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*APPLICATION NUMBER:*

**761036Orig1s000**

**MEDICAL / STATISTICAL REVIEW(S)**

## CLINICAL and STATISTICAL REVIEW

**Application Type** Original BLA  
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**Established Name** daratumumab  
**(Proposed) Trade Name** Darzalex  
**Applicant** Janssen Biotech, Inc.

**Formulations** 100mg/5mL, 400mg/20mL  
**Dosing Regimen** 16mg/kg intravenously once every week for 8 weeks, then once every 2 weeks for 16 weeks, then once every four weeks  
**Proposed Indication** For the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent.  
**Intended Population** ≥18 years of age

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## Glossary

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AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CR	complete response
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	good clinical practice
hr(s)	hour(s)
HR	hazard ratio
IA	Immunomodulating agent
IMWG	International Myeloma Working Group
IND	Investigational New Drug
ITT	intent to treat
kg	kilogram
m	months
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg	milligram per kilogram
MM	multiple myeloma
MR	minimal response
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not evaluable
NME	new molecular entity
ORR	objective response rate
OSI	Office of Scientific Investigation
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetics
PR	partial response
PT	Preferred Term
PMR	post-marketing requirement
RCT	randomized, controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sCR	stringent complete response
SOC	System Organ Class
TEAE	treatment emergent adverse event
TTP	time-to-progression
VGPR	very good partial response

## 1 Executive Summary

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### 1.1. Product Introduction

Daratumumab is a human monoclonal immunoglobulin G1 (IgG1) that binds to the cell surface molecule CD38. The proposed dose is 16 mg/kg actual body weight given weekly for 8 weeks, then every two weeks for 16 weeks, then every four weeks until disease progression. The infusion is diluted before given intravenously to a patient in an appropriate healthcare setting. Infusion time is at least (b) (4) hours for the first infusion and will take at least (b) (4) hours for subsequent infusions. Pre-medications and post-infusion medications are required.

The proposed indication is for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an immunomodulatory agent. Daratumumab is a new molecular entity.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness based on response rate, a surrogate endpoint for survival. This conclusion was based on the results of two clinical trials of daratumumab treatment of adult patients with relapsed or refractory multiple myeloma: a Phase 1/2 trial dose escalation with dose expansion of five dose schedule regimens and a Phase 2 randomized dosing trial with dose expansion.

Of 124 patients enrolled to the Phase 2 trial, 106 received the proposed dose and were the focus of the efficacy analysis. Results showed that ORR was achieved by 31 (29%) patients (95% CI: 21-39%) with a median DOR of 7.4 months. The results for the primary endpoint were consistent across the subpopulations tested. Stringent Complete Response was achieved by 3 (3%) patients (95% CI: 1-8%). Very Good Partial Response was achieved by 10 (9%) patients (95% CI: 5-17%).

Supportive evidence came from the 42 patients who received the proposed dose on the Phase 1/2 trial. ORR was achieved by 15 (36%) patients (95% CI: 22-52%) with a median DOR of 6.9 months.

### 1.3. Benefit-Risk Assessment

### **Benefit-Risk Summary and Assessment (page 1 of 2)**

Daratumumab is a human monoclonal immunoglobulin G1 (IgG1) that binds to the cell surface molecule CD38. The proposed indication is for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an immunomodulatory agent. Multiple myeloma is a plasma cell neoplasm characterized by the proliferation and accumulation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating immunoglobulin and/or free light chains, depressed immunity, and end-organ damage. CD38 glycoprotein is found on the surface of many cells, including hematopoietic cells at different levels of expression on the lineages. Myeloma plasma cells usually express strong CD38, similar to normal plasma cells. As a new molecular entity, daratumumab provides a novel mechanism of action for the treatment of patients with multiple myeloma. The benefit-risk assessment supports accelerated approval under Subpart H (21 CFR 314.510) for the proposed indication.

Multiple myeloma accounts for about 2% of all cancers and 17% of hematologic malignancies. An estimated 26,850 new cases of myeloma will occur in the U.S. in 2015 with an estimated 11,240 deaths. The diagnosis is most common in the 6<sup>th</sup> and 7<sup>th</sup> decades of life. Myeloma is more common in men than women and occurs twice as frequently in African Americans as in Caucasians. Myeloma is not found in children and only rarely in adults less than 30 years of age. With the introduction of chemotherapy, median survival is extended to 24 to 30 months from a natural history median survival of 7 months. The introduction of corticosteroids, proteasome inhibitors, immunomodulating agents, and stem cell transplant has further extended median survival to 5 to 6 years. Treatment responses are often transient; myeloma is not considered curable. Patients who are refractory or relapsed to both an immunomodulating agent and the proteasome inhibitor demonstrate low response rates. The median overall survival of patients with multiple myeloma who have received multiple salvage therapies is 9 months.

The efficacy of daratumumab was based on the results of two clinical trials of treatment of patients with relapsed or refractory multiple myeloma: a Phase 1/2 dose escalation trial with dose expansion of five dose schedule regimens and a Phase 2 randomized dosing trial with dose expansion. The optimal dose (16 mg/kg) and regimen was studied in a two arm, open-label trial of single-agent daratumumab. The primary endpoint was ORR. Of the 124 patients enrolled, 106 received the proposed dose and were the focus of the efficacy analysis. Patients had received a median of 5 prior treatments. Results showed that ORR was achieved by 31 (29%) patients (95% CI: 21-39%) with a median DOR of 7.4 months. Stringent Complete Response was achieved by 3 (3%) patients (95% CI: 1-8%). Very Good Partial Response was achieved by 10 (9%) patients (95% CI: 5-17%). Data to support the effectiveness of daratumumab came from the 42 patients who received the proposed dose on the Phase 1/2 trial. ORR was achieved by 15 (36%) patients (95% CI: 22-52%) with a median DOR of 6.9 months.

### **Benefit-Risk Summary and Assessment (page 2 of 2)**

The safety dataset included 237 patients with multiple myeloma treated with daratumumab as monotherapy on three trials. For the 156 patients at the proposed dose, the median time on treatment was 3.3 months (range: 0 to 20.0 months). For the subgroup of patients treated with daratumumab 16 mg/kg, key results from the review of safety through 30 days after the last dose of daratumumab showed that the SOCs with the highest rates of patients with SAEs were Infections and infestations (13%) and General disorders and administrative site conditions (8%). The most common SAEs were pneumonia (6%), general health deterioration (3%), pyrexia (3%), hypercalcemia (3%), cross-match incompatible (2%), and herpes zoster (2%). The most common (>20%) TEAE were fatigue, anemia, nausea, back pain, neutropenia, pyrexia, cough, thrombocytopenia, and upper respiratory infection. Pneumonia was reported for 11%. A grade  $\geq 3$  TEAE occurred in 56% of patients. The most common (>5%) were anemia, thrombocytopenia, neutropenia, and pneumonia. In the analysis of adverse events of specific interest, infusion reactions occurred with a median time of onset of 90 minutes. Four patients experienced Grade 2 or 3 bronchospasm within 90 minutes of initiation of daratumumab. The incidence of infusion interruptions due to adverse reactions was 40%. Cross-matching of RBCs for transfusion may be delayed. Daratumumab binds to CD38 on RBCs and causes agglutination when added to Coombs reagent. False positive indirect and direct Coombs test may result and persist for up to 6 months.

Patients entered into the trials were heavily pretreated and refractory to multiple lines of therapy, including the most effective therapies available. The enrolled population also appears consistent in terms of age and comorbidities with the U.S. population of patients with end-stage multiple myeloma. Response rates are consistent with the affect seen in other recent trials of new drugs for multiple myeloma and appear clinically meaningful. The primary risk to patients appears to be infusion reactions but adequate determination of safety cannot be made without an appropriate comparator arm in randomized trials. As a new molecular entity with a novel mechanism of action, prescribers will have a new treatment option to offer their patients with multiple myeloma. In addition to Phase 3 trials in patients with untreated multiple myeloma, the applicant has fully enrolled two randomized Phase 3 trials in patients with relapsed or refractory multiple myeloma: lenalidomide and dexamethasone with and without daratumumab, and bortezomib and dexamethasone with and without daratumumab. Successful completion and submission of either trial may be adequate, after review, for regular approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Survival for patients with relapsed or refractory multiple myeloma who have received available therapies is less than one year</li> <li>Disease response to treatment is reduced with each course of treatment received.</li> <li>Multiple myeloma is a symptomatic and life-threatening disease</li> </ul>	Relapsed or refractory multiple myeloma is a progressive and fatal disease.
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>Multiple myeloma is considered not curable with available chemoimmunotherapies</li> <li>Current treatments have toxicities that may limit their use</li> </ul>	Effective treatment for relapsed or refractory multiple myeloma is needed.
<b>Benefit</b>	<ul style="list-style-type: none"> <li>In 106 patients (median number of prior treatments: 5) on one single arm trial: the overall response rate was 29%, and the median duration of response was 7.4 months</li> <li>3 patients had a stringent complete response, 10 had a very good partial response</li> <li>In 42 patients who received the proposed dose in another trial: the overall response rate was 36%, and the median duration of response was 6.9 months</li> <li>Results from randomized trials with comparator arms are not yet available</li> </ul>	Treatment with daratumumab provided response in the treatment of relapsed or refractory multiple myeloma.
<b>Risk</b>	<ul style="list-style-type: none"> <li>Infusion reactions occurred in 48% of patients. Severe reactions were airway narrowing, shortness of breath, low oxygen level, and high blood pressure</li> <li>Common serious reactions were pneumonia, general physical health deterioration, fever, high calcium level, cross-match incompatible testing for red blood cell transfusion, and herpes zoster</li> <li>Red blood cell transfusions may be delayed to daratumumab interference with cross-match testing</li> </ul>	The overall short-term safety profile appears acceptable for patients with relapsed or refractory multiple myeloma.
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>Serious and life-threatening toxicities were avoided by pre-medication, monitoring, infusion interruptions and rate reductions, and post-infusion medications</li> <li>Daratumumab interference with cross-match testing for red blood cell transfusions caused transfusion delays</li> </ul>	The Prescribing Information and the Patient Information will provide 1) information on reducing risks from infusion reactions, 2) information on interference with cross-match testing for red blood cell transfusions and provide instructions on alternative solutions.

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Multiple myeloma (MM) is a plasma cell neoplasm characterized by the proliferation and accumulation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating immunoglobulin and/or free light chains, depressed immunity, and end-organ damage.

Multiple myeloma accounts for an estimated 1.6% of all cancers and 16.6% of hematologic malignancies. An estimated 26,850 new cases of myeloma will occur in the U.S. in 2015 with an estimated 11,240 deaths. The diagnosis is most common in the 6<sup>th</sup> and 7<sup>th</sup> decades of life. Myeloma is more common in men than women (7.9 vs. 5.1 per 100,000 persons per year). African Americans or Blacks are the most affected race and account for twice as many new cases of myeloma than Whites: 12.8 vs. 5.8 per 100,000 persons per year (Howlader, Noone, et al. 2015). Myeloma is not found in children.

With the introduction of chemotherapy, median survival is extended to 24 to 30 months from a natural history median survival of 7 months. The introduction of corticosteroids, proteasome inhibitors, immunomodulating agents, and stem cell transplant has further extended median survival to 5 to 6 years (Kumar, Rajkumar, et al. 2008).

### 2.2. Analysis of Current Treatment Options

Treatment of multiple myeloma is typically initiated when symptoms develop. Patients with symptomatic myeloma often respond to cytotoxic chemotherapy. However, responses are often transient; myeloma is not considered curable with available treatments. Table 1 lists all FDA approvals for multiple myeloma.

Current treatment regimens tend to be comprised of two to three agents; most all patients receive a proteasome inhibitor (bortezomib or carfilzomib) and an immunomodulatory agent (lenalidomide, pomalidomide, thalidomide) both early and late in the course of treatment of their disease.

Treatment for relapsed and/or refractory myeloma depends on disease- and patient-specific features, initial treatment regimen, and the duration of responses to initial and subsequent treatment. Single drug or combination regimens, stem cell transplant, or clinical trial therapy are all options for patients with relapsed or refractory myeloma. In patients who are refractory or relapsed to both an immunomodulating agent and the proteasome inhibitor bortezomib, ORR ( $\geq$ PR) ranged from 24% to the first therapy to 6% after the 5<sup>th</sup> regimen (Kumar, Lee, et al.

2012). The median overall survival of patients with multiple myeloma who have received multiple salvage therapies is 9 months.

Approvals for drugs in multiple myeloma have been supported by improvements in time-to-progression (TTP) or progression-free survival (PFS). Both include objective tumor progression measured in time from randomization; TTP does not include deaths. Accelerated approvals have been supported by overall response rate (ORR) results from single-arm trials.

When compared to dexamethasone alone as a single agent or in combination with dexamethasone, the agents bortezomib, lenalidomide, and thalidomide each demonstrated improvements of 2.7 to 16 months in TTP. In trials adding an investigational agent to a known single- or double-agent treatment regimen, differences in median PFS or TTP ranged from 2.8 to 8.7 months.

**Table 1 Currently Available Treatment for Multiple Myeloma**

<b>Drug Name Indication</b>	<b>Trial Type</b>	<b>Approval Date, Type</b>	<b>Approval Basis</b>	<b>Survival Benefit?</b>
Cytosan (cyclophosphamide) <i>For treatment of MM</i>		1959 <i>Regular</i>	Case series	NE
Alkeran tablet (melphalan) <i>For palliative treatment of MM</i>		1964 <i>Regular</i>	Case series	NE
BiCNU (carmustine) <i>For MM, with prednisone</i>		1977 <i>Regular</i>	Case series	NE
Alkeran injection (melphalan) <i>For palliative treatment of MM for whom oral therapy is not appropriate</i>	Alkeran IV injection + pred (n=203) vs. oral melphalan + pred (n=107)	1992 <i>Regular</i>	Response rate at 22 weeks: Oral 44% vs. IV 38%	NE
Velcade (bortezomib) <i>For 3<sup>rd</sup> line MM</i>	Single arm trial (n=256)	2003 <i>Accelerated</i>	ORR 28%	NE
Velcade (bortezomib) <i>For 2<sup>nd</sup> line MM</i>	RCT of Velcade vs. dex (n=669)	2005 <i>Regular</i>	TTP: 6.2 m. vs. 3.5 m. ΔTTP 2.7 m.	Yes HR 0.57, p<0.05 (median f/u 8.3 m.)
Velcade (bortezomib) <i>For untreated MM</i>	RCT of Velcade + melphalan + pred (VMP) vs. melphalan + pred (MP) (n=682)	2008 <i>Regular</i>	PFS: 18.3 m. vs. 14 m. Δ PFS 4.3 m.	Yes HR 0.61, p=0.0078

Drug Name <i>Indication</i>	Trial Type	Approval <i>Date, Type</i>	Approval Basis	Survival Benefit?
Revlimid (lenalidomide) <i>For 2<sup>nd</sup> line MM, with dex</i>	Two RCTs of Revlimid + dex vs. dex (n=341, n=351)	2006 <i>Accelerated</i>	Trial 1 TTP: 8.5 m. vs. 4.6 m. Δ TTP 3.9 m. Trial 2 TTP: NE (Rev+dex) vs. 4.6 m.	No
Thalomid (thalidomide) <i>For newly diagnosed MM</i>	Two RCTs: Thalomid + dex vs. dex (n =207) Thalomid + dex vs. placebo (n=470)	2006 <i>Accelerated</i>	Trial 1 ORR: 52% vs. 36% Trial 2 TTP: 22.5 m. vs. 6.5 m. Δ TTP 16 m.	Difference not statistically significant
Doxil (doxorubicin HCL liposome) <i>For 2<sup>nd</sup> line MM (no prior Velcade)</i>	RCT of Doxil + bort vs. bort (n=646)	2007 <i>Regular</i>	TTP: 9.3 m. vs. 6.5 m. Δ TTP 2.8 m.	No
Kyprolis (carfilzomib) <i>For 3<sup>rd</sup> line MM</i>	Single arm trial (n=266)	2012 <i>Accelerated</i>	ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8 m.	NE
Kyprolis (carfilzomib) <i>For 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> line MM, with len and dex</i>	Kyprolis + len/dex vs. len/dex (n=792)	2015 <i>Regular</i>	PFS: 26.3 m. vs. 17.6 m. Δ PFS 8.7 m.	Difference not statistically significant
Pomalyst (pomalidomide) <i>For 3<sup>rd</sup> line MM</i>	Pomalyst + dex vs. Pomalyst (n=221)	2013 <i>Accelerated</i>	PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.	NE
Pomalyst (pomalidomide) <i>For 3<sup>rd</sup> line MM</i>	Pomalyst + dex vs. Dex (n=455)	2015 <i>Regular</i>	PFS: 3.6 m. vs. 1.8 m. OS: 12.4 m. vs. 5.8m.	Yes HR 0.70, p=0.009
Farydak (panobinostat) <i>For 3<sup>rd</sup> line MM, with bort and dex</i>	RCT Farydak + bort/dex vs. bort/dex (n=768)	2015 <i>Accelerated</i>	Subgroup: prior tx bort and immunomodulatory agent and median 2 prior therapies (n=193) PFS: 10.6 m. vs. 5.8 m.	Difference not statistically significant

bort = bortezomib, dex = dexamethasone, len = lenalidomide, mDOR = median duration of response, m = months, MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone, RCT = randomized controlled trial, TTP = time to progression, Δ = difference

### 3 Regulatory Background

#### 3.1. U.S. Regulatory Actions and Marketing History

Daratumumab is a new molecular entity and is not currently marketed.

### 3.2. Summary of Pre-submission/Submission Regulatory Activity

The key U.S. pre-submission regulatory activities are provided in Table 2.

**Table 2 Regulatory History**

Date	Meeting or event
Jul 2007	pre-IND
Oct 2007	IND with clinical trial in relapsed multiple myeloma submitted
Jan 2013	EOP1 meeting to discuss two proposed phase 2/3 trials
Apr 2013	Fast Track Designation
May 2013	Designated a Breakthrough Therapy for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent
Jul 2013	Type B post-BT meeting to discuss the sponsor's comprehensive development program, product comparability, bortezomib dosing in their add-on trial, and daratumumab dose selection
Jan 2014	Type B meeting to discuss comparability drug product issues and proposed phase 3 trials in relapsed MM
May 2014	Type B EOP2 meeting to discuss two randomized add-on trials in patients with newly diagnosed multiple myeloma who are ineligible for transplant
Jun 2014	Type B meeting to discuss a trial of daratumumab as first line treatment in newly diagnosed hematopoietic stem cell transplant-eligible patients
Sep 2014	Type C meeting to discuss the use of the reflex assays proposed for the serum SPE/IFE assessments in daratumumab clinical studies
Dec 2014	Type C pre-pre-BLA (without trial results), primarily CMC
Mar 2015	Type B pre-BLA, discussed content of integrated analysis and summaries, analysis of infusion reactions, development of mitigation strategies for product interference with blood bank typing and determination of disease response

Daratumumab has FDA Orphan Drug Designation for the treatment of multiple myeloma and is therefore exempt from the Pediatric Research Equity Act pediatric study requirements.

### 3.3. Foreign Regulatory Actions and Marketing History

Daratumumab is not currently marketed in any country. The applicant's clinical development program has included consultation and interaction with European regulatory authorities and national agencies.

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

#### 4.1. **Office of Scientific Investigations (OSI)**

The Office of Scientific Investigations conducted inspections for Protocol MMY2002 at the clinical sites in Charlotte, NC (Site US10782) and in Philadelphia, PA (Site US10555) and for Protocol GEN501 in Boston, MA (Site 50125). These sites had the highest accrual, highest response rate, and/or highest rate of protocol deviations per patient. The inspection at Site 50125 was preliminarily classified as Voluntary Action Indicated for regulatory deficiencies, but according to the inspection review, there were no significant issues identified at any of the clinical sites that would affect the analyses.

The Sponsor (Janssen) was also audited. Inspection review determined that data submitted by the sponsor appear acceptable in support of the requested indication and that no specific action was indicated.

#### 4.2. **Product Quality**

Daratumumab is a human monoclonal immunoglobulin G1 (IgG1) that binds to the cell surface molecule CD-38. The protein contains [REDACTED] (b) (4) and has a molecular weight of approximately 148 kDa. During the course of the clinical trials, changes were made to the manufacturing process. Product from both processes was used in the pivotal trial to establish comparability. Manufacturing reviewers indicated that these materials were comparable to each other and that the commercial process material was comparable to that from the earlier manufacturing process.

The reviewers conclude that the manufacture of Darzalex (daratumumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. Approval was recommended.

#### **Immunogenicity**

Two immunoassay methods were used to detect anti-daratumumab antibodies in serum samples from clinical trials. Both assays were insufficiently sensitive to make an accurate determination of anti-drug antibodies. The reviewers recommend post-marketing requirements to develop and validate an assay with an appropriate level of tolerance to concentrations of daratumumab in clinical trial serum samples.

#### 4.3. **Clinical Microbiology**

Daratumumab is formulated without preservatives. Growth promotion studies demonstrated that the preparation for administration supported microbial growth. The reviewers agreed with the instructions to infuse the product within [REDACTED] (b) (4) hours at room temperature using an in-line 0.2

micron filter. Approval was recommended.

#### 4.4. **Nonclinical Pharmacology/Toxicology**

Daratumumab was found to bind to human and chimpanzee CD38, but not to CD38 from mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Repeat-dose toxicology studies of intravenous daratumumab were conducted in chimpanzees and monkeys.

In animals, daratumumab was found to target the hematopoietic and lymphatic systems, in addition to the liver and spinal cord and nervous system. Findings include:

- Hematopoietic and lymphatic systems: Increases in red blood cells, hemoglobin, and hematocrit; decreases in white blood cells and platelets (chimpanzee and monkey); lymphoid depletion/atrophy in thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch (monkey only).
- Liver: Elevated AST, ALT (chimpanzee only).
- Cytokine response reaction (chimpanzees only): Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest leading to one mortality.
- Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.

The applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. The Pre-clinical Pharmacology/Toxicology reviewer recommended approval.

#### 4.5. **Clinical Pharmacology**

Data from 232 patients with relapsed multiple myeloma enrolled in the three monotherapy trials were included in the analyses conducted the clinical pharmacology reviewers. The reviewers determined that the evidence of effectiveness and the proposed dose and regimen was sufficiently supported. The reviewers recommended approval.

##### 4.5.1. **Mechanism of Action**

CD38 protein has multiple functions such as receptor mediated adhesion, signaling and enzymatic activity. The binding of daratumumab to CD38 on the surface of tumor cells leads to complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell phagocytosis (ADCP), cell apoptosis, and modulation of CD38 enzymatic activity.

#### 4.5.2. Pharmacodynamics

The exposure-efficacy analysis showed that the objective response rate increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations  $\geq 270$   $\mu\text{g/mL}$  (median exposure). However, this analysis was confounded by baseline risk factors such as disease severity and the lack of control arm. There was no exposure-safety relationship for infusion related reactions, thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased rates of  $\geq$  grade 3 treatment emergent adverse events (TEAE), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. Additional data are needed to confirm this potential safety signal, and to characterize the safety of daratumumab in patients with multiple myeloma and baseline hepatic impairment. The reviewers recommend a post-marketing study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

#### 4.5.3. Pharmacokinetics

Daratumumab pharmacokinetics were linear and dose-proportionate over the range of doses tested in the clinical trial patients with multiple myeloma. The volume of distribution was 4.7 L and the elimination half-life was approximately 18 days. The central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Other intrinsic factors, including age, gender, mild to severe renal impairment and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab. No dose adjustment is needed for these intrinsic factors.

### 4.6. Devices and Companion Diagnostic Issues

The Division of Molecular Genetics and Pathology within the Center for Devices and Radiological Health reviewed the analytical validation report for the daratumumab-specific immunofixation assay (DIRA) under development by the sponsor. This was submitted to support the confirmation of daratumumab interference in testing required to make a determination of complete response (and stringent complete response) in patients with multiple myeloma. The reflex assay is needed because the drug product may interfere with standard serum protein electrophoresis and immunofixation assessments. The assay was used in trials submitted in this Application.

The reviewers find the assay acceptable for the purposes of clinical studies. Given the lack of specificity identified in the report, additional investigation of patient samples and validation are required before the assay can be considered reliable to confirm daratumumab interference.

#### **4.7. Consumer Study Reviews**

The Division of Medication Error Prevention and Analysis reviewed the proposed Prescribing Information and the proposed carton and vial labels. They identified improvements for both to increase the readability and prominence of important information, promote safe use of the product, and mitigate confusion. These recommendations were followed in the relevant documents.

## **5 Sources of Clinical Data and Review Strategy**

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### **5.1. Table of Clinical Studies**

The applicant submitted data from 5 clinical trials of daratumumab. Of these 5 trials, 3 were studies of daratumumab monotherapy for treatment of multiple myeloma and 2 were studies of daratumumab in combination with treatments of multiple myeloma. Table 3 lists the trials emphasized in this review.

**Table 3 Clinical Trials**

Trial and Status	Trial Design and Primary Endpoint	Regimen, Schedule, Route	Treatment Duration/ Follow up	No. of Patients Enrolled	Study Population	Countries and No. of Centers
<b>Controlled Studies to Support Efficacy and Safety</b>						
<b>Uncontrolled Studies to Support Efficacy and Safety</b>						
MMY2002 Ongoing	Phase 2, open-label efficacy of 2 dosing regimens  ORR (≥PR)	<i>Group A:</i> daratumumab 16 mg/kg IV on Days 1, 8, 15, and 22 of Cycles 1 and 2 (qw dosing), on Days 1 and 15 of Cycles 3 to 6 (q2w dosing), and on Day 1 of Cycle 7 and subsequent cycles (q4w dosing) <i>Group B:</i> daratumumab 8 mg/kg IV for all cycles (q4w dosing)	Until disease progression, Unacceptable toxicity, or discontinuation of study treatment	<i>Group A:</i> 106 <i>Group B:</i> 18 <i>Planned:</i> Up to 150	MM after ≥3 prior therapies including a PI and an IA or is double refractory to both a PI and an IA	Canada: 6 Spain: 4 US: 16
GEN501 Ongoing	Phase 1/2 <i>Part 1:</i> Open-label, dose escalation <i>Part 2:</i> Open-label, single-arm  Safety	<i>Part 1:</i> daratumumab 0.005 to 24 mg/kg IV <i>Part 2:</i> daratumumab 8 or 16 mg/kg IV	<i>Part 1:</i> 8 weeks <i>Part 2:</i> 96 weeks or until unacceptable toxicity or disease progression	<i>Part 1:</i> 32 <i>Part 2:</i> 72 <i>Planned:</i> Up to 112	Relapsed/refractory MM	<i>Part 1:</i> Denmark: 2 Netherlands: 1 Sweden: 1 <i>Part 2:</i> Denmark: 2 Sweden: 2 Netherlands: 1 US: 1
<b>Studies to Support Safety</b>						
GEN503 Ongoing	Phase 1/2, open-label, dose escalation  Safety	28-day cycle regimen for both phases: <u>Daratumumab</u> on days 1, 8, 15, and 22 of Cycles 1 and 2 (qw dosing), on Days 1 and 15 of Cycles 3 to 6 (q2w dosing), and on Day 1 of Cycle 7 and subsequent cycles (q4w dosing). <u>Lenalidomide</u> 25 mg/day PO on Days 1-21 <u>Dexamethasone</u> 40 mg/week <i>Phase 1:</i> daratumumab 2 to 16 mg/kg IV <i>Phase 2:</i> daratumumab 16 mg/kg IV	Until disease progression or unacceptable toxicity	<i>Phase 1:</i> 13 <i>Phase 2:</i> 32 <i>Planned:</i> 42 to 58	Relapsed/refractory MM	Denmark: 2 Netherlands: 1 UK: 2 Italy: 2 US: 1 France: 3

Trial and Status	Trial Design and Primary Endpoint	Regimen, Schedule, Route	Treatment Duration/ Follow up	No. of Patients Enrolled	Study Population	Countries and No. of Centers
MMY1001 Ongoing	Phase: 1b Open-label, nonrandomized  Safety, tolerability, and dosing with VD, VMP, Pom- dex, and VTD	In the VD, VTD, and VMP regimens, daratumumab qw IV for 6 wks (equivalent to 2x VD/VTD cycles and 1x VMP cycle). Subsequently, q3w in combination with applicable backbone treatment regimen. In the Pom-dex regimen, daratumumab qw IV for 2 cycles, then q2w for 4 cycles, and thereafter q4w. <u>Backbone Regimens:</u> In VD and VTD, bortezomib 1.3 mg/m <sup>2</sup> SC injection twice a week for four 21-day cycles, followed by qw injections for 14 cycles or until transplant; dex 20 mg on the day of and after bortezomib or daratumumab; thalidomide 100 mg PO daily for 21 days. In VMP, bortezomib 1.3 mg/m <sup>2</sup> SC injection twice a week for one 6-week cycle, followed by qw for subsequent cycles; melphalan 9 mg/m <sup>2</sup> PO, and prednisone 60 mg/m <sup>2</sup> PO on Days 1 to 4 of each cycle. In the Pom-dex regimen, pomalidomide 4 mg/day PO once daily on Days 1 to 21 days of a 28-day cycle. Dex 40 mg PO (subjects ≤75yrs) or 20 mg PO (subjects >75 yrs) per week.	For the maximal allowed treatment duration or until disease progression, unacceptable toxicity, or discontinuation of study treatment	VD+Dara=6 VTD+Dara=11 VMP+Dara=8 Pom-dex+Dara=24 Planned: 130	Symptomatic MM and measurable secretory disease	France: 6 Spain: 6 US: 9

Trial and Status	Trial Design and Primary Endpoint	Regimen, Schedule, Route	Treatment Duration/ Follow up	No. of Patients Enrolled	Study Population	Countries and No. of Centers
<b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b>						
MMY1002 Ongoing	Phase 1, open-label, dose escalation  Tolerability and safety	<i>Treatment Phase:</i> <i>First Period:</i> intense dosing regimen for Weeks 1-9: first infusion (Week 0) with a 3-week resting period followed by 6 qw dosing until Week 8 (total 7 infusions). <i>Second Period:</i> less intense dosing regimen from Week 10 until End of Treatment in 28 days Cycles: q2w infusions until Week 24 (total 8 infusions, from Cycle 1 to Cycle 4), then q4w infusions (from Cycle 5). Two dose levels: 8 mg/kg and 16 mg/kg.	Until disease progression, unmanageable AEs, or discontinuation of study treatment	8 mg/kg: 4 16 mg/kg: 5 Planned: Up to 12	Japanese with relapsed or refractory MM	Japan: 2

AE = adverse event; dara = daratumumab; dex = dexamethasone; IA = immunomodulating agent; IV = intravenous; kg = kilogram; m = meter; mg= milligram; MM = multiple myeloma; PI = proteasome inhibitor; PO = *per os* (by mouth); pom = pomalidomide; qw = once every week; q2w = every 2 weeks; q4w = every 4 weeks; SC = subcutaneous; VD = Velcade + dexamethasone; VMP = Velcade + melphalan + prednisone; VTD = Velcade + thalidomide + dexamethasone

## 5.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant information in the public domain

Clinical data was provided in the Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model Implementation). Also submitted were the define files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The reviewers were able to duplicate the analysis results based on the applicant's submitted datasets.

This review was primarily based on analyses of Trials MMY2002 and GEN501. These two trials provide efficacy and safety data for 106 and for 42 patients respectively, who received the proposed marketing dose. Historical data from recent treatment trials in patients with relapsed and/or refractory multiple myeloma were required to provide context to the interpretation of the results of these single-arm trials.

Results from the 5 trials listed in Table 3 were used in the analysis of safety. The review emphasis was placed on the daratumumab 16mg/kg monotherapy dose proposed for marketing.

Sections 6 and 7 of this Review were performed jointly by Mr. Miller and Dr. Wang. Analysis by Dr. Wang was performed using SAS 9.4 (SAS Institute, Inc.) Analyses by Mr. Miller were performed largely using JMP 11.0 (SAS Institute, Inc.). MedDRA Adverse Events Diagnostic (MAED) 1.3 (Clinical Trials and Surveys Corporation & FDA) was used to assess for safety signals. Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

## **6 Review of Relevant Individual Trials Used to Support Efficacy**

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### **6.1. Trial MMY2002**

#### **6.1.1. Study Design**

##### **Overview and Objective**

Trial MMY2002 is an open-label, multicenter, phase 2, two-part trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose and schedule randomization and expansion cohorts using the early and final drug products. The primary objective of Part 1 was to select the optimal dose and schedule; for Part 2, overall response rate (ORR) was the primary efficacy endpoint. The secondary objectives were to evaluate: safety and tolerability of daratumumab, DOR, TTR, TTP, PFS, OS, exploration of biomarkers, and predictive of response to daratumumab.

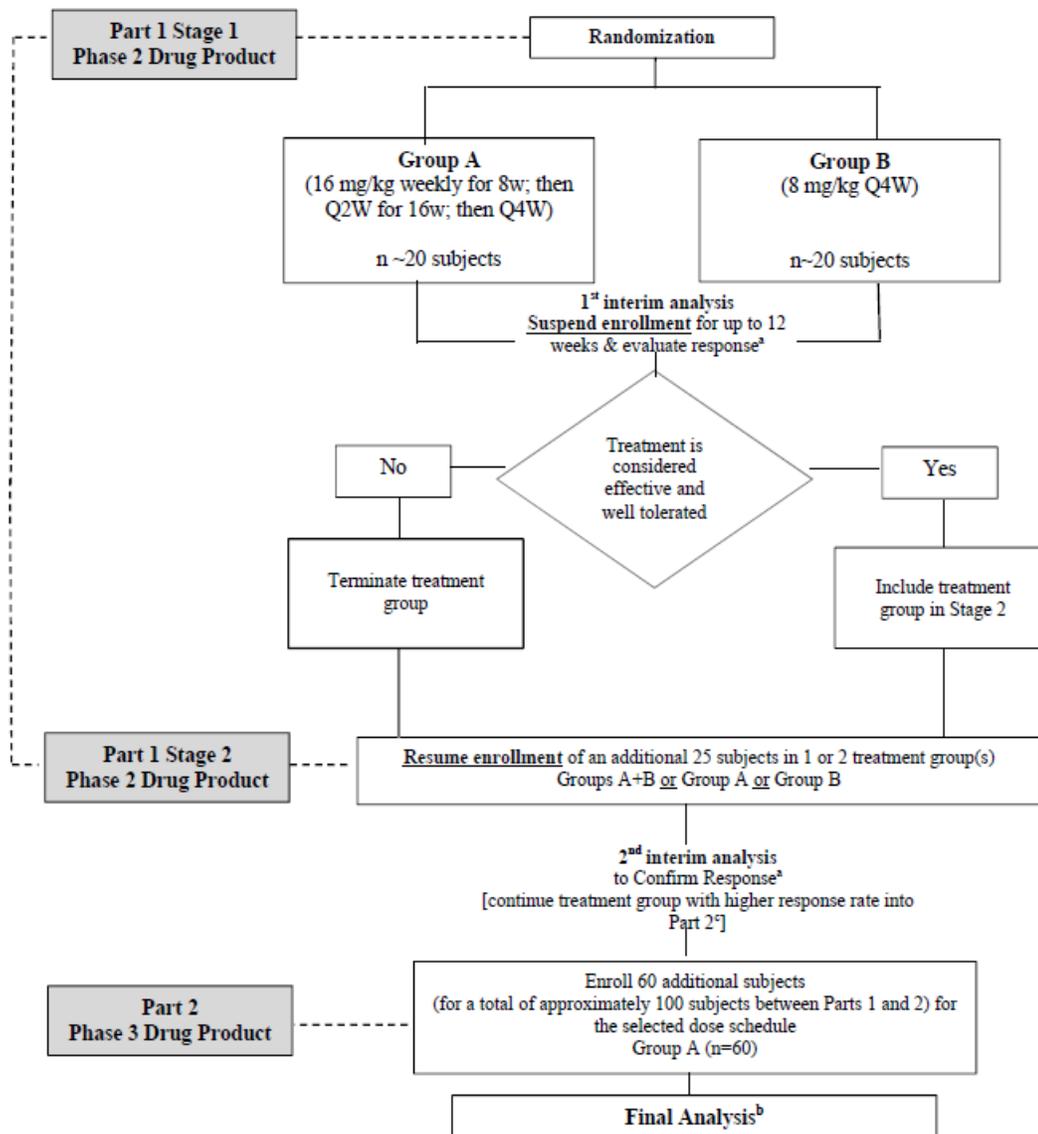
##### **Trial Design**

The key eligibility criteria was for up to 150 patients with multiple myeloma who had received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulating agent, or whose disease was double refractory to agents in both of these classes. Refractory disease was defined as nonresponse while on therapy or progression of disease within 60 days of stopping therapy for patients who achieved a minimal response (MR) or better.

After the screening period (a maximum 21 days), treatment started and was continued until disease progression, for unacceptable toxicity, or for other reasons listed in the protocol. After treatment, follow-up was to continue until death, consent withdrawal, loss of contact/lost to follow-up, or the end of study.

The planned study design (from the protocol) is shown in Figure 1. Patients were centrally randomized to Group A or B. Group A received the dose regimen of 16mg/kg weekly for 8 weeks, 16mg/kg every 2 weeks for 16 weeks, then 16mg/kg every 4 weeks. This dose was selected as it appeared to maximally saturate the target of CD38 for all time points in a majority of patients. Patients in Group B received 8mg/kg every 4 weeks. This dose was selected to better determine the dose response relationship while maintaining near complete CD38 suppression.

**Figure 1 Trial MMY2002 Schematic**



<sup>a</sup> Response will be assessed by the Sponsor based on available data (eg, pharmacodynamics, efficacy, safety, biomarkers).

<sup>b</sup> Confirmation of response by the IRC is required.

<sup>c</sup> If only 1 treatment group proceeded to Part 1 Stage 2, this will be the dose that is used in Part 2 of the study.  
 Q2W=every 2 weeks; Q4W=every 4 weeks; w=week(s)

[Source: Jansen Clinical Study Report, Section 3.1.1, p.25/1926, in M5.3.5.2]

Diagnostic criteria and the definition of need for treatment included in the eligibility criteria are consistent with the target population in the U.S. Patients were required to have documented multiple myeloma as defined by the criteria below and evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

- Prior documentation of monoclonal plasma cells in the bone marrow  $\geq 10\%$  or presence

of a biopsy-proven plasmacytoma.

- Presence of measurable disease at baseline as defined by any of the following:
  - Serum M-protein level  $\geq 1.0$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours; or
  - IgA multiple myeloma: Serum M-protein level  $\geq 0.5$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours; or
  - Light chain multiple myeloma: Serum immunoglobulin free light chain (FLC)  $\geq 10$  mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.
- Evidence of response (i.e., achieved  $\geq 25\%$  reduction in M-protein for  $\geq 6$  weeks [MR]) to at least 1 of their prior treatment regimens.

The expectations for prior treatments received are also consistent with contemporary treatment of multiple myeloma in the U.S. Patients were required to have received an alkylating agent ( $\geq 2$  cycles or 2 months) either alone or in combination with other myeloma treatments. One course of an alkylating agent for autologous stem cell transplantation alone or in combination was acceptable. Patients must have also:

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

OR

- Disease was double refractory to a PI and an IA. For subjects who received more than 1 type of PI, their disease was to be refractory to the most recent one. Similarly, for those who received more than 1 type of IA, their disease was to be refractory to the most recent one.

A single line of therapy could consist of 1 or more agents, and could include induction, hematopoietic stem cell transplantation, and maintenance therapy (specified in protocol). Radiotherapy, bisphosphonate, or a single short course of steroids (i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

Only patients 18 years of age and older were allowed to enter the trial. This is appropriate as multiple myeloma does not occur in children and is rare in adults less than 30 years of age. An ECOG performance status of 0, 1, or 2 was required.

Key exclusion criteria were:

- Previous daratumumab or other anti-CD38 therapies
- Anti-myeloma treatment within 2 weeks before Cycle 1, Day 1
- Non-secretory multiple myeloma based upon standard M-component criteria (i.e., measurable serum/urine M-component) unless the baseline serum FLC level was elevated
- Allogeneic stem cell transplant or ASCT within 12 weeks before Cycle 1, Day 1

- Cumulative corticosteroids more than the equivalent of  $\geq 140$  mg of prednisone within the 2-week period before Cycle 1, Day 1
- History of other malignancy within 5 years before Cycle 1, Day 1 (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, was considered cured with minimal risk of recurrence)
- Clinical signs of meningeal involvement of multiple myeloma

Excluded were patients with the following comorbidities:

- Chronic obstructive pulmonary disease
- Hepatitis B, hepatitis C, or HIV
- Clinically significant cardiac disease
  - Myocardial infarction within one year
  - Unstable or uncontrolled angina or heart failure NYHA Class III-IV
  - Arrhythmias requiring treatment or intervention
  - Prolonged QT interval at screening (QTcF  $>470$  msec)

Given that multiple myeloma occurs in older patients who may likely have one of these comorbidities, the applicability of the findings to the overall multiple myeloma population may be limited. Given the early phases of study and the limited experience with the agent, exclusion of some co-morbidities was warranted. Future trials with expanded inclusion criteria will be necessary to better understand how to safely treat such patients.

Cycle 1 Day 1 was to occur within 72 hours after randomization. The first visit of a cycle was to be 4 weeks after the start of the previous cycle. Patients would continue to receive study agent until disease progression, unacceptable toxicity, or other reasons listed in the protocol.

The infusion solution was to be prepared as a 1000-mL or 500-mL dilution of daratumumab in sterile, pyrogen-free 0.9% sodium chloride. Daratumumab was to be administered as an IV infusion given through a well-functioning IV catheter using an infusion pump or syringe pump. The study agent was to be filtered by using an inline filter (0.2  $\mu$ M) during the infusion. Each dose was to be calculated based on the patient's weight rounded to the nearest kilogram. All infusions were to be performed as outpatient visits.

Patients received daratumumab at their randomized dose and schedule. Doses given within 3 days of the scheduled dose were permitted. The first daratumumab infusion was to be diluted in 1,000 mL of 0.9% NaCl and administered at an initial rate of 50 mL/hr. If the first infusion was well-tolerated (defined by an absence of  $>$ Grade 1 infusion-related reactions during the first 3 hours), then the second infusion was to be diluted in 500 mL of 0.9% NaCl and administered at an initial rate of 50 mL/hr and increased by 50-mL/hr increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hr. In the absence of infusion-related reactions/hypersensitivity, the rate of the infusion was to be escalated in increments of 50-

mL/hr every 60 minutes in the first 3 hours to a maximum rate of 200 mL/hr. The applicant's infusion guidelines are provided in Table 4.

**Table 4 Daratumumab Infusion Guidelines**

First Infusion		Second Infusion		Subsequent Infusions	
Time (minutes)	mL/hr	Time (minutes)	mL/hr	Time (minutes)	mL/hr
0-60	50	0-60	50 <sup>a</sup>	0-60	100 <sup>b</sup>
61-120	100	61-120	100	61-120	150
121-180	150	121-180	150	121-180	200
181-240	200	181-	200 <sup>e</sup>	181- <sup>d</sup>	200 <sup>e</sup>
241-300	200				
301-360	200				
361- <sup>c</sup>	200 <sup>e</sup>				
<b>Total mL to be infused</b>	<b>1000 mL</b>		<b>500 mL</b>		<b>500 mL</b>

- <sup>a</sup> If the patient's first infusion of daratumumab is well-tolerated (defined as an absence of > Grade 1 infusion-related reactions during the first 3 hours), the second infusion will be administered at an initial rate of 50 mL/hour and increased by 50-mL/hour increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hour. If the previous infusion rate is not well-tolerated, instructions for the first infusion rate will be used.
- <sup>b</sup> If the patient's first 2 infusions of daratumumab are well-tolerated (defined as an absence of > Grade 1 infusion-related reactions during a final infusion rate of  $\geq 100$  mL/hour), subsequent infusions will be administered at an initial rate of 100 mL/hour and increased by 50-mL/hour increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hour. If the previous infusion rate is not well-tolerated, instructions for the second infusion rate will be followed.
- <sup>c</sup> Infusion should be completed in approximately 6 hours and 30 minutes
- <sup>d</sup> Infusion should be completed in approximately 3 hours and 15 minutes.
- <sup>e</sup> Any overflow that remains in the IV bag should also be given to ensure that all drug is infused.

[Source: Jansen Clinical Study Report, Section 3.6, p. 32/1926, in M5.3.5.2]

All patients were to receive pre-infusion medications one hour ( $\pm 15$  minutes) prior to each daratumumab dose. For the first and second infusions, methylprednisolone 100mg IV (or an equivalent intermediate- or long-acting corticosteroid) was given. Intravenous administration was recommended, and oral substitution was allowed. For subsequent daratumumab infusions, 60 mg of IV methylprednisolone was given. Also one hour prior to all daratumumab infusions, acetaminophen 650 to 1000mg orally (or paracetamol) and diphenhydramine 25 to 50 mg (or equivalent) was to be given.

For the prevention of delayed infusion reactions, all patients were to receive an oral corticosteroid equivalent to 20mg methylprednisolone once daily for the 2 days following all daratumumab infusions. Recommendations for patients with compromised pulmonary function (e.g., FEV1 <75% predicted) included consideration of additional antihistamine, short-acting  $\beta_2$  adrenergic receptor agonist aerosol, or other control treatments.

Daratumumab infusions were to be delayed for the following:

- Grade 4 hematologic toxicity, or Grade 3 or higher thrombocytopenia with bleeding
- Grade 3 or higher non-hematologic toxicities with the following exceptions
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment
  - Grade 3 diarrhea that responds to antidiarrheal treatment
  - Isolated Grade 3  $\gamma$ -glutamyl transferase elevation
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Among other reasons, treatment was to be discontinued if a dose was delayed for more than 28 days if 3 consecutive planned doses were missed for reasons other than toxicity. No dose modifications (increase or decrease) to the 16mg/kg dose were allowed.

Observation by trained study staff at the clinic was required during infusions to monitor for infusion related reactions and intervene as necessary. Specific monitoring criteria were provided, including the following:

- Patients should be treated with acetaminophen, antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. Bronchospasm, urticaria, or dyspnea, may require antihistamines, oxygen, corticosteroids, and/or bronchodilators. Hypotension may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

Recommended concomitant therapies included:

- Bisphosphonates for patients with evidence of lytic destruction of bone or with osteopenia
- Tumor lysis syndrome prophylaxis (e.g., hydration, allopurinol) for at-risk patients with high tumor burden
- *Pneumocystis jirovecii* pneumonia prophylaxis
- Herpes zoster reactivation prophylaxis during the Treatment phase

Permitted therapies while on daratumumab included full supportive care, including colony stimulating growth factors, erythropoietin, transfusion, and hydration for prevention of myeloma-related kidney disease.

Patients were assessed for safety every week during the first 2 cycles, every 2 weeks for cycles 3-6, and then every 4 weeks while on treatment. There were 2 monthly post-treatment visits and patients were then followed every 12 weeks for survival. Patients were assessed for efficacy by:

- bone marrow aspirate/biopsy after 3 cycles and to confirm sCR, CR, or relapse from CR
- skeletal survey as clinically indicated to determine response or progression
- assessment of extramedullary plasmacytomas for patients with a history of

plasmacytomas or as clinically indicated, every 4 weeks by physical examination and every 12 weeks for radiologic assessment

The applicant's tables of the protocol schedule of events are provided as Table 5.

**Table 5 Trial MMY2002 Schedule of Procedures and Events**

Assessments	Study Visits										
	Screening Phase <sup>a</sup>	Treatment Phase						Follow-up Phase			
		Cycles 1 & 2 <sup>b</sup>				Cycles 3-6 <sup>b</sup>		Cycles 7+ <sup>b</sup>	EOT <sup>c</sup>	FUP <sup>d</sup>	Survival <sup>d</sup>
Study Day	-21 to -1	1	8	15	22	1	15	1	Post-Treatment Week 4	Post-Treatment Week 8	q12wks
Informed consent	Subjects must sign the informed consent form before any study-specific procedures are performed.										
Eligibility criteria	X										
Spirometry test (subjects with COPD or asthma)	X										
Demography/height/medical history	X										
Physical examination	X	Only a symptom-directed physical examination is required									
Weight <sup>e</sup>		X	X	X	X	X	X	X	X		
Vital sign measurements <sup>e</sup>	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X				X		X	X		
Electrocardiogram	X	Day 1 of Cycles 2, 4, 6, and every 2 cycles thereafter							X		
Part 1 Dosing											
-Treatment Group A:											
Daratumumab 16 mg/kg dosing (IV) <sup>f</sup>		X	X	X	X	X	X	X			
Pre and postinfusion medications <sup>g</sup>		X	X	X	X	X	X	X			
-Treatment Group B:											
Daratumumab 8 mg/kg dosing (IV) <sup>f</sup>		X				X		X			
Pre and postinfusion medications <sup>g</sup>		X				X		X			
Part 2 Dosing		One of the above regimens will be used, dependent upon results from Part 1									
Adverse event monitoring		Continuous from time of ICF until 30 days after last study drug dose								Dara-related SAEs	
Concomitant medication recording		Continuous from time of ICF until 30 days after last study drug dose									

Assessments	Study Visits										
	Screening Phase <sup>a</sup>	Treatment Phase						Follow-up Phase			
		Cycles 1 & 2 <sup>b</sup>				Cycles 3-6 <sup>b</sup>		Cycles 7+ <sup>b</sup>	EOT <sup>c</sup>	FUP <sup>d</sup>	Survival <sup>d</sup>
Laboratory Assessments <sup>h</sup>	-13 to -1										
Blood type assessment/wallet card	X										
Urine or serum pregnancy test (women of childbearing potential only)	-7 to C1D1 dosing	As clinically indicated									
Biochemistry <sup>i</sup>	X	X				X		X	X		
Hematology <sup>j</sup>	X	X	X	X	X	X	X	X	X		
Biomarkers: See Table 2											
Pharmacokinetics, immunogenicity, blood sample for drug product characterization: See Table 3											

Assessments	Study Visits										
	Screening Phase <sup>a</sup>	Treatment Phase						Follow-up Phase			
		Cycles 1 & 2 <sup>b</sup>				Cycles 3-6 <sup>b</sup>		Cycles 7+ <sup>b</sup>	EOT <sup>c</sup>	FUP <sup>d</sup>	Survival <sup>d</sup>
Disease Evaluations (Blood/Urine) <sup>kkk</sup>											
Study Day	-13 to -1	1	8	15	22	1	15	1	Post-Treatment Week 4	Post-Treatment Week 8	q12wks
Serum β <sub>2</sub> -microglobulin	X										
Qlg (IgA, IgM, IgG, IgD, IgE)	X										
SPEP	X	X				X		X	X <sup>k</sup>	X <sup>k</sup>	
UPEP (24-hr urine sample)	X <sup>k</sup>	X				X		X	X <sup>k</sup>	X <sup>k</sup>	
Serum calcium corrected for albumin	X	X				X		X	X <sup>k</sup>	X <sup>k</sup>	
Serum FLC & serum/urine immunofixation	X	When CR is suspected or maintained all subjects, for light chain MM subjects serum FLC to be performed Day 1 of every cycle/every 28 days (+/-3days)									
Disease Evaluations (Other) <sup>k</sup>	-21 to -1										
Bone marrow aspirate/biopsy <sup>l</sup>	X <sup>l</sup>	At C4D1 (±7 days) and to confirm sCR, CR, or relapse from CR (immunohistochemistry or immunofluorescence)									
Skeletal survey <sup>m</sup>	X <sup>m</sup>	As clinically indicated									
Assess extramedullary plasmacytomas <sup>n</sup>	X <sup>n</sup>	Measurable sites every 4 weeks (if applicable) (for physical examination) and every 12 weeks (for radiologic) for subjects with a history of plasmacytomas or as clinically indicated for others								X <sup>k</sup>	
Subsequent therapy/Survival <sup>d</sup>											X <sup>d</sup>

Abbreviations: C1D1=Cycle 1, Day 1; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; FLC=free light chain; FUP=Follow-up Phase; ICF=informed consent form; IV=intravenous; Qlg=quantitative immunoglobulins; MM=multiple myeloma; MRI=magnetic resonance imaging; PK=pharmacokinetics; PD=progressive disease; SAE=serious adverse event; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis

- The Screening Phase begins when the first Screening procedure is conducted. Screening tests should be performed within 21 days of Cycle 1 Day 1 except for laboratory assessments, disease evaluations (see footnote k), and pregnancy testing.
- All cycles are 28 days. Cycle 1 Day 1 should occur within 72 hours of randomization if applicable.
- The EOT Visit will occur 4 weeks after the last dose of study drug or as soon as possible before the start of subsequent therapy. In addition, blood draws are required at 1 week and 2 weeks after the last dose for biomarker and PK assessments, as shown in Table 2 and Table 3. If a subject discontinues and moves on to subsequent therapy, all attempts should be made to collect any remaining scheduled pharmacokinetic/immunogenicity/biomarker samples.
- All subjects are to have a Follow-up Visit 8 weeks after the last dose of study drug. For subjects who discontinue study drug before PD, disease evaluations should be performed as specified in footnote k. After PD is documented, survival status, subsequent anticancer treatment, and response to subsequent anticancer treatment will be recorded for all subjects until study end.
- Weight and vital signs are to be measured only on study drug dosing days. For the first and second infusions, vital signs are to be measured at the following time points: immediately before the start of the infusion; at 30 minutes, 1 hour, 90 minutes, 2 hours, and 3 hours 30 minutes after the start of the infusion; at the end of the infusion; and 30 minutes, 1 hour, and 2 hours after the end of the infusion. In case of an infusion-related reaction, maintain these vital sign timepoints in relation to the initial start of infusion (See Section 6.4.3). For all other infusions, vital signs will be measured immediately before the infusion start and at the end of the infusion.
- Every effort should be made to keep subjects on the planned dosing schedule; however, doses within 3 days of the scheduled dose will be permitted. For Treatment Group B, in Cycle 1, dosing should occur on a Monday or Tuesday, so that the PK sampling does not fall over a weekend. Refer to Section 6.2 for details on the daratumumab infusion.
- Subjects will receive preinfusion medications before all daratumumab infusions, and postinfusion medications on the 2 days following all daratumumab infusions (beginning the day after the infusion). Refer to Sections 6.4.1 and 6.4.2 for additional information.
- Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug.
- Testing may be performed up to 2 days before the study drug administration day. Results of these laboratory tests must be evaluated before each study drug administration. At Cycle 1 Day 1, these tests do not need to be repeated if they have been performed within 5 days. Hematology testing on Day 15 of Cycles 3 to 6 is optional for Treatment Group B.
- Samples must be sent to the central laboratory.
- Disease evaluations must be performed as follows:
  - Serum and urine tests are to be performed within 14 days before Cycle 1 Day 1. It is not mandatory to collect these samples again at the Cycle 1 Day 1 visit unless central lab results are not available for screening for any reason. If the 24-h urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained.
  - Results from skeletal survey and radiologic plasmacytoma assessments performed as routine follow up for subject's disease within 42 days before Cycle 1 Day 1 and bone marrow aspirate/biopsy within a maximum of 42 days before Cycle 1 Day 1 may be used without these tests being repeated.
  - Serum and urine tests are to be performed every 28 days on the scheduled assessment day (±3 days). All responses (including PD based on biochemical investigations) require 2 consecutive assessments by central lab for confirmation. Once PD is confirmed, subsequent disease assessment timepoints are not required.
  - For subjects who discontinue study drug before PD, disease evaluations should continue to be performed at the frequency specified below until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent to study participation, or end of the study whichever occurs first. Once PD is confirmed subsequent disease assessment timepoints are not required.
    - Every 4 weeks (±3 days): SPEP and 24-hour UPEP assessments, and serum calcium corrected for albumin
    - Every 4 weeks (±3 days): physical examination of extramedullary plasmacytomas
    - Every 12 weeks (±14 days): radiologic imaging of extramedullary plasmacytomas
    - When CR is suspected or maintained: serum FLC, serum/urine immunofixation; when sCR is suspected: bone marrow analysis (as per footnote l).
    - As clinically indicated: skeletal survey
    - Evidence of clinical relapse will also be documented at the time at which it is first detected.
- Perform bone marrow aspirate and/or biopsy locally at Screening for disease characterization (morphology, cytogenetics [by conventional karyotype and/or fluorescence in-situ hybridization], and at least 1 of the following: immunohistochemistry, immunofluorescence, or flow cytometry). At C4D1 (±7 days), bone marrow aspirate and/or biopsy done locally at a minimum for morphology and when applicable for CR (morphology); for sCR: immunohistochemistry, immunofluorescence (requires kappa/lambda ratio from analysis of ≥100 cells; see Table 6 footnote a), or 2- to 4-color flow cytometry. Additional bone marrow aspirates of up to 5 mL collected during these time points will be sent to a central laboratory and may be used for biomarker analyses to assess CD38 expression levels, to determine bone marrow immunophenotype, to evaluate expression of complement inhibitory proteins (CIP), and to investigate markers of resistance and progression.
- A skeletal survey, including the cranium, is required at Screening. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression) for all subjects.
- Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. The methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will be monitored for PD only.

Exploratory Biomarker and Pharmacogenomic Blood Sample Collection

Assessments	Study Visits												Follow-up Phase		
	Screening Phase	Treatment Phase										EOT	FUP	Survival	
		Cycle 1					Cycle 2		Cycles 3-6		Cycle 7+				
Study Day	-21 to -1	1	2	4	8	15	22	1	15	1	15	1	Post-Treatment Weeks 1,2,4	Post-Treatment Week 8	q12wks
Bone marrow aspirate/biopsy	See Table 1														
Pharmacogenomic <sup>a</sup>															
Whole blood (PGx-FcγR, C1QA, C1QB)	X														
Biomarkers <sup>a</sup>															
Treatment Group A:															
Whole blood for immunophenotyping		X				X		X		X		C7, C8, C12 only	Week 1, 2, 4		
Plasma for sCD38 and complement proteins		X	X	X	X	X		X		X		C7, C8, C12 only	Week 1, 2, 4		
Treatment Group B:															
Whole blood for immunophenotyping		X	X	X	X	X	X	X		X		C7, C8, C12 only	Week 1, 2, 4	X	
Plasma for sCD38 and complement proteins		X	X	X	X	X	X	X		X		C7, C8, C12 only	Week 1, 2, 4	X	
Whole blood for ADCC		X						X		C3 only			Week 4 only		
Serum for CDC and proteomics		X						X		C3 only			Week 4 only		
Serum for pathophysiological biomarkers of infusion reaction		X <sup>b</sup>													

ADCC=antibody-dependent cell-mediated cytotoxicity; CDC=complement dependent cytotoxicity; EOT=End of Treatment; FcγR=FC gamma receptors; FUP=Follow-up; PGx=pharmacogenomics

Note: All samples must be taken prior to dosing unless otherwise specified.

a) Samples must be sent to the central laboratory or specialty laboratory. Pharmacogenomic sampling is optional.

b) Blood samples will be collected from all subjects before infusion and at 4 hours after the start of infusion.

[Source: Jansen Clinical Protocol 54767414MMY2002, Section 3.6, pp. 18-22/92, in M5.3.5.2]

## Study Endpoints

The primary endpoint was ORR, defined as the proportion of patients who achieve a partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) based on the International Myeloma Workshop Consensus Panel 1 criteria (Rajkumar, Harousseau, et al. 2011) using results from a central laboratory. Investigator-determined response was made on an ongoing basis while the sponsor used a computerized algorithm to derive response and progressive disease assessment. An independent review committee (IRC) was established to review data and assess response of all patients on trial.

Secondary endpoints included:

- Clinical benefit rate, which included minimal response, PR, VGPR, CR, and sCR
- Time to disease progression defined as the number of days from the start of daratumumab to the date of progressive disease
- Progression-free survival defined as the time from the start of daratumumab to disease progression or death
- Time to response defined as the time from the start of daratumumab to response of PR or better
- Duration of response defined as the interval from an initial response of PR or better to

disease progression

- Overall survival defined from the start of daratumumab to death
- Serum/urine M-protein or FLC reduction
- Change in the percentage of bone marrow plasma cells
- Overall safety of daratumumab by evaluation of the incidence of treatment emergent adverse events, death, laboratory results, vital signs, physical examination findings, and ECG results.

*Comment: No clinical outcome assessments, such as patient-reported outcomes, were included in this trial.*

### **Statistical Analysis Plan**

The study consisted of 2 parts. In Part 1, a Simon's randomized 2-stage design was utilized to establish an optimal dose schedule, with subjects randomized to 8 mg/kg or 16 mg/kg groups. Within each randomized treatment group, a 2-stage design was utilized to allow an inefficacious dose schedule to be terminated early for futility. Phase 2 drug product was used in Part 1 of the study. The objective of Part 2 was to descriptively characterize the Phase 3 drug product with respect to pharmacokinetics, pharmacodynamics, efficacy, and safety at the dose selected in Part 1. Central randomization was implemented in Part 1 Stage 1.

### **Sample Size Considerations**

Up to 150 subjects were planned (up to 90 subjects enrolled in Part 1 and 60 subjects in Part 2). The null hypothesis is that the ORR is at most 15%, and the alternative hypothesis is that the ORR is at least 40%. With a one-sided  $\alpha$  of 2.5%, and a power of 85%, the total sample size within each randomized treatment group in Part 1 is 36 response-evaluable subjects. Assuming a non-evaluable rate of 10%, a total of up to 40 subjects were to be enrolled within each randomized treatment group. The Stage 1 analysis was to be performed when approximately 15 subjects were enrolled in each treatment group with sufficient data i.e., up to 8 weeks of treatment, to be evaluable for response. Future enrollment into each treatment group was to be terminated if it was determined that the treatment group during the first stage was considered ineffective and/or not well tolerated. If a treatment group proceeded to the second stage with a total of 36 evaluable subjects combined across both stages, the null hypothesis will be rejected if 11 or more responses were observed.

If both treatment groups proceed to Stage 2, a sample size of 36 evaluable subjects per treatment group will also lead to a probability of 89% if the best treatment group has a true ORR of 40% while other treatment groups have a true ORR of 25% or less.

If it is determined at the end of Part 1 that a treatment group will be further evaluated in Part 2, then up to an additional 60 subjects will be enrolled in Part 2 and treated with Phase 3 drug

product. This will bring the total number of subjects treated during the study up to approximately 100 for the selected treatment group.

All treated Analysis Set: All subjects who received at least 1 dose of daratumumab were used for all efficacy and safety analyses.

Per-Protocol Analysis Set: The per-protocol analysis set excluded all treated subjects who have had major protocol deviations due to not meeting all inclusion/exclusion criteria.

The primary efficacy summaries are based on IRC assessment. Efficacy results based on the computerized algorithm assessment, which was to be validated by the IRC, are also presented.

Efficacy Analysis Method for ORR: The efficacy analysis population was based on all treated analysis set. The number and percentage of subjects in response categories were tabulated by treatment group. The analysis for ORR was performed based on both IRC assessment and algorithm assessment. The kappa statistic and 95% CI were calculated for agreement between IRC assessment and the computerized algorithm assessment for response. Descriptive summaries and forest plots were to be provided for the subgroups

Efficacy Analysis Method for TTP: Median TTP and the corresponding 95% CI were provided for subjects in the 16 mg/kg group.

Efficacy Analysis Method for PFS: Median PFS and the corresponding 95% CI were provided for subjects in the 16 mg/kg group only given the small sample size in the 8 mg/kg group.

Efficacy Analysis Method for Time to Response: Descriptive statistics (mean, standard deviation, median, and range) were provided to summarize time to response and time to best response for responders in the 16 mg/kg group.

Efficacy Analysis Method for DOR: Median duration of response and the corresponding 95% CI were provided for subjects in the 16 mg/kg group.

Efficacy Analysis Method for OS: Median OS and the corresponding 95% CI were provided for subjects in the 16 mg/kg group only given the small sample size in the 8 mg/kg group.

*Reviewer comment: Time to event endpoints cannot be evaluated based on a single arm trial.*

### Interim Analysis

The study was designed with 2 pre-planned interim analyses for futility and efficacy respectively. The two interim analyses were performed at the end of Stage 1 in Part 1 to select a dose schedule with a higher ORR using Phase 2 drug product. The second interim analysis was performed at the end of Stage 2 of Part 1 to evaluate the effectiveness and tolerability of the 2 dose schedules in Part 1 before the initiation of Part 2.

## Protocol Amendments

Modifications to the protocol and relation to patient enrollment are highlighted in Table 6. No major enrollment criteria or endpoints were changed. These changes likely did not impact the integrity of the trial or interpretation of the results.

**Table 6 Trial MMY2002 Landmarks and Protocol Amendments**

Date	Landmark
11 Jul 2013	Original protocol
26 Nov 2013	34 patients enrolled Amendment 1 <ul style="list-style-type: none"> <li>Increased sample size to approximately 20 subjects per treatment group in Part 1 Stage 1 (from 15)</li> <li>Administration guidelines changed from mg/hr to mL/hr</li> <li>Added an alternative treatment group (Group C; at the discretion of the Sponsor) in Part 1, Stage 2, if either or both of the existing Treatment Groups A or B were considered as ineffective and/or not well tolerated</li> <li>Platelet count criteria was revised to <math>&lt;75 \times 10^9/L</math> for patients whom <math>&gt;50\%</math> of bone marrow nucleated cells are plasma cells; otherwise platelet count <math>&lt;50 \times 10^9/L</math> in patients with bone marrow plasma cells <math>\leq 50\%</math></li> </ul>
07 Feb 2014	41 patients enrolled Amendment 2 <ul style="list-style-type: none"> <li>Increased the number of patients in Part 2 to approximately 60 (from 30), following the discontinuation of the dose schedule of 8 mg/kg every 4 weeks (Treatment Group B) at the end of Stage 1. This provided for the exposure of approximately 100 patients to the 16mg/kg dosing regimen.</li> <li>Removed treatment Group C</li> <li>Modified biomarker (serum CD38 and complement proteins) sampling time points based on findings from Part 1</li> <li>Allowed crossover for patients in Group B to Group A</li> <li>Changed the timing of the one treatment bone marrow biopsy from 8 weeks to 12 weeks</li> <li>Modified platelet count criteria to <math>&lt;50 \times 10^9/L</math> (transfusion support within 7 days before the laboratory test was not permitted)</li> </ul>
06 Jun 2014	Last patient enrolled (n = 124)
09 Jul 2014	Amendment 3 <ul style="list-style-type: none"> <li>Changed the timing of the one treatment bone marrow biopsy from Cycle 3 to Cycle 4, Day 1</li> </ul>
09 Jan 2015	Last subject observation prior to submission of the BLA
30 June 2015	120 day safety update

## Data Quality and Integrity: Sponsor's Assurance

The Sponsor incorporated a strategy to assure data quality and integrity. These included the selection of qualified investigators and appropriate study sites, review of protocol procedures

with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions were to be provided for collection, handling, storage, and shipment of samples. Guidelines for eCRF completion were to be provided and reviewed with study-site personnel before the start of the study. The sponsor was to review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies were to be resolved with the investigator, as appropriate. The data in the study database was to be verified for accuracy and consistency with data sources.

### 6.1.2. Study Results

#### Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

#### Financial Disclosure

The applicant submitted financial disclosure information from all investigators for this trial. No financial interests or arrangements were reported (see Financial Disclosure in the Appendix).

#### Patient Disposition

Of the 157 patients screened for trial enrollment, 124 were enrolled and treated. At the data cut-off date for this analysis, 85% of patients on 16mg/kg had discontinued treatment. Most patients discontinued for progression of disease, 5% discontinued for an adverse event.

**Table 7 Trial MMY2002 Patient Disposition**

Analysis set: All Treated	8 mg/kg N=18	16 mg/kg N= 106	Total N=124
<b>Discontinuations</b>	16 (88.9%)	90 (84.9%)	106 (85.5%)
Progressive disease	16 (88.9%)	82 (77.4%)	98 (79.0%)
Adverse Event	0	5 (4.7%)	5 (4.0%)
Withdrawal of consent	0	3 (2.8%)	3 (2.4%)
Death	0	0	0

#### Protocol Violations/Deviations

Major protocol violations occurred in 9 patients on 16mg/kg. All seven patients who did not meet entry criteria should have been excluded for one or more of the following: absolute neutrophil count  $\leq 1 \times 10^9/L$ , hemoglobin  $\leq 75$  g/L, platelet  $< 50 \times 10^9/L$ , platelet transfusion within 7 days of first dose, or CrCl  $\leq 20$  mL/min/1.73 mm<sup>2</sup>. Narratives provided for each patient

were reviewed; no unexpected toxicity was reported for these patients.

**Table 8 Trial MMY2002 Major Protocol Deviation; All Treated Analysis Set**

	8 mg/kg N=18	16 mg/kg N= 106	Total N=124
<b>Major protocol deviation</b>	2 (11.1%)	9 (8.5%)	11 (8.9%)
Entered but did not satisfy criteria	2 (11.1%)	5 (4.7%)	7 (5.6%)
Dosed while experiencing Grade 4 thrombocytopenia	0	3 (2.8%)	3 (2.4%)
Screening ECG not done	0	1 (0.9%)	1 (0.8%)

### Demographic Characteristics

The median age of all treated patients was 64 years, 52% were male. Most (82%) subjects were White, 12% of subjects were Black or African American. The majority of patients were from U.S. (87%). In the 16 mg/kg group the median age was 64 years; 49% of subjects were male. Most subjects (79%) were White, and 14% were Black or African American.

Compared to the U.S. population of patients with multiple myeloma, where the incidence is higher in men than women and in African Americans than other races, this trial is somewhat limited in representation. In terms of median age, percentage of patients over 65 years, and percentage of African American patients, this trial was successful in enrolling greater numbers of these patients than other trials in multiple myeloma that the Agency has reviewed. Also considering the relatively large cohorts of patients with renal dysfunction (see Safety population demographic Table 23) and the prior treatments received (see Prior therapy Table 10), the population enrolled appears representative of patients with relapsed and refractory myeloma today.

**Table 9 Trial MMY2002 Demographic Characteristics; All Treated Analysis Set**

	8 mg/kg N=18	16 mg/kg		Total N=106	Total N=124
		Part 1 N=41	Part 2 N=65		
<b>Sex</b>					
Male	12 (66.7%)	25 (61.0%)	27 (41.5%)	52 (49.1%)	64 (51.6%)
Female	6 (33.3%)	16 (39.0%)	38 (58.5%)	54 (50.9%)	60 (48.4%)
<b>Age</b>					
Mean years (SD)	64.2 (7.7)	62.6 (10.39)	63.1 (9.82)	62.9 (10.00)	63.1 (9.68)
Median (years)	65.5	63.0	64.0	63.5	64.0
Min, max (years)	(49, 76)	(31, 84)	(32, 84)	(31, 84)	(31, 84)
<b>Age Group</b>					
≥ 18 - < 65 years	8 (44.4%)	23 (56.1%)	35 (53.8%)	58 (54.7%)	66 (53.2%)
≥ 65 years					
> 65 - < 75 years	8 (44.4%)	13 (31.7%)	23 (35.4%)	36 (34.0%)	44 (35.5%)
≥ 75 years	2 (11.1%)	5 (12.2%)	7 (10.8%)	12 (11.3%)	14 (11.3%)

	8 mg/kg N=18	16 mg/kg		Total N=106	Total N=124
		Part 1 N=41	Part 2 N=65		
<b>Race</b>					
White	17 (94.4%)	33 (80.5%)	51 (78.5%)	84 (79.2%)	101 (81.5%)
Black or African American	0	4 (9.8%)	11 (16.9%)	15 (14.2%)	15 (12.1%)
Asian	0	1 (2.4%)	3 (4.6%)	4 (3.8%)	4 (3.2%)
Other	1 (5.6%)	3 (7.2%)	0	3 (2.7%)	4 (3.2%)
<b>Region</b>					
United States	15 (83.3%)	28 (68.3%)	47 (72.3%)	75 (70.8%)	90 (86.5%)
Rest of the World	3 (16.7%)	13 (31.7%)	18 (27.7%)	31 (29.2%)	34 (13.5%)

### Baseline Characteristics

In the 16 mg/kg group, the time since initial diagnosis was 4.8 years, the median number of prior lines of therapy was 5; 82% of subjects had more than 3 prior lines of therapy. All patients had been treated with a proteasome inhibitor and with an immunomodulatory agent. Eighty five subjects (80%) had a prior autologous stem cell transplant (ASCT). Specific therapies are provided in Table 10.

**Table 10 Trial MMY2002 Prior Therapy; All Treated Analysis Set**

	8 mg/kg N=18	16 mg/kg		Total N=106	Total N=124
		Part 1 N=41	Part 2 N=65		
<b>Number of lines of prior therapy</b>					
≤3	6 (33.3%)	8 (19.5%)	11 (16.9%)	19 (17.9%)	25 (20.2%)
>3	12 (66.7%)	33 (80.5%)	54 (83.1%)	87 (82.1%)	99 (79.8%)
Mean (SD)	5.1 (2.35)	5.3 (2.10)	5.7 (2.50)	5.6 (2.35)	5.5 (2.35)
Median	5.0	5.0	5.0	5.0	5.0
Range	(2, 11)	(2, 11)	(2, 14)	(2, 14)	(2, 14)
<b>Prior proteasome inhibitor</b>					
Bortezomib	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Carfilzomib	6 (33.3%)	19 (46.3%)	34 (52.3%)	53 (50.0%)	59 (47.6%)
<b>Prior immunomodulating agent</b>					
Lenalidomide	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Pomalidomide	9 (50.0%)	26 (63.4%)	41 (63.1%)	67 (63.2%)	76 (61.3%)
Thalidomide	6 (33.3%)	14 (34.1%)	33 (50.8%)	47 (44.3%)	53 (42.7%)
<b>Prior chemotherapy</b>					
Alkylating agents	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Anthracyclines	12 (66.7%)	16 (39.0%)	39 (60.0%)	55 (51.9%)	67 (54.0%)
<b>Prior ASCT</b>					
Prior ASCT	17 (94.4%)	34 (82.9%)	51 (78.5%)	85 (80.2%)	102 (82.3%)
<b>Prior radiotherapy</b>					
Prior radiotherapy	3 (16.7%)	18 (43.9%)	19 (29.2%)	37 (34.9%)	40 (32.3%)

Patients enrolled to the trial received therapies and regimens appropriate for their disease. Most patients were refractory to one or more available agents as detailed in Table 11.

**Table 11 Trial MMY2002 Refractory Status to Prior Therapy; All Treated Analysis Set**

	8 mg/kg N=18	16 mg/kg			Total N=124
		Part 1 N=41	Part 2 N=65	Total N=106	
<b>Refractory by class</b>					
Both proteasome inhibitor and immunomodulating agent	15 (83.3%)	39 (95.1%)	62 (95.4%)	101 (95.3%)	116 (93.5%)
Proteasome inhibitor only	1 (5.6%)	1 (2.4%)	2 (3.1%)	3 (2.8%)	4 (3.2%)
Immunomodulating agent only	0	1 (2.4%)	0	1 (0.9%)	1 (0.8%)
<b>Refractory by agent</b>					
Bortezomib	16 (88.9%)	38 (92.7%)	57 (87.7%)	95 (89.6%)	111 (89.5%)
Carfilzomib	6 (33.3%)	19 (46.3%)	32 (49.2%)	51 (48.1%)	57 (46.0%)
Lenalidomide	16 (88.9%)	40 (97.6%)	53 (81.5%)	93 (87.7%)	109 (87.9%)
Pomalidomide	9 (50.0%)	26 (63.4%)	41 (63.1%)	67 (63.2%)	76 (61.3%)
Thalidomide	4 (22.2%)	9 (22.0%)	20 (30.8%)	29 (27.4%)	33 (26.6%)
Alkylating agent	13 (72.2%)	30 (73.2%)	52 (80.0%)	82 (77.4%)	95 (76.6%)
<b>Refractory by last line of therapy</b>	15 (83.3%)	39 (95.1%)	64 (98.5%)	103 (97.2%)	118 (95.2%)

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All daratumumab infusions were given under observation. The mean relative dose intensity was 99% of the target dose.

All patients were on concomitant medications. The most common ( $\geq 50\%$ ) therapeutic classes were analgesics (91%), anti-virals (83%), anti-bacterials (73%), psycholeptics (68%), acid-related disorder drugs (63%), and bone structure and mineralization drugs (52%). The most common concomitant medication therapeutic classes started after starting daratumumab were analgesics (68%), anti-bacterials (61%), antihistamines (35%), acid-related disorder drugs (33%), corticosteroids (30%), psycholeptics (24%), mineral supplements (23%), obstructive airway disease drugs (22%), and anti-virals (20%).

Granulocyte-colony stimulating factors were used in 11% of the patient population, initiated in 7% after starting daratumumab. Erythropoietin stimulating agents were used in 11% of the patient population, initiated in 9% after starting daratumumab.

Medications started specifically for management of infusion reactions are discussed in Section 8.5.1.

### Efficacy Results – Primary Endpoint

The primary analysis population consisted of data from patients enrolled to part 1 and part 2 combined. The objective response rate (ORR) which included partial response or better, among

all patients treated with 16 mg/kg was 29%, including 3 stringent complete responses and 10 very good partial responses (VGPR); i.e., VGPR or better was observed in 13 of 106 (12%) patients treated with 16 mg/kg. The ORR among patients treated with 8 mg/kg daratumumab was 11%, which did not meet the protocol specified criteria for continuation of this dose.

None of the complete responses in this trial were impacted with the interference of daratumumab on serum protein electrophoresis and immunofixation assays used. Two of the three patients with stringent complete responses had IgA myeloma disease and one had free light chain only disease; none had IgG kappa myeloma protein disease.

Patients on trial who had a best response of VGPR and persistent positive immunofixation or SPEP were tested using an assay under development by the applicant. This assay has been validated for clinical trial use only. None of the other responses tested demonstrated interference with daratumumab, meaning VGPR was confirmed to be the best response.

**Table 12 Trial MMY2002 Objective Response Rates based on IRC Assessment; All Treated Analysis Set**

	8 mg/kg				16 mg/kg			
	N=18		Part 1 N=41		Part 2 N=65		Total N=106	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
<b>ORR</b>	2 (11.1%)	(1.4%, 34.7%)	13 (31.7%)	(18.1%, 48.1%)	18 (27.7%)	(17.3%, 40.2%)	31 (29.2%)	(20.8%, 38.9%)
Stringent Complete Response	0		2 (4.9%)	(0.6%, 16.5%)	1 (1.5%)	(0.0%, 8.3%)	3 (2.8%)	(0.6%, 8.0%)
Complete Response	0		0		0		0	
Very good partial response	1 (5.6%)	(0.1%, 27.3%)	6 (14.6%)	(5.6%, 29.2%)	4 (6.2%)	(1.7%, 15.0%)	10 (9.4%)	(4.6%, 16.7%)
Partial response	1 (5.6%)	(0.1%, 27.3%)	5 (12.2%)	(4.1%, 26.2%)	13 (20.0%)	(11.1%, 31.8%)	18 (17.0%)	(10.4%, 25.5%)

Objective response rate was also determined by a computerized algorithm (see Table 13). There was high concordance of the ORR results between IRC and computerized algorithm assessments (kappa coefficient 0.98 [95% CI: 94%, 100%]). The ORR based on the computerized algorithm assessment was 28.3% (95% CI= [20.0%, 37.9%]) which is consistent with the primary ORR result based on IRC assessment.

**Table 13 Trial MMY2002 Objective Response Rates based on Computerized Algorithm**

	8 mg/kg				16 mg/kg			
	N=18		Part 1 N=41		Part 2 N=65		Total N=106	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
<b>ORR</b>	2 (11.1%)	(1.4%, 34.7%)	13 (31.7%)	(18.1%, 48.1%)	17 (26.2%)	(16%, 38.5%)	30 (28.3%)	(20.0%, 37.9%)
Stringent Complete Response	0		2 (4.9%)	(0.6%, 16.5%)	0		2 (1.9%)	(0.2%, 6.6%)
Complete Response	0		0		1 (1.5%)	(0.0%, 8.3%)	1 (0.9%)	(0.0%, 5.1%)
Very good partial response	1 (5.6%)	(0.1%, 27.3%)	6 (14.6%)	(5.6%, 29.2%)	4 (6.2%)	(1.7%, 15.0%)	10 (9.4%)	(4.6%, 16.7%)
Partial response	1 (5.6%)	(0.1%, 27.3%)	5 (12.2%)	(4.1%, 26.2%)	12 (18.5%)	(9.9%, 30.0%)	17 (16.0%)	(9.6%, 24.4%)

An analysis of ORR (IRC assessed) based on per-protocol analysis set was also performed. The ORR based on per-protocol analysis set was 30.7% (95% CI= [21.9%, 40.7%]) which is again consistent with the primary ORR result.

**Table 14 Trial MMY2002 Objective Response Rates based on IRC Assessment; Per-protocol Analysis Set**

	8 mg/kg				16 mg/kg			
	N=16		Part 1 N=39		Part 2 N=62		Total N=101	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
<b>ORR</b>	2 (12.5%)	(1.6%, 38.3%)	13 (33.3%)	(19.1%, 50.2%)	18 (29.0%)	(18.2%, 41.9%)	31 (30.7%)	(21.9%, 40.7%)
Stringent Complete Response	0		2 (5.1%)	(0.6%, 17.3%)	1 (1.6%)	(0.0%, 8.7%)	3 (3.0%)	(0.6%, 8.4%)
Complete Response	0		0		0		0	
Very good partial response	1 (6.3%)	(0.2%, 30.2%)	6 (15.4%)	(5.9%, 30.5%)	4 (6.5%)	(1.8%, 15.7%)	10 (9.9%)	(4.9%, 17.5%)
Partial response	1 (6.3%)	(0.2%, 30.2%)	5 (12.8%)	(4.3%, 27.4%)	13 (21.0%)	(11.7%, 33.2%)	17 (17.8%)	(10.9%, 26.7%)

*Reviewer comment: During the pre-NDA meeting, the agency requested additional justification for analysis performed on the combination of part 1 and part 2. The justification was determined to provide for a valid analysis. For this review, analyses were performed for parts 1 and 2 separately as well as for combination of the two parts.*

### Data Quality and Integrity – Reviewers’ Assessment

The clinical reviewer audited a sample of case report forms for consistency with datasets and patient narratives. The overall quality and integrity of the application was acceptable.

### Efficacy Results – Secondary and other relevant endpoints

Time to Response: Based on IRC assessment of the 31 patients with response on 16mg/kg, the median time to response was 1 month (range: 0.9 to 5.6 months).

Duration of Response: Based on IRC assessment of the 31 patients with response, after a median duration of follow-up of 9.3 months, the median duration of response was 7.4 months.

**Table 15 Trial MMY2002 Duration of Response:  
Responders in All Treated Analysis Set**

	16 mg/kg N=31
<b>Duration of Response</b>	
Number of events (%)	17 (54.8%)
Number of censored (%)	14 (45.2%)
Median*, months (95% CI)	7.4 (5.5, NE)
Range, months	1.2, 13.1+

\* Kaplan-Meier estimate; NE = not estimable; + censored

### Dose/Dose Response

There were no large dose-ranging trials. Dose modifications for toxicity or for lack of efficacy were not studied.

### Durability of Response

There were too few patients on treatment for long duration to assess the effect of daratumumab over time. Only 4% of patients were on treatment for 12 months or more.

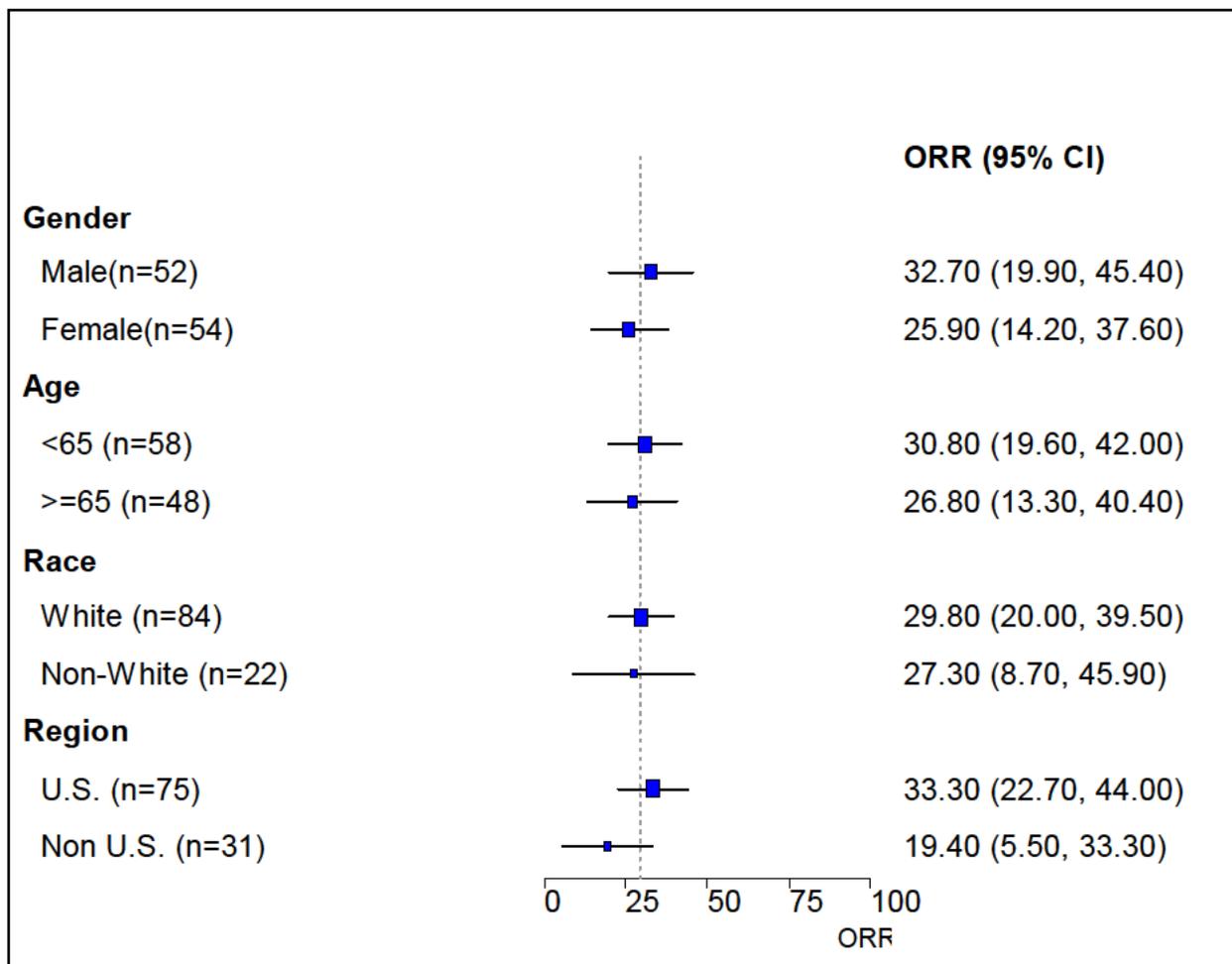
### Persistence of Effect

No patients were retreated with daratumumab after daratumumab was discontinued.

### Additional Analyses Conducted on the Individual Trial

Analyses of objective response rates were consistent among the demographic subgroups based on age, gender, and race. A difference was observed between U.S. and non-U.S. populations but the difference is not significant given the limited sample size.

**Figure 2 Trial MMY2002 Subgroup Analyses on Objective Response Rates based on IRC Assessment; All Treated – 16 mg/kg Group**



## 6.2. Trial GEN501

### 6.2.1. Study Design

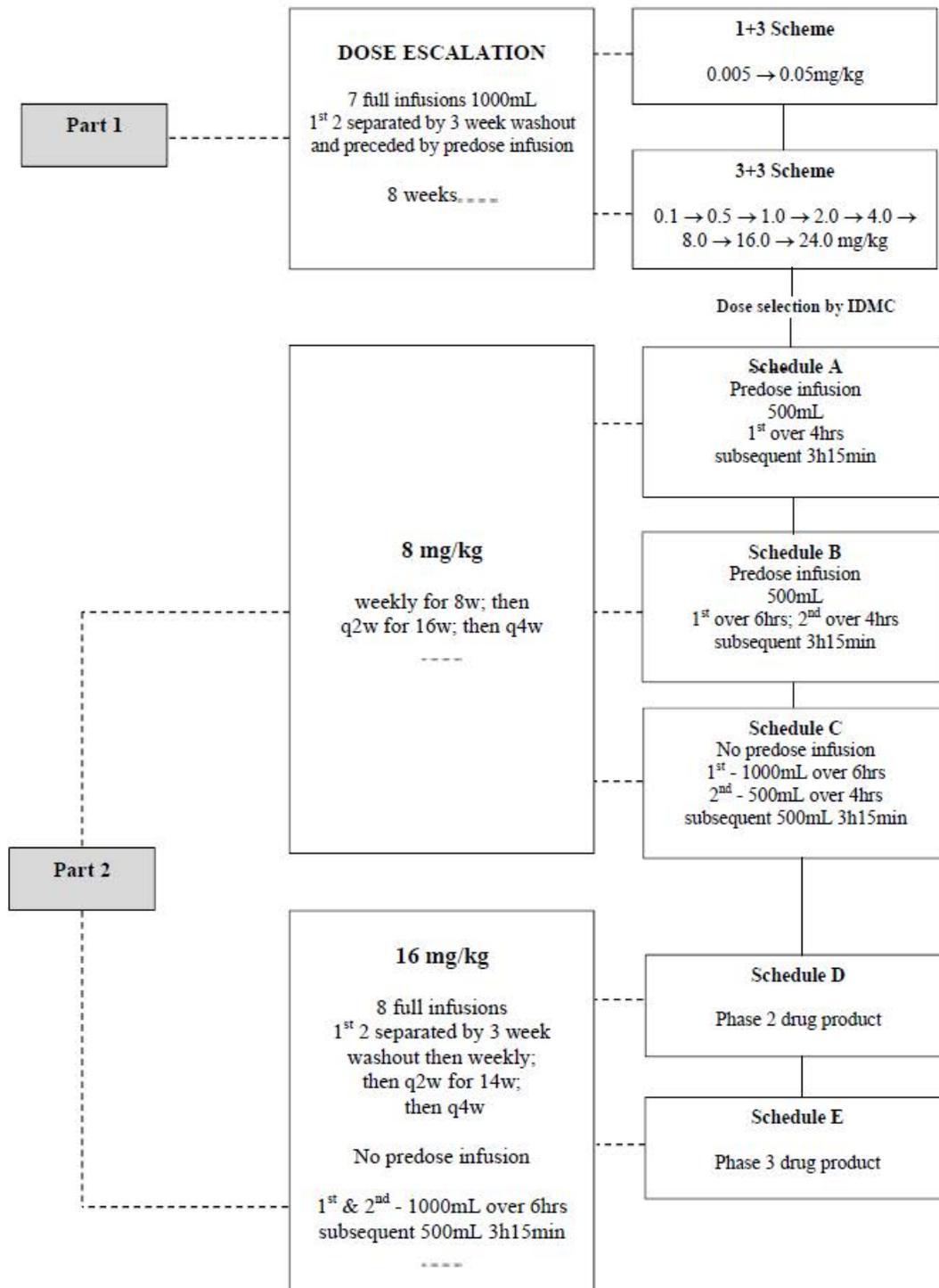
#### Overview and Objective

Trial GEN501 is the first-in-human, open-label, multicenter, phase 1 and 2 trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose escalation cohorts and explored various dosing schedules. The primary objective was to establish the safety profile of daratumumab. The primary efficacy endpoint was overall response rate.

### **Trial Design**

Trial GEN501 is an open-label, safety study divided into 2 parts. Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. Eligible were patients with multiple myeloma relapsed or refractory to at least 2 different cytoreductive therapies and without further established treatment options. Details of the design are shown in Figure 3.

**Figure 3 Trial GEN501 Schematic**



[Source: Jansen Clinical Study Report, Section 3.1.1, p.28/2817, in M5.3.5.2]

## **Study Endpoints**

Objective response rate (ORR) was defined as the proportion of subjects who achieved a partial response (PR) or better.

## **Statistical Analysis Plan**

The primary objective was to establish the safety profile of monotherapy daratumumab.

### Sample Size Considerations

In Part 1, a maximum of 62 patients were planned (1 + 3 + 3, at the 2 lowest dose levels and 3 + 3 at each of the remaining eight dose levels). This plan was considered sufficient, based on pre-clinical studies, to establish the safety basis for escalation to the next dose level. Up to 80 patients were to be enrolled in Part 2. This yields a maximum total of 112 patients.

### Efficacy Analysis Method for ORR

As the primary objective of the trial was safety, no formal statistical hypothesis testing was planned.

## **Data Quality and Integrity: Sponsor's Assurance**

The Sponsor incorporated a strategy to assure data quality and integrity. These included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions were to be provided for collection, handling, storage, and shipment of samples. Guidelines for eCRF completion were to be provided and reviewed with study-site personnel before the start of the study. The sponsor was to review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies were to be resolved with the investigator, as appropriate. The data in the study database was to be verified for accuracy and consistency with data sources.

## **6.2.2. Study Results**

### **Compliance with Good Clinical Practices**

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

## Financial Disclosure

The applicant submitted financial disclosure information from all investigators for this trial. No financial interests or arrangements were reported (see Financial Disclosure in the Appendix).

## Demographic Characteristics

Among patients on the 16 mg/kg arm, the majority were male (64%) and White (76%). The median age was 64 years old and 10% were 75 years of age or older. The trial population appears representative in terms of age and prior treatments. Refer to Table 16, Table 17, and Table 18 for patient characteristics.

**Table 16 Trial GEN501 Demographic Characteristics**

	8 mg/kg N=30	16 mg/kg N=42	Total N=72
<b>Sex</b>			
Male	21 (70.0%)	27 (64.3%)	48 (66.7%)
Female	9 (30.0%)	15 (35.7%)	24 (33.3%)
<b>Age</b>			
Mean years (SD)	58.6 (10.05)	63.8 (8.27)	61.6 (9.34)
Median (years)	58.5	64.0	61.0
Min, max (years)	(38, 76)	(44, 76)	(38, 76)
<b>Age Group</b>			
≥ 18 - < 65 years	21 (70%)	22 (52.4%)	43 (59.7%)
> 65 - < 75 years	8 (26.7%)	16 (38.1%)	24 (33.3%)
≥ 75 years	1 (3.3%)	4 (9.5%)	5 (6.9%)
<b>Race</b>			
White	15 (50.0%)	32 (76.2%)	47 (65.3%)
Black or African American	1 (3.3%)	1 (2.4%)	2 (2.8%)
Asian	0	0	0
Other	0	1 (2.4%)	1 (1.4%)
Not Reported	14 (46.7%)	8 (19.0%)	22 (30.6%)

## Other Baseline Characteristics

Over 80% of patients received 3 or more prior lines of therapy. All patients received prior bortezomib and 95% received prior lenalidomide; 74% of the patients had prior ASCT.

**Table 17 Trial GEN501 Prior Therapy**

	8 mg/kg N=30	16 mg/kg N=42	Total N=72
<b>Number of lines of prior therapy</b>			
≤3	6 (20.0%)	16 (19.5%)	22 (30.6%)
>3	24 (80.0%)	26 (80.5%)	50 (69.4%)
Mean (SD)	4.9 (2.02)	4.9 (2.61)	4.9 (2.37)
Median	4.0	4.0	4.0
Range	(3, 10)	(2, 12)	(2, 12)
<b>Prior proteasome inhibitor</b>			
Bortezomib	30 (100.0%)	42 (100.0%)	72 (100.0%)
Carfilzomib	2 (6.7%)	8 (19.0%)	10 (13.9%)
<b>Prior immunomodulating agent</b>			
Lenalidomide	29 (96.7%)	40 (95.2%)	69 (95.8%)
Pomalidomide	2 (6.7%)	15 (35.7%)	17 (23.6%)
Thalidomide	20 (66.7%)	19 (45.2%)	39 (54.2%)
<b>Prior ASCT</b>	24 (80.0%)	31 (73.8%)	55 (76.4%)
<b>Prior radiotherapy</b>	3 (16.7%)	7 (16.7%)	12 (16.7%)

Sixty-four percent of patients were considered refractory to both a proteasome inhibitor and an immunomodulating agent.

**Table 18 Trial GEN501 Refractory Status to Prior Therapy**

	8 mg/kg N=30	16 mg/kg N=42	Total N=72
<b>Refractory by class</b>			
Both proteasome inhibitor and immunomodulating agent	19 (63.3%)	27 (64.3%)	46 (63.9%)
Proteasome inhibitor only	2 (6.7%)	3 (7.1%)	5 (6.9%)
Immunomodulating agent only	6 (20.0%)	4 (9.5%)	10 (13.9%)
<b>Refractory to last line of therapy</b>	25 (83.3%)	32 (76.2%)	57 (79.2%)

### Efficacy Results - Primary Endpoint

The objective response rate (ORR) which included partial response or better, among all patients treated with 16 mg/kg was 35.7% (95% CI= [21.6%, 52%]), including 2 complete responses (CR), 2 very good partial responses (VGPR) and 11 partial responses (PR). The ORR among subjects treated with 8 mg/kg daratumumab was 10% (95% CI=[2.1%, 26.5%]).

Two of the complete responses in this trial were affected by the interference of daratumumab with the serum protein electrophoresis and immunofixation assays used. Using the applicant's assay under development, patients with a best response of VGPR were tested for daratumumab interference at Day 274. Two patients were identified as achieving complete

response of the original myeloma clone subtype. One of these patients was determined to be in CR at Day 302 using currently available response assessment methods. At Day 331, another assessment of response demonstrated a positive immunofixation result.

*Reviewer Comment: Given the lack of availability of an assay to determine interference with daratumumab or availability of the anti-idiotypic daratumumab used to develop an assay, assessment of complete responses in patients with IgG kappa myeloma protein will be affected. As SPEP and IFE are not consistently positive in a patient on daratumumab, determination of relapse may also be complicated.*

*There is potential for daratumumab to interfere with a prescriber's determination of disease response and alternative methods to overcome this are not available. The prescribing information for daratumumab should reflect responses as they were determined using currently available methods. Section 14 of the Prescribing Information will then present these results: ORR (36%) with 1 CR, 3 VGPR, and 11 PRs.*

**Table 19 Trial GEN501 Objective Response Rates based on Computerized Algorithm; All Treated Analysis Set**

	8 mg/kg		16 mg/kg				Total	
	N=30		Phase 2 drug product N=20		Phase 3 drug product N=22		N=42	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
<b>ORR</b>	3 (10.0%)	(2.1%, 26.5%)	8 (40.0%)	(19.1%, 63.9%)	7 (31.8%)	(13.9%, 54.9%)	15 (35.7%)	(21.6%, 52.0%)
Stringent Complete Response	0		0		0		0	
Complete Response	0		2 (10.0%)	(1.2%, 31.7%)	0		2 (4.8%)	(0.6%, 16.2%)
Very good partial response	0		1 (5.0%)	(0.1%, 24.9%)	1 (4.5%)	(0.1%, 22.8%)	2 (4.8%)	(0.6%, 16.2%)
Partial response	3 (10.0%)	(2.1%, 26.5%)	5 (25.0%)	(8.7%, 49.1%)	6 (27.3%)	(10.7%, 50.2%)	11 (26.2%)	(13.9%, 42.0%)

## Efficacy Results - Secondary and other relevant endpoints

Time to Response: For the 15 responders in the 16 mg/kg group, the time to first response was 0.92 months (range: 0.5 to 3.2 months). The median duration of response has not been reached for the 16 mg/kg group.

Duration of Response: Based on the 15 patients with response, the median duration of response was not estimable by Kaplan-Meier analysis. The range was 2.2 to 13.1+ months.

**Table 20 Trial GEN501 Duration of Response: Responders in All Treated Analysis Set**

	8 mg/kg N=3	16 mg/kg N=15
<b>Duration of Response</b>		
Number of events (%)	3 (100%)	4 (26.7%)
Number of censored (%)	0	11 (73.3%)
Median*, months (95% CI),	6.9 (6.2, 10.6)	NE (5.6, NE)
Range, months	6.2, 10.6	2.2, 13.1+

\* Kaplan-Meier estimate; NE = not estimable; + censored

## 7 Integrated Review of Effectiveness

### 7.1. Assessment of Efficacy across Trials

This application primarily relies on results from a single arm phase 2 trial. Findings from the other clinical trials of daratumumab submitted are consistent with these findings. Given the heterogeneity of the doses, regimens, populations, and drug combinations used, assessment of efficacy across trials is limited.

### 7.2. Additional Efficacy Considerations

#### 7.2.1. Considerations on Benefit in the Post-market Setting

While patient populations enrolled to clinical trials tend to differ in various ways from the broader population of patients with cancers, there are no clear signals noted in this review that would suggest differences in disease response.

### 7.3. Integrated Assessment of Effectiveness

The efficacy of daratumumab was based on the results of two clinical trials of treatment of adult patients with relapsed or refractory multiple myeloma: a Phase 1/2 dose escalation trial

with dose expansion of five dose schedule regimens (GEN501) and a Phase 2 randomized dosing trial with dose expansion (MMY2002). The optimal dose (16 mg/kg) and regimen was studied primarily in MMY2002, in a two arm, open-label trial of single-agent daratumumab. The primary endpoint was ORR. Of the 124 enrolled, 106 received the proposed dose and were the focus of the efficacy analysis. Results showed:

- ORR was achieved by 31 (29%) patients (95% CI: 21-39%) with a median DOR of 7.4 months.
- The results for the primary endpoint were consistent across the subpopulations tested.
- Stringent Complete Response was achieved by 3 (3%) patients (95% CI: 1-8%). Very Good Partial Response was achieved by 10 (9%) patients (95% CI: 5-17%).

Data to support the effectiveness of daratumumab came from the 42 patients who received the proposed dose on Trial GEN501. ORR was achieved by 15 (36%) patients (95% CI: 22-52%) with a median DOR of 6.9 months.

## 8 Review of Safety

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### 8.1. Safety Review Approach

The clinical review of safety for this BLA was based on the safety data from the five studies listed in Table 3 in Section 5.1. All patients had relapsed or refractory multiple myeloma and had received at least one dose of daratumumab.

Population pharmacokinetic simulations suggest that the Phase 2 drug product had 24% (95% CI: 3%, 40%) lower exposure (max  $C_{trough}$ ) than the Phase 3 drug product planned for commercial scale marketing. Explorations for whether this clinical pharmacology finding correlates with risk were performed.

### 8.2. Review of the Safety Database

#### 8.2.1. Overall Exposure

Safety data were available for 331 patients treated with various doses and schedules of daratumumab. Data from the three monotherapy studies were pooled to provide an integrated safety data base of 237 patients. Of these, 156 patients received the proposed dose of 16mg/kg. Data from two studies of daratumumab with other agents were pooled for 94 patients; 84 of these patients received 16mg/kg.

**Table 21 Safety Population, Size and Denominators**

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review n=331			
Clinical Trial Groups	New Drug (n=331)	Active Control (n=0)	Placebo (n=0)
Normal Volunteers	0	0	0
Controlled trials conducted for this indication	0	0	0
All other than controlled trials conducted for this indication	237	0	0
Controlled trials conducted for other indications	94	0	0

The median duration of treatment was 2.6 months. In patients receiving daratumumab at 16 mg/kg, the median duration of treatment was 3.3 months and the mean was 4.5 months. Refer to Table 22 for dose, infusion, and duration specifics for the safety population.

**Table 22 Duration of Exposure**

	All doses n=237		≤4 mg/kg n=23		8 mg/kg n=55		16 mg/kg n=156		24 mg/kg n=3	
<b>Month(s)</b>										
Median	2.6		1.4		2.6		3.3		1.9	
Range	0; 20.0		0.1; 21.9		0; 19.5		0; 20.0		1.0; 2.1	
	n	%	n	%	n	%	n	%	n	%
<1	44	18.6	7	30.4	14	25.5	22	14.1	1	33.3
1 to <3	92	38.8	16	69.6	21	38.2	53	34.0	2	66.7
3 to <6	36	15.2	0	0	9	16.4	27	17.3	0	0
6 to <9	27	11.4	0	0	5	9.1	22	14.1	0	0
9 to <12	11	4.6	0	0	2	3.6	9	5.8	0	0
≥12	27	11.4	0	0	4	7.3	23	14.7	0	0
<b>Total dose mg/kg</b>										
Mean	158		7		77		209		144	
Median	141		4		70		177		170	
Range	0; 528		0; 30		8; 232		2; 528		81; 182	
<b>Total infusions</b>										
Mean	11.4		5		9		13		6	
Median	10		5		9		12		7	
Range	1; 33		1; 7		1; 26		1; 33		3; 7	

## 8.2.2. Relevant characteristics of the safety population

As discussed in the review of the patient population enrolled to the primary trial, the safety population also appears representative of patients with relapsed and refractory myeloma today. Demographics and baseline for the safety population are provided in Table 23. All 237 patients had relapsed and/or refractory multiple myeloma and received single-agent daratumumab on a clinical trial.

**Table 23 Demographics of Safety Population**

	All doses n=237		16mg/kg n=156	
	n	%	n	%
<b>Sex</b>				
Male	139	58.6	84	53.8
Female	98	41.4	72	46.2
<b>Age</b>				
Mean years (SD)	62.4 (9.33)		62.9 (9.50)	
Median (years)	63		63	
Min, max (years)	31, 84		31, 84	
<b>Age Group</b>				
18 - < 65 years	133	56.1	86	55.1
> 65 - < 75 years	84	35.4	54	34.6
≥ 75 years	20	8.4	16	10.3
<b>Race</b>				
White	180	75.9	119	76.3
Black or African American	17	7.2	16	10.3
Asian	13	5.5	9	5.8
Other, Unknown, or Not Reported	27	11.4	12	7.7
<b>Ethnicity</b>				
Hispanic or Latino	10	4.2	10	6.4
Not Hispanic or Latino	173	73.0	135	86.5
Unknown	54	22.8	11	7.1
<b>Region</b>				
United States	110	46.4	89	57.1
Canada	22	9.3	22	14.1
Europe	96	40.5	40	25.6
Japan	9	3.8	5	3.2
<b>ECOG Performance Status</b>				
0	74	31.2	46	29.5
1	149	62.9	100	64.1
2	14	5.9	10	6.4
<b>Weight Groups</b>				
<55 kg	24	23.2	20	12.8
55-100 kg	190	80.2	119	76.3
100 kg	23	9.7	17	10.9

	All doses n=237		16mg/kg n=156	
	n	%	n	%
<b>Renal Dysfunction</b>				
≥90 mL/min	71	30.0	44	28.2
60-<90 mL/min	86	36.3	51	32.7
30-<60 mL/min	73	30.8	56	35.9
15-<30 mL/min	6	2.5	4	2.6
<15 mL/min	1	0.4	1	0.6
<b>Hepatic Dysfunction</b>				
Normal	197	83.5	134	86.5
Mildly impaired <sup>1</sup>	39	16.5	21	13.5

<sup>1</sup> (total bilirubin ≤ULN and AST>ULN) or (total bilirubin 1-1.5xULN)

### 8.2.3. Adequacy of the safety database

The demographics of the safety population are adequately consistent with those of the intended population.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity were identified during the course of the review, or in the course of clinical investigational site inspections. Overall the submission was well-organized with appropriate analyses and detailed reports and summaries. Responses to requests for additional information were rapid and complete. The well-prepared Application contributed to an expedited review time frame.

### 8.3.2. Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) excluded events that started and ended before start of the investigational agent. Adverse events were reported down to the verbatim term. The severity of TEAEs and the toxicity of laboratory parameters were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Where indicated, some adverse events are presented as grouped terms.

### 8.3.3. Routine Clinical Tests

The schedule of safety evaluations for each protocol was described in Sections 5 and 6. The frequency of monitoring was considered adequate within the context of the study.

## 8.4. Safety Results

### 8.4.1. Deaths

Of the 237 patients treated with daratumumab in the development program, 56 (24%) died. Most deaths (41 patients, 17%) occurred more than 30 days after the last dose of daratumumab.

**Table 24 Deaths**

	All doses n=237		16mg/kg n=156	
	n	%	n	%
All	56	23.6	40	25.3
Within 30 days of last dose of daratumumab	15	6.3	14	9.0

Within 30 days of the last dose of daratumumab, 1 patient who received 8mg/kg died, and 14 patients who received 16mg/kg died. FDA reviewed all narratives to confirm the cause of deaths. FDA considered the cause of death to be the primary malignancy when supported by objective evidence of disease progression. The majority of deaths were due to multiple myeloma (11 patients, 5%).

There was insufficient evidence to consider disease the primary cause of death for one patient:

*Patient 100125* was a 63 year old female treated with daratumumab 16 mg/kg for relapsed multiple myeloma. At baseline, the serum M-protein was 7.8 g/dL, urine M-protein was 236.7mg/24 hours, and a bone marrow aspirate contained 1.5% plasma cells. Pre-treatment corrected calcium levels during the screening period started at 3.54 mmol/L (Grade 4) on day -14 to 2.90 mmol/L (Grade 1) on Day -1; zoledronic acid was given on Day -14. Despite meeting exclusion criteria on Cycle 1, Day 1 for hemoglobin 62 g/L and platelet count  $49 \times 10^9/L$ , the patient was treated on Days 1 and 8. The patient was transfused 2 units packed RBCs on Day 1. On Day 8, the hemoglobin was 68 g/L and the patient was reported to have Grade 2 hypercalcemia. No calcium level was recorded. The patient died on Day 14 of general health deterioration determined by the investigator to be progressive disease. There was no documentation of disease reassessment to the support the investigator's conclusion. No other adverse reactions were reported.

There were 3 deaths related to adverse events. One death was due to pneumonia and one death was due to H1N1 influenza. One death due to aspiration pneumonia could not be ruled out:

*Patient 100084* was an 80 year old female treated with daratumumab 16 mg/kg for relapsed multiple myeloma. Infusion on Cycle, 1 Day 1 proceeded without adverse reaction for the first

90 minutes. At 100 minutes, the patient had acute distress respiratory syndrome attributed to aspiration of a drink. Daratumumab was permanently discontinued; the patient was sedated and intubated. Anemia, device-related infection, pyrexia, and bronchospasm occurred prior to transition to palliative care on Day 22. On Day 28, the patient died of cardiorespiratory arrest determined by the investigator to be due to general physical health determination. FDA concurs that an adverse event was the cause of death, but cannot rule out that an infusion reaction to daratumumab may have been the root cause of death.

#### 8.4.2. Serious Adverse Events

An SAE occurring within 30 days of the last dose of daratumumab was reported for 74 (31%) of the 237 patients treated on all clinical trials of single-agent daratumumab. In the group of 156 patients treated with daratumumab 16mg/kg, 51 (33%) experienced a serious adverse event.

**Table 25 Serious Adverse Events**

System Organ Class	All doses n=237		16mg/kg n=156	
	n	%	n	%
Infections and infestations	25	10.55	20	12.82
General disorders and administration site conditions	13	5.49	13	8.33
Musculoskeletal and connective tissue disorders	8	3.38	6	3.85
Blood and lymphatic system disorders	7	2.95	3	1.92
Renal and urinary disorders	7	2.95	3	1.92
Gastrointestinal disorders	6	2.53	5	3.21
Investigations	6	2.53	4	2.56
Metabolism and nutrition disorders	6	2.53	6	3.85
Respiratory, thoracic and mediastinal disorders	6	2.53	4	2.56
Injury, poisoning and procedural complications	5	2.11	3	1.92
Nervous system disorders	5	2.11	3	1.92
Cardiac disorders	3	1.27	3	1.92
Psychiatric disorders	2	0.84	2	1.28
Vascular disorders	2	0.84	2	1.28
Hepatobiliary disorders	1	0.42	1	0.64
Immune system disorders	1	0.42	0	0
Neoplasms benign, malignant and unspecified	1	0.42	0	0
Reproductive system and breast disorders	1	0.42	0	0

There were 128 SAEs occurring on treatment or within 30 days of follow-up. SAEs considered at least possible related to daratumumab were reported for 21 (9%) patients in the group of all patients treated with single agent daratumumab.

There were 95 SAEs occurring in the subgroup of patients receiving daratumumab 16mg/kg. The most common ( $\geq 2\%$ ) were pneumonia (6%), general physical health deterioration (3%), pyrexia (3%), hypercalcemia (3%), cross-match incompatible (2%), and herpes zoster (2%).

Of these, 15 (10%) were reported to be at least possibly related to daratumumab. The most common ( $\geq 2\%$ ) related SAEs were pneumonia (3%), herpes zoster (2%), and cross-match incompatible (2%).

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-emergent adverse events led to treatment discontinuation in 11 (5%) patients. In the 156 patients on daratumumab 16 mg/kg, the reasons were general health deterioration, H1N1 influenza, hypercalcemia, pneumonia, and spinal cord compression. With other doses of daratumumab, there were other TEAEs that led to discontinuation and were determined to be at least possibly related to daratumumab: bronchospasm, cytokine release syndrome, flushing, hepatic dysfunction abnormal, and hypersensitivity.

#### 8.4.4. Significant Adverse Events

NCI CTCAE Grade 3 and 4 (severe) events are provided in Table 27. The most common ( $\geq 5\%$ ) were anemia (17%), thrombocytopenia (14%), neutropenia (12%), and pneumonia (6%).

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events were assessed through 30 days after the last dose of daratumumab. The numbers of patients with a TEAE are shown in Table 26 by SOC in decreasing order of incidence in the entire safety population.

**Table 26 Treatment Emergent Adverse Events by SOC**

System Organ Class	All doses n=237		16mg/kg n=156	
	n	%	n	%
General disorders and administration site conditions	152	64.14	106	67.95
Respiratory, thoracic and mediastinal disorders	136	57.38	96	61.54
Musculoskeletal and connective tissue disorders	126	53.16	95	60.9
Infections and infestations	124	52.32	91	58.33
Gastrointestinal disorders	122	51.48	87	55.77
Blood and lymphatic system disorders	106	44.73	80	51.28
Metabolism and nutrition disorders	82	34.6	65	41.67
Nervous system disorders	81	34.18	56	35.9
Skin and subcutaneous tissue disorders	54	22.78	37	23.72
Renal and urinary disorders	52	21.94	26	16.67
Vascular disorders	48	20.25	29	18.59
Investigations	37	15.61	22	14.1
Psychiatric disorders	37	15.61	29	18.59
Injury, poisoning and procedural complications	32	13.5	29	18.59
Eye disorders	24	10.13	17	10.9
Cardiac disorders	17	7.17	13	8.33
Hepatobiliary disorders	13	5.49	8	5.13
Neoplasms benign, malignant and unspecified	10	4.22	9	5.77

System Organ Class	All doses n=237		16mg/kg n=156	
	n	%	n	%
Ear and labyrinth disorders	8	3.38	6	3.85
Immune system disorders	8	3.38	3	1.92
Reproductive system and breast disorders	8	3.38	5	3.21
Congenital, familial and genetic disorders	1	0.42	1	0.64

A TEAE was reported in 155 patients who received daratumumab at 16mg/kg; 56% of patients had a Grade 3 or 4 adverse reaction. The numbers of patients with common ( $\geq 10\%$ ) TEAE are shown in Table 27.

**Table 27 Treatment Emergent Adverse Events by PT**

Preferred Term	16mg/kg n=156			
	All Grade		Grade 3-4	
	n	%	n	%
Fatigue	61	39.10	3	1.92
Anemia	42	26.92	27	17.31
Nausea	42	26.92	0	0.00
Back pain	36	23.08	3	1.92
Neutropenia	35	22.44	19	12.18
Pyrexia	33	21.15	2	1.28
Cough	33	21.15	0	0.00
Thrombocytopenia	31	19.87	22	14.10
Upper respiratory tract infection	31	19.87	1	0.64
Arthralgia	26	16.67	0	0.00
Nasal congestion	26	16.67	0	0.00
Diarrhea	25	16.03	1	0.64
Nasopharyngitis	24	15.38	0	0.00
Dyspnea	24	15.38	1	0.64
Constipation	23	14.74	0	0.00
Decreased appetite	23	14.74	1	0.64
Pain in extremity	23	14.74	1	0.64
Vomiting	21	13.46	0	0.00
Musculoskeletal chest pain	19	12.18	2	1.28
Headache	19	12.18	2	1.28
Hypercalcemia	18	11.54	5	3.21
Pneumonia <sup>1</sup>	17	10.90	9	5.77
Chills	16	10.26	0	0.00

<sup>1</sup> Pneumonia included the Preferred Terms: Lobar pneumonia, Pneumonia, Pneumonia streptococcal

#### 8.4.6. Laboratory Findings

Table 28 shows the incidence of worst post-baseline abnormality in common laboratory tests

reported during treatment or within 30 days of the last dose of daratumumab. Approximately 3% of the results were not graded by the applicant. There was insufficient information to apply grades to the missing test results. The most common Grade  $\geq 3$  non-hematologic abnormalities were hypercalcemia (7%), hyponatremia, hyperuricemia, and hypophosphatemia (all 4%).

**Table 28 Maximum Laboratory Abnormalities**

Preferred Term	16mg/kg n=156			
	All Grade		Grade 3-4	
	n	%	n	%
<b>Hematology</b>				
Lymphopenia	112	71.79	61	39.10
Neutropenia	93	59.62	31	19.87
Leukopenia	89	57.05	29	18.59
Thrombocytopenia	75	48.08	28	17.95
Anemia	70	44.87	30	19.23
Lymphocytes increased	5	3.21	1	0.64
<b>Chemistry</b>				
Hypoalbuminemia	62	39.74	5	3.21
Hypercalcemia	49	31.41	11	7.05
Hypocalcemia	48	30.77	0	0.00
Hyponatremia	45	28.85	6	3.85
Creatinine increased	33	21.15	3	1.92
Aspartate aminotransferase (AST) increased	32	20.51	2	1.28
Hypokalemia	30	19.23	5	3.21
Hyperuricemia	26	16.67	6	3.85
Alanine aminotransferase (ALT) increased	23	14.74	1	0.64
Alkaline phosphatase increased	20	12.82	1	0.64
Hypoglycemia	19	12.18	1	0.64
Hypomagnesemia	17	10.90	0	0.00
Hypophosphatemia	17	10.90	6	3.85
Hyperkalemia	13	8.33	4	2.56
Hypoalbuminemia	12	7.69	0	0.00
Bilirubin increased	11	7.05	1	0.64
Hyperglycemia	9	5.77	0	0.00
Hypernatremia	8	5.13	0	0.00
Creatine phosphokinase (CPK) increased	6	3.85	2	1.28
Hypermagnesemia	5	3.21	1	0.64
Cholesterol increased	3	1.92	0	0.00
Hypertriglyceridemia	1	0.64	0	0.00

#### 8.4.7. Vital Signs

The applicant's review of vital signs concluded that no safety signal was identified. FDA analysis is presented in Table 29 and lists the proportion of patients with outlier vital signs at any time on study. No patients had a recorded Grade  $\geq 3$  fever, but 14-15% had hypotension and 8-9%

had tachycardia.

**Table 29 Critical Vital Signs**

Vital sign limit	All doses n=237		16mg/kg n=156	
	n	%	n	%
Systolic blood pressure ≥160 mm Hg	91	38.4	50	32.1
Systolic blood pressure <90 mm Hg	35	14.8	22	14.1
Diastolic blood pressure ≥ 100 mm Hg	38	16.0	17	10.9
Heart rate <50 beats per minute	9	3.8	5	3.2
Heart rate >120 beats per minute	21	8.9	12	7.7
Temperature >40°C	0	0	0	0

Absolute changes in vital signs from various time points during and after the first infusion of daratumumab are listed in Table 30. There was a lowering in blood pressure within hours of the start of the infusion.

**Table 30 Change in Vital Signs with Initial Infusion**

16mg/kg, n=156	Median (range) absolute change at:				
	Infusion 1 Hr	Infusion 2 Hrs	End of infusion	Post-infusion 1 Hr	Post-infusion 2 Hrs
Systolic blood pressure (mm Hg)	-4 (-46, 53)	-3 (-47, 35)	2 (-34, 67)	2.5 (-32, 37)	8.5 (-34, 55)
Diastolic blood pressure (mm Hg)	-3 (-29, 16)	-2 (-32, 27)	-1 (-26, 26)	3 (-26, 23)	3.5 (-28, 24)
Heart rate (beats per minute)	-2 (-24, 38)	0 (-25, 39)	2 (-28, 29)	2.5 (-30, 33)	4 (-25, 42)
Respiratory rate (breaths per minute)	0 (-4, 4)	0 (-4, 6)	0 (-4, 6)	0 (-4, 4)	0 (-3, 8)
Temperature (°C)	0 (-1, 1.3)	0.1 (-0.8, 2.1)	0 (-1.5, 1.2)	0 (-1.3, 1.5)	0 (-1.5, 1.1)

#### 8.4.8. Electrocardiograms (ECGs)

As daratumumab is a large protein, inhibition of hERG was not expected, and an hERG assay was not performed. TEAEs related to ECG changes were reviewed along with all cardiac adverse events. There were no QT prolongations reported. The incidence of bradycardia and tachycardia were described in Section 8.4.7.

#### 8.4.9. QT

The Interdisciplinary Review Team for QT studies was consulted to review the submitted TQT information. This included the study report for Trial GEN501, the electronic datasets, and waveforms submitted to the ECG warehouse. The consult team findings follow:

No clear dose-dependent QTc effect was observed. Based on concentration-QTc analysis, no evident exposure-response relationship was observed after adjusting for infusion effect. The

predicted  $\Delta$ QTcF is less than 10 ms with upper bound less than 20 ms at the therapeutic  $C_{max}$  of 1000 ug/mL, suggesting no clinically relevant QT prolongation of daratumumab.

Recommended addition to the prescribing information includes: DARZALEX as a large protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that DARZALEX has the potential to delay ventricular repolarization.

#### 8.4.10. Immunogenicity

No neutralizing antibodies were detected in tested samples, possibly because the assays used were insufficiently sensitive to detect anti-drug antibody. Refer to Section 4.2 and the CMC review for details.

### 8.5. Analysis of Submission-Specific Safety Issues

#### 8.5.1. Infusion Reactions

Infusion reactions were recorded in unique electronic case report forms as adverse events and assigned a toxicity grade. A pre-defined set of infusion reaction adverse events was not provided; instead, investigators would make the determination of whether the event was related to the infusion. The preferred term *infusion related reaction* was not used and the grade assigned was not based on the clinical consequences of the reaction or the action taken.

FDA analysis of infusion reactions included all adverse reactions that occurred within 24 hours of the infusion. FDA adjudication of grading for infusion reactions was done for 53 adverse events. Grade 1 events for which an intervention occurred were increased to Grade 2 for 52 events. Interventions included *infusion interruption, infusion rate decrease, or additional therapy given*. One grade 2 event was changed to grade 3 for the reason *inability to complete infusion*.

In the 16 mg/kg group, 75 (48%) patients experienced an infusion reaction. The median time of adverse event relative to the start of the infusion was 90 minutes (range: 1 to 557 minutes). Nearly all (71 of 75) patients had an adverse reaction with the first infusion. There were 8 (5%) patients with a reaction to the second infusion, and 6 (4%) patients with a reaction to the third or subsequent infusions. All Grade 3 reactions occurred during the first infusion. There were 11 patients (7%) who had reactions during two or more infusions. The incidence of infusion interruptions due to adverse reactions was 40%. The incidence in descending incidence by system organ class then preferred term are listed in Table 31.

**Table 31 Adverse Infusion Reactions**

System Organ Class Preferred Term	16mg/kg n=156			
	All Grade n	%	Grade 3-4 n	%
Respiratory, thoracic and mediastinal disorders	76	48.72	5	3.21
Nasal congestion	17	10.90	0	0.00
Cough	12	7.69	0	0.00
Rhinitis allergic	10	6.41	0	0.00
Throat irritation	9	5.77	0	0.00
Dyspnea	8	5.13	1	0.64
Bronchospasm	4	2.56	3	1.92
Sneezing	3	1.92	0	0.00
Throat tightness	3	1.92	0	0.00
Hypoxia	2	1.28	1	0.64
Oropharyngeal pain	2	1.28	0	0.00
Wheezing	2	1.28	0	0.00
Allergic cough	1	0.64	0	0.00
Laryngeal edema	1	0.64	0	0.00
Laryngitis allergic	1	0.64	0	0.00
Nasal disorder	1	0.64	0	0.00
General disorders and administration site conditions	22	14.10	0	0.00
Chills	11	7.05	0	0.00
Pyrexia	5	3.21	0	0.00
Chest discomfort	1	0.64	0	0.00
Chest pain	1	0.64	0	0.00
Fatigue	1	0.64	0	0.00
Influenza like illness	1	0.64	0	0.00
Infusion site bruising	1	0.64	0	0.00
Pain	1	0.64	0	0.00
Gastrointestinal disorders	18	11.54	0	0.00
Nausea	8	5.13	0	0.00
Vomiting	7	4.49	0	0.00
Abdominal pain upper	1	0.64	0	0.00
Diarrhea	1	0.64	0	0.00
Paresthesia oral	1	0.64	0	0.00
Skin and subcutaneous tissue disorders	5	3.21	0	0.00
Pruritus	3	1.92	0	0.00
Rash macular	1	0.64	0	0.00
Urticaria	1	0.64	0	0.00
Eye disorders	4	2.56	0	0.00
Eye pruritus	2	1.28	0	0.00
Vision blurred	2	1.28	0	0.00
Cardiac disorders	3	1.92	0	0.00
Palpitations	1	0.64	0	0.00
Sinus tachycardia	1	0.64	0	0.00
Tachycardia	1	0.64	0	0.00
Musculoskeletal and connective tissue disorders	3	1.92	0	0.00
Back pain	2	1.28	0	0.00

System Organ Class Preferred Term	16mg/kg n=156			
	All Grade		Grade 3-4	
	n	%	n	%
Myalgia	1	0.64	0	0.00
Nervous system disorders	3	1.92	0	0.00
Headache	3	1.92	0	0.00
Vascular disorders	3	1.92	1	0.64
Hypertension	2	1.28	1	0.64
Flushing	1	0.64	0	0.00
Immune system disorders	2	1.28	0	0.00
Cytokine release syndrome	1	0.64	0	0.00
Seasonal allergy	1	0.64	0	0.00
Psychiatric disorders	2	1.28	0	0.00
Anxiety	1	0.64	0	0.00
Delirium	1	0.64	0	0.00

### Bronchospasm

In the dose escalation trial GEN501, 3 patients experienced 6 events of bronchospasm during daratumumab infusion or up to 48 hours later. One event was grade 1, four were grade 2, and one was grade 3; two were considered serious. All patients had a history of pulmonary disease (asthma, chronic obstructive pulmonary disease) or pneumonia. Due to the delayed onset of bronchospasm, the protocol was amended to require post-infusion corticosteroids.

Of all patients on Trial MMY2002, 4 (3%) patients experienced Grade 2 or 3 bronchospasm. All occurred 60 to 90 minutes after starting the daratumumab infusion. Only one patient had a history of airway disease. After symptomatic treatment and resolution of symptoms, two patients were able to tolerate and complete the infusion. All four patients tolerated subsequent daratumumab infusions. There were no additional reports of delayed onset bronchospasm.

### 8.5.2. Infections

Infections were common for patients treated with daratumumab. Patients with multiple myeloma tend to experience a high rate of infections. Factors such as impaired lymphocyte function, suppression of normal plasma cell function, and hypogammaglobulinemia contribute to the incidence of infections. Prophylactic treatments include vaccinations, antibiotics, antivirals, and IV immunoglobulin.

In the safety population, the most common infections were upper and lower respiratory tract infections. The most common serious infection was pneumonia. There were no TEAEs of febrile neutropenia. There were no clear differences across doses or based on duration of exposure. Based on the single arm trials, there is no clear increase in the incidence or type of infection compared to the overall population of patients with multiple myeloma.

### 8.5.3. Hemolysis

CD38 is expressed on red blood cells. There was no pre-clinical evidence of complement-mediated lysis of RBCs with daratumumab. In early clinical trials, at doses  $\leq 1\text{mg/kg}$ , there were 3 patients with TEAEs of Grade 1 hemolysis, defined by NCI CTCAE as laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin). None of the patients had a decrease in hemoglobin of 2 gm or more. Analysis of haptoglobin, LDH, bilirubin, and hemoglobin revealed no clear patterns.

There was one report of Grade 1 RBC agglutination without clinical consequence. No action was taken, and the event resolved. There were no other cases of hemolysis reported in subsequent dosing.

### 8.5.4. Direct and Indirect Coombs Test

Daratumumab binds to CD38 on RBCs and when added to Coombs reagent, causes agglutination. This can lead to false-positive direct and indirect antiglobulin testing. Coombs testing was sporadically collected and reported in Trials GEN501 and MMY2002. Adverse events of cross-match incompatible were reported in 3 (1%) of patients.

In Trial MMY1002, indirect and direct Coombs testing of all patients was included in the protocol. All 9 (100%) had a positive indirect Coombs and 6 (67%) had a positive direct Coombs within 5 hours of the first daratumumab infusion. Of these 6 positive direct Coombs tests, 2 were also positive at baseline.

Interference may persist for up to six months after the last infusion of daratumumab. Daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum (Chapuy et al 2015). The determination of ABO and Rh are not affected. Mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

Across the safety population, the rate of RBC transfusions was 24%. There were no reported transfusion reactions.

#### Risk Mitigation

The applicant submitted a plan detailing methods to educate health care providers and patients of this risk. The educational materials reviewed are consistent with the proposed Prescribing Information. In part, and specific to the blood bank community, the applicant has participated with an international transfusion medicine collaborative to generate the DTT validation method, has sponsored an educational session at the American Association of Blood Banks

(AABB) Annual Meeting this month, and will distribute an information bulletin to members of the AABB.

#### **8.5.5. Drug Product**

Given a change in manufacturing of the daratumumab drug product during clinical trial enrollment, additional patients were enrolled to Trial MMY2002. The drug product intended for commercial use was given to 92 patients at 16 mg/kg. Compared to 64 patients who were given the earlier drug product at 16 mg/kg, the incidence of treatment emergent adverse events was similar.

#### **8.5.6. Hepatic Function**

Additional analyses were conducted based on the findings from the clinical pharmacology review in the subgroup of patients with baseline mild hepatic impairment. This was defined using the NCI Organ Dysfunction criteria as normal total bilirubin with elevated AST or a bilirubin up to and including a total bilirubin of 1.5 times the upper limit of normal. Despite a slightly lower mean maximal trough concentration, there was a higher incidence of TEAEs.

Of the patients who received daratumumab 16 mg/kg, 21 with mild hepatic dysfunction at baseline were enrolled. None had elevated total bilirubin, all had elevated AST, five had elevated ALT, and one had elevated ALP. Review of laboratory values, shifts over time, and adverse events by incidence, grade, and duration revealed no safety signals. As with other subgroup analyses, the small sample size and lack of comparator arm do not allow for clinically meaningful interpretation.

### **8.6. Specific Safety Studies/Clinical Trials**

No studies or trials were conducted to evaluate a specific safety concern.

### **8.7. Additional Safety Explorations**

#### **8.7.1. Human Carcinogenicity or Tumor Development**

An evaluation of second primary malignancies was conducted. One case of adenocarcinoma with liver metastasis was diagnosed in a 73 year old male. The patient had received six prior lines of therapy for multiple myeloma and was treated with daratumumab for nearly 6 months before progressing. The second primary malignancy was diagnosed approximately 15 months later. The other malignancies reported were non-melanoma skin cancers in 6 (3%) patients. No secondary cancer signals were identified.

#### **8.7.2. Human Reproduction and Pregnancy**

There has been no daratumumab exposure in pregnant or lactating women.

### 8.7.3. **Pediatrics and Assessment of Effects on Growth**

There has been no daratumumab exposure in pediatric patients.

### 8.7.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There was no experience of overdose in clinical trials. The highest dose evaluated was 24mg/kg in 3 patients. The maximum tolerated dose was not reached.

## 8.8. **Safety in the Post-market Setting**

### 8.8.1. **Safety Concerns Identified Through Post-market Experience**

Daratumumab is not marketed in any country. There are no post-market safety data.

### 8.8.2. **Expectations on Safety in the Post-market Setting**

As none of the available data are from trials with a control arm, future analysis of ongoing randomized trials will be instrumental in establishing a clear understanding of risks of daratumumab.

## 8.9. **Additional Safety Issues From Other Disciplines**

There are no additional safety issues that were not presented elsewhere in this review.

## 8.10. **Integrated Assessment of Safety**

The safety dataset included 237 patients with multiple myeloma treated with daratumumab as monotherapy on three trials. For the 156 patients at the proposed dose, the median time on treatment was 3.3 months (range: 0.0 to 20.0 months). Data were also provided for 94 patients with multiple myeloma who were treated with daratumumab in combination with other agents from two trials; these results were not included in the integrated safety assessment due to confounding from the additional agents.

The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events, and common laboratory tests. There was no safety data in children. A thorough QT study was not conducted, but the application included a pooled analysis of ECG data.

There were 56 patients who died, including 15 within 30 days of the last dose of daratumumab. Overall, 73% of the deaths were considered related to multiple myeloma. Four deaths that occurred within 30 days of the last dose of daratumumab were considered at least possibly related to daratumumab. Two were due to infection, one was due to pneumonia resulting from aspiration during the first infusion of daratumumab, and there was insufficient information to

confirm progression of disease as determined by the investigator.

For the subgroup of patients treated with daratumumab 16 mg/kg, key results from the review of safety through 30 days after the last dose of daratumumab showed the following:

- In the analysis of adverse events of specific interest, infusion reactions occurred with a median time of onset of 90 minutes. Four patients experienced Grade 2 or 3 bronchospasm within 90 minutes of initiation of daratumumab.
- The incidence of infusion interruptions due to adverse reactions was 40%.
- The SOCs with the highest rates of patients with SAEs were Infections and infestations (13%) and General disorders and administrative site conditions (8%).
- The most common SAEs were pneumonia (6%), general health deterioration (3%), pyrexia (3%), and hypercalcemia (3%).
- The most common (>20%) TEAE were fatigue, anemia, nausea, back pain, neutropenia, pyrexia, cough, thrombocytopenia, and upper respiratory infection. Pneumonia was reported for 11%.
- A grade  $\geq 3$  TEAE occurred in 56% of patients. The most common (>5%) were anemia, thrombocytopenia, neutropenia, and pneumonia.

Cross-matching of RBCs for transfusion may be delayed. Daratumumab binds to CD38 on RBCs and causes agglutination when added to Coombs reagent. False positive indirect and direct Coombs test may result and persist for up to 6 months.

## **9 Advisory Committee Meeting and Other External Consultations**

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This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

## **10 Labeling Recommendations**

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### **10.1. Prescribing Information**

The following are recommended major changes to daratumumab prescribing information based on this review:

- **1 INDICATIONS AND USAGE:** Add accelerated approval basis and contingency for continued approval.
- **6 ADVERSE REACTIONS:** Add specific information on the timing, severity, and characteristics on infusion reactions. Add limitations of immunogenicity findings. Add treatment emergent laboratory abnormalities as the incidence was underrepresented in the adverse event data.
- **7 DRUG INTERACTIONS:** Add information on interference with indirect antiglobulin tests. Add information on interference with Serum Protein Electrophoresis and Immunofixation Tests.
- **14 CLINICAL STUDIES:** Remove instances [REDACTED] (b) (4).
- **17 PATIENT COUNSELING INFORMATION and PATIENT INFORMATION:** Add information for on interference with blood testing and with determination of complete response.

## 10.2. Patient Labeling

Review of the Patient Labeling by the Division of Medical Policy Programs in the Office of Medical Policy is ongoing. Based on this review, we recommend adding information on interference with blood testing and on determination of complete response. The risks of the product do not warrant a Patient Medication Guide.

## 11 Risk Evaluation and Mitigation Strategies (REMS)

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Given the favorable safety profile of this drug, there are no additional risk management strategies beyond recommended labeling. Subsequent subsections are not applicable for this review and have been omitted. Review of the Application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not needed to ensure the benefits of daratumumab exceed its risks.

## 12 Post-marketing Requirements and Commitments

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Successful completion of either PMR 1 or 2 may be adequate, after review, for regular approval.

PMR 1: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3003, a Phase 3, 2-arm, randomized, parallel-group trial of lenalidomide and

dexamethasone with or without daratumumab in patients with previously treated multiple myeloma. Enrollment of (b) (4) patients completed in June 2015.

PMR 2: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3004, a Phase 3, 2-arm, randomized, parallel-group trial of bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma. Enrollment of (b) (4) patients completed in July 2015.

## 13 Appendices

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### 13.1. References

Anderson KC, Kyle RA, Rajkumar SV, et al. (2008) Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 22(2): 231-9.

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Kumar SK, Rajkumar SV, Dispenzieri A, et al. (2008) Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111 (5): 2516-20.

Rajkumar SV, Harousseau J-L, Durie B, et al. (2011) Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 117 (18): 4691-4695.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.

### 13.2. Financial Disclosure

#### Covered Clinical Studies: MMY2002 and GEN501

Was a list of clinical investigators provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Total number of investigators identified: <u>294 (229 from MMY2002, 65 from GEN501)</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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)): <u>Does not apply</u>		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>Does not apply</u>		
Significant payments of other sorts: <u>Does not apply</u>		
Proprietary interest in the product tested held by investigator: <u>Does not apply</u>		
Significant equity interest held by investigator in Sponsor of covered study: <u>Does not apply</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes <input type="checkbox"/> <u>Does not apply</u>	No <input type="checkbox"/>
Is a description of the steps taken to minimize potential bias provided?	Yes <input type="checkbox"/> <u>Does not apply</u>	No <input type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason?	Yes <input type="checkbox"/> <u>Does not apply</u>	No <input type="checkbox"/>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARRY W MILLER  
10/28/2015

YAPING WANG  
10/28/2015

YUAN L SHEN  
10/28/2015

ALBERT B DEISSEROTH  
10/29/2015

## Secondary (Clinical Team Leader) Review

<b>Date</b>	October 26, 2015
<b>From</b>	Albert Deisseroth, MD, PhD
<b>Subject</b>	Secondary (Clinical Team Leader) Review
<b>BLA Number</b>	BLA 761036
<b>Applicant</b>	Janssen Biotech, Inc.
<b>Date of Submission</b>	July 9, 2015
<b>PDUFA Goal Date/ Planned Action Date</b>	March 9, 2016/November 17, 2015
<b>Established/Proprietary Name</b>	Daratumumab/Darzalex <sup>TM</sup>
<b>Dosage Regimen</b>	16 mg/kg weekly during weeks 1-8; every two weeks during weeks 9-24; Every four weeks from week 25 onwards until progression
<b>Dosage Form/Strength</b>	100 mg/5mL and 400 mg/20 mL (20 mg/mL) for injection
<b>Approved Indication</b>	Treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD
<b>Recommendation:</b>	Accelerated Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Barry Miller
Clinical Pharmacology	Jeanne Fourie Zirkelbach, PhD and Bahru Habtermariam, PharmD
Pharmacometrics	Lian Ma, PhD and Nitin Mehrotra, PhD
Genomics	Robert Schuck, PhD
CMC Product Quality	Tura Camilli, PhD and Jee Chung, PhD
CDER, OPQ, OPF, DIA	Laura Fontan, PhD and Peter Qiu, PhD
CMC (Drug Product)	Natalia Pripuzova, PhD and Patricia Hughes, PhD
CMC (Drug Substance)	Maria Jose Lopez-Barragan and Patricia Hughes, PhD
Nonclinical	Emily Place, PhD, and Christopher Sheth, PhD
Biostatistics	Yaping Wang, PhD and Yuan Li Shen, PhD
DRISK	Joyce Weaver, PharmD and Cynthia LaCivita, PharmD
Project Manager	Jessica Boehmer

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**1. EXECUTIVE SUMMARY:** (This section was derived in part from the reviews of Barry Miller, Jeanne Fourie Zirkelbach and Emily Place).

On July 9, 2015, Janssen Biotech, Inc. submitted BLA 761036 which requested approval for daratumumab (Darzalex) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent.

According to the Applicant, daratumumab is designed to target CD38 positive B-cells and plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme (cyclic ADP ribose hydrolase), which is involved in the production of nucleotide metabolites. CD38 is expressed in human hematopoietic cells such as lymphocytes (CD4+ and CD8+ T cells and B cells), as well as natural killer cells and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone.

Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or HuMab- 3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). The in vitro studies demonstrated that daratumumab and HuMab-CD38 bound to purified human CD38 with high affinity as shown by KD values in the low nanomolar (nM) range. Both antibodies also bound to several lymphoma cell lines. Daratumumab induced myeloma tumor cell lysis through complement-dependent cytotoxicity (CDC), whereas HuMab-CD38 has far less CDC activity. Daratumumab, HuMab-CD38 and rituximab were shown to elicit similar maximal lysis (approximately 40%) of lymphoma cells in vitro through antibody-dependent cell-mediated cytotoxicity (ADCC), and daratumumab is approximately twice as potent as either HuMab-CD38 or rituximab. Daratumumab and a variant (DARA-K322A) with an altered residue in the Fc region were shown to induce macrophage-mediated phagocytosis (antibody-dependent cellular phagocytosis (ADCP)) in malignancies expressing CD38. Daratumumab also promotes apoptosis through Fc mediated cross-linking, in vitro. According to the Applicant, binding of daratumumab to CD38 on NK cells results in their death, whereas this is not necessarily the case with normal T cell lymphocytes.

The key registration trial (MMY2002) was an open-label, single arm, phase 2 trial in which the proposed patient population of 106 individuals who received 16mg/kg of daratumumab until disease progression. The primary endpoint was independent review committee–assessed overall response rate (ORR), calculated as the proportion of subjects who achieved a partial response (PR) or better during treatment or the follow-up phase. The final analysis for trial MMY2002 showed an ORR of 29%, with a median time to response of 1 month, and a median duration of response of 7.4 months.

Daratumumab efficacy was supported by GEN501, a first-in-human phase1/2 monotherapy dose-escalation trial in patients with relapsed or refractory multiple myeloma. Trial GEN501 was the first-in-human, open-label, multicenter, phase 1 and 2 trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose escalation cohorts and explored various dosing

schedules. The primary objective was to establish the safety profile of daratumumab. The primary efficacy endpoint was overall response rate (ORR). Trial GEN501 was divided into 2 parts. Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. Eligible were patients with multiple myeloma relapsed or refractory to at least 2 different cytoreductive therapies and without further established treatment options. In Part 2, 42 patients were treated at the 16 mg/kg dose of daratumumab.

Patients entered into these trials were heavily pretreated and refractory to multiple lines of a PI and IMiD:

- a. 97% were refractory to the last line of therapy
- b. 77% were refractory to alkylating agents
- c. 95% were double refractory
- d. 66% were refractory to 3 of the 4 following therapies: bortezomib, lenalidomide, carfilzomib or pomalidomide.
- e. 63% were refractor to pomalidomide
- f. 48% were refractory to carfilzomib

Patients entered into MMY2002 were very heavily pretreated:

- a. 100% prior PI
- b. 100% prior IMiD
- c. 100% prior alkylating agents
- d. 80% prior bone marrow transplant

The response rates are shown below in Table 1:

**Table 1: Efficacy Results from MMY002 and GEN501**

Trial	MMY002 (16 mg/kg) N=106	GEN501 (16 mg/kg) N=42
ORR	29.2%	35.7%
sCR	2.8%	0.0%
CR	0.0%	4.8%
VGPR	9.4%	4.8%
PR	17.0%	26.2%
DOR (median in months)	7.4	Not reached with 65% responders disease free at 12 months

The analysis in a safety population of 156 patients treated with 16 mg/kg of daratumumab showed that there were no deaths attributable to daratumumab and no TEAEs considered by the investigator to be related to study drug which led to a discontinuation of treatment. There were no cases of febrile neutropenia, no increase in infection over time, and no patients positive for

anti-daratumumab antibodies. Only 3% of patients had grade 3 infusion reactions and none of these led to discontinuation of daratumumab.

In addition to these two completed single arm trials (MMY002 and GEN501), the Applicant has the following Phase 3 trials under development in previously untreated patients with myeloma:

- a. Velcade/Melphalan and Prednisone with and without daratumumab
- b. Lenalidomide and low dose dexamethasone with and without daratumumab
- c. Velcade/thalidomide and low dose dexamethasone with and without daratumumab.

The Applicant also has the following Phase 3 trials under development in relapsed refractory patients with myeloma:

- a. Lenalidomide and low dose dexamethasone with and without daratumumab
- b. Velcade and low dose dexamethasone with and without daratumumab.

In view of these results, the Secondary (Clinical Team Leader) Reviewer recommends accelerated approval on the basis of his conclusion that there is a positive risk/benefit ratio for the use of daratumumab in the proposed indication of treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD

**Regulatory Recommