In summary, there is a positive DR relationship for safety but a negative DR relationship for primary efficacy. As shown in Figure 26, the target daratumumab serum concentration for MM is 236 mg/L, and the high daratumumab exposure in BW≤ 50 kg may not improve efficacy and may increase the rate of grade 3 or higher neutropenia. From a benefit-risk perspective, reducing the dose is recommended to match exposures in patients with higher body weight (>50 kg).

Figure 26: Grade 3 or 4 Neutropenia vs. SC Dose Per kg Body Weight of SC Arm



Source: FDA OCP briefing slide.

Simulations demonstrated that daratumumab 1200 mg in BW≤50 kg patients can match 1800 mg in BW≤50 kg at population level (Table 30).

Table 30: Simulated Exposure for Recommended 2 Doses for Male and non-IgG Patients: 1200 mg for WT ≤ 50 kg & 1800 mg for WT > 50 kg Data

WT (kg)	Dose (mg)	Cmin8 (mg/L)	AUC8 (g*h/L)
30	1200	605	107
35	1200	543	96
40	1200	492	87
45	1200	448	79
50	1200	411	73
51	1800	668	117
65	1800	540	95
73	1800	484	85
100	1800	356	63
135	1800	260	46

Source: FDA reviewer's analysis based on sponsor's final PPK model.

In summary, the results of the Pharmacometrics review suggest reducing the dose to 1200 mg as SC dose for MM patients with BW≤50 kg.

18.3.2 Additional Clinical Pharmacology Communication with Applicant Regarding Neutropenia

On February 7, 2020, the FDA issued the following information request to the Applicant:

> "Reference is made to daratumumab BLA 761145. FDA has concerns with the increased incidence of Grade 3/4 neutropenia observed in the Dara SC arm (13.1%, 34/260) as compared to that in the Dara IV arm (7.8%; 20/258) in the pivotal study MMY3012. The differences were primarily driven by the higher incidence of Grade 3/4 neutropenia in the lower body weight (BW) subgroups (≤ 65 kg), with 20.4% for SC arm vs 8.7% for IV arm. The incidence of overall infections, Grade 3 or 4 infections, treatment discontinuations due to neutropenia or febrile neutropenia, and serious TEAEs related to neutropenia were all similar between the IV and SC arms in this BW subgroup, however, this does not address our concerns. FDA found that patients with BW ≤ 50 kg, the incidence of Grade 3/4 neutropenia was several-fold higher in the Dara SC arm than IV arm, and the observed mean maximum trough concentration of SC arm was 80% higher than IV arm. Provide justifications for why or why not, a dose adjustment for the lower BW subgroups to mitigate the safety risk is needed."

The following is part of the Applicant's response to the information request:

> **"**The Sponsor acknowledges the higher incidence of Grade 3/4 neutropenia observed in the daratumumab SC arm compared to the daratumumab IV arm in subjects with bodyweight (BW) ≤50 kg. Per the Agency's request, justification of the flat-dose and additional analyses exploring the basis of this observed difference are provided here. Also included in this response are further analyses of this group's PK data. There are two critical points of note:
>
> **1.** An imbalance in pre-existing neutropenia in low BW (≤50 kg) subjects likely accounts for the observed difference in Grade 3/4 neutropenia seen in low BW subjects between the two arms, 45.5% of subjects in the daratumumab SC arm had pretreatment Grade 2 or higher neutropenia compared with 19% in the daratumumab IV arm.
>
> **2.** Daratumumab exposure does not appear to be associated with treatment emergent Grade 3/4 neutropenia."

FDA acknowledges that more patients in the daratumumab SC arm had pre-treatment Grade 2 or higher neutropenia than in the daratumumab IV arm. However, FDA does not agree that this difference in pre-treatment Grade 2 or higher neutropenia fully contributed to the observed difference in Grade 3/4 neutropenia seen in low BW patients between the two arms.

The FDA reviewer's analysis demonstrates that pre-existing neutropenia in low BW (≤50 kg) subjects does not account for the observed difference in Grade 3/4 neutropenia (Figure 22). Representing BW ≤50 kg Grade 3 or 4 neutropenia patients, the first box of the right panel is higher than the other three boxes. This makes the applicant's statement: "pre-existing neutropenia in low BW (≤50 kg) subjects likely accounts for the observed difference in Grade 3/4 neutropenia seen in low BW subjects between the two arms, 45.5% of subjects in the daratumumab SC arm had

pretreatment Grade 2 or higher neutropenia compared with 19% in the daratumumab IV arm" inconsequential as the majority of grade 3/4 events on treatment came from subjects not with grade 2 neutropenia at screening.

For patients with similar pre-existing neutropenia, incidences of Grade 3/4 neutropenia were consistently higher in the daratumumab SC arm than in the daratumumab IV arm for patients with BW ≤ 50 kg, BW ≤ 65 kg, and all patients. Therefore, the observed difference in Grade 3/4 neutropenia seen in lower BW patients between the two arms was not caused by the imbalance in pre-existing neutropenia in lower BW (≤50 kg) patients (Table 31).

Table 31: Incidence of Grade 3/4 Neutropenia for patients categorized by pre-treatment Neutropenia grade for Dara IV vs Dara SC for all patients, patients with BW≤ 65 kg and BW≤ 50 kg

Grade 3/4 Neutropenia Incidence	All Patients		≤ 65 kg		≤ 50 kg	
	Dara IV n=258	Dara SC n=260	Dara IV n=92	Dara SC n=93	Dara IV n=21	Dara SC n=22
Patients with Pre-treatment Grade ≥2 Neutropenia	13.5% (5/37)	26.1% (12/46)	11.1% (2/18)	40% (8/20)	0 (0/3)	20% (1/5)
Patients with No Pre-treatment or Grade 1 Neutropenia	6.8% (15/221)	10.3% (22/214)	8.1% (6/74)	15.1% (11/73)	5.6% (1/18)	29.4% (5/17)

Source: FDA reviewer's independent analysis

18.4 Additional Safety Analyses Conducted by FDA

Not Applicable.

18.5 Clinical Appendices

18.5.1 MMY3012 Eligibility Criteria

Inclusion Criteria:

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. Evidence of a response (PR or better based on investigator's determination of response by IMWG criteria) to at least 1 prior treatment regimen.
4. 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.

5. 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). A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.
   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.
6. ECOG Performance Status score of 0, 1, or 2.
7. 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 × 10^9/L (prior growth factor support is permitted);
   - Platelet count ≥50 × 10^9/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;
   - Total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required);
   - Estimated creatinine clearance >20 mL/min per 1.73m^2;
   - Albumin-corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium 6.5 mg/dL (≤1.6 mmol/L).
8. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.
9. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.
10. Each subject (or their legally acceptable representative) must sign an Informed Consent Form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

<u>Exclusion Criteria:</u>

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. The only exception is emergency use of a short

course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) before treatment.

3. Received autologous stem cell transplant within 12 weeks before the date of randomization, or the subject has previously received allogeneic stem cell transplant (regardless of timing).
4. Plans to undergo a stem cell transplant prior to progression of disease on this study (these subjects should not be enrolled to reduce disease burden prior to transplant).
5. History of malignancy (other than multiple myeloma) 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, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.
6. Clinical signs of meningeal involvement of multiple myeloma.
7. Either of the following:
   - Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) is <50% of predicted normal. Note that FEV1 testing also is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
   - Known moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification. (Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.)
8. Any of the following:
   - Known to be seropositive for human immunodeficiency virus (HIV)
   - Known to be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
   - Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
9. Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.
10. Clinically significant cardiac disease, including:
    - Myocardial infarction within 6 months before date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).
    - Uncontrolled cardiac arrhythmia (Grade 2 or higher by NCI-CTCAE Version 4.03) or clinically significant ECG abnormalities.
    - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula >470 msec.
11. Known allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, mAbs, human proteins, or their excipients (refer to daratumumab IB11), or known sensitivity to mammalian-derived products.
12. Plasma cell leukemia (>2.0 × 109/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein,

and skin changes) or amyloidosis.
13. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
14. Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.
15. Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
16. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study drug (except for investigational anti-myeloma treatments, which cannot be taken within 2 weeks before Cycle 1 Day 1).
17. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. Kyphoplasty or vertebroplasty are not considered major surgery. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question whether a procedure is considered a major surgery, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study.
18. Plasmapheresis within 28 days before randomization.

18.5.2 MMY2040 Eligibility Criteria

Inclusion Criteria:

1. ≥18 years of age.
2. Multiple myeloma diagnosed according to the IMWG diagnostic criteria
3. Measurable, secretory disease 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 MM, for subjects without measurable disease in the serum or the urine: serum Ig FLC ≥10 mg/dL and abnormal FLC ratio.
4. Meets one of the sets of the following criteria:
   a. 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)
   b. 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: presence of important comorbid condition(s) will make stem cell transplant intolerable for the subject. Sponsor review of these comorbid conditions and approval is required before the first dose of study treatment.
   c. For inclusion into the D-Rd for relapsed or refractory disease:
      - Relapsed disease is defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment

- Refractory disease is defined as either <25% reduction in M-protein or confirmed progressive disease (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
  - A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.
- 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

d. For inclusion in the D-Kd cohort for relapsed or refractory disease:
- Subject must have received only 1 prior line of therapy for MM which included at least 2 consecutive cycles of lenalidomide therapy
- A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.
- Subject must have achieved a response (PR or better based on investigator's evaluation of response by the IMWG criteria) to the first treatment regimen
- Subject must have progressed from or be refractory to the first line of treatment as defined below:
  - Relapsed disease is defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment
  - Refractory disease is defined as confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment (primary refractory patients are not eligible)

5. ECOG Performance Status grade of 0, 1, or 2.
6. Pretreatment clinical laboratory values during the Screening Phase (all cohorts):
   a. Hemoglobin ≥7.5 g/dL (≥4.65 mmol/L); D-Kd cohort 8.0 g/dL (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
   b. Absolute neutrophil count ≥1.0 × 10^9/L (prior growth factor support is permitted);
   c. Platelet count for D-Rd, D-Kd, and D-VRd cohorts >75 × 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count); for the D-VMP cohort: platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count ≥50 × 10^9/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count);
   d. Aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN);
   e. Alanine aminotransferase (ALT) ≤2.5 × ULN;
   f. For the D-Rd cohort: total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required); for the D-Kd, D-VMP, and D-VRd cohorts: total bilirubin ≤1.5 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
   g. Estimated creatinine clearance ≥40 mL/min (D-VMP cohort) or ≥30 mL/min (D-VRd and D-Rd cohorts); or ≥20 mL/min (D-Kd cohort)
   h. Corrected serum calcium ≤13.5 mg/dL (≤3.4 mmol/L) or free ionized calcium 6.5 mg/dL (≤1.6 mmol/L).

7. D-VRd and D-Rd cohorts: A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at screening, the first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing. D-VMP and D-Kd cohorts: A woman of childbearing potential must have a negative serum or urine pregnancy test at screening within 14 days prior to dosing. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.
8. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse, or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy), and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing, continue during the study, and for 3 months after receiving the last dose of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing study treatment (even after a successful vasectomy).
9. During the study, and for 3 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) and men must agree not to donate sperm for the purposes of assisted reproduction.
10. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion Criteria:

1. Prior or concurrent exposure to any of the following:
    - Daratumumab or other anti-CD38 therapies
    - Approved or investigational treatments for MM (including but not limited to conventional chemotherapies, IMiDs, or PIs) within 2 weeks of Cycle 1 Day 1
    - Maximum of 40 mg dexamethasone (or equivalent) daily for a maximum of 4 days up to 21 days prior to the 1st dose
    - Investigational drug (including investigational vaccines) or an invasive investigational medical device within 4 weeks or 5 half-lives (whichever is longer) before Cycle 1 Day 1, or is currently enrolled in another investigational study
    - ASCT within 12 weeks before the date of administration of study treatment, or allogeneic stem cell transplant (regardless of timing) for the D-Rd and D-Kd cohorts
    - For D-Rd cohort, only: Refractory to lenalidomide, (ie, subjects who had progression of disease while receiving lenalidomide therapy or within 60 days of ending lenalidomide therapy) or who are intolerant to lenalidomide (ie, discontinued due to any drug-related adverse event) while on lenalidomide treatment are not eligible for the lenalidomide-containing cohorts
    - For D-Kd cohort, only: Subject has previously received carfilzomib
2. History of malignancy (other than multiple myeloma) 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, that in the opinion of the investigator, with concurrence with the

sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.

3. Exhibits clinical signs of meningeal involvement of MM.
4. Either of the following:
   - Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) is <50% of predicted normal. Note that FEV1 testing also is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
   - Known moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification. (Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.)
5. Any of the following:
   - Known to be seropositive for human immunodeficiency virus (HIV)
   - Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
6. Known to be seropositive for hepatitis C (Anti-HCV antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
7. Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.
8. Clinically significant cardiac disease, including:
   - Myocardial infarction within 6 months before Cycle 1 Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).
   - Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities; or screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula >470 msec.
   - For K-Dd cohort only:
     - Transthoracic echocardiogram showing left ventricular ejection fraction (LVEF) <40%;
     - Uncontrolled hypertension, defined as an average systolic blood pressure >159 mmHg or diastolic >99 mmHg despite optimal treatment
9. Allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to daratumumab Investigator's Brochure and rHuPH20 Investigator's Brochure) or known sensitivity to mammalian-derived products. For D-Kd cohort only: allergy, hypersensitivity, or intolerance to Captisol.
10. Plasma cell leukemia, Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) or amyloidosis.
11. Unable to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
12. Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.

13. Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
14. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. Kyphoplasty or vertebroplasty are not considered major surgery. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question whether a procedure is considered a major surgery, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study.
15. Plasmapheresis within 28 days before Cycle 1 Day 1.
16. For D-VRd and D-VMP cohorts: Received a strong CYP3A4 inducer within 5 half-lives prior to randomization.
17. For D-VMP arm: neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. For D-Kd cohort: neuropathy or neuropathic pain Grade 3 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Emily Place, PhD, MPH	OOD/DHOT	Sections:	Select one: ✓ Authored ✓ Approved
	Signature: Emily J. Place -S Digitally signed by Emily J. Place -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Emily J. Place -S, 0.9.2342.19200300.100.1.1=2001028525 Date: 2020.04.24 11:13:54 -04'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections:	Select one: ✓ Authored ✓ Approved
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Clinical Pharmacology Reviewer	Yibo Wang, PhD	OCP/DCPI	Sections:	Select one: ✓ Authored ✓ Approved
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Clinical Pharmacology Team Leader	Hong Zhao, PhD	OCP/DCPII	Sections:	Select one: ✓ Authored ✓ Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S			
Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections:	Select one: ✓ Authored ✓ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Team Leader	Justin Earp, PhD	OCP/DPM	Sections:	Select one: ✓ Authored ✓ Approved
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Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections:	Select one: ✓ Authored ✓ Approved
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Clinical Reviewer	Andrea Baines, MD, PhD	OOD/DHMII	Sections:	Select one: ✓ Authored ✓ Approved
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Clinical Team Leader	Bindu Kanapuru, MD	OOD/DHMII	Sections:	✓ Select one: Authored ✓ Approved
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Statistical Reviewer	Haiyan Chen, PhD	OB/DBIX	Sections:	Select one: ✓ Authored ✓ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Yu-te Wu, PhD	OB/DBIX	Sections:	Select one: ✓ Authored ✓ Approved
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Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections:	Select one: ✓ Authored ✓ Approved
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Associate Director for Labeling	Stacy Shord, PharmD, BCOP, FCCP	OOD/DHMII	Sections: 1.1	Select one: ✓ Authored ✓ Approved
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Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHMII	Sections:	Select one: ✓ Authored ✓ Approved
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Division Director (Clinical), Acting	Nicole Gormley, MD	OOD/DHMII	Sections:	Select one: ✓ Authored ✓ Approved
	Signature: Nicole J. Gormley -S			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIMBERLY L SCOTT
04/30/2020 05:13:46 PM

BINDU N KANAPURU
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NICOLE J GORMLEY
05/01/2020 10:01:50 AM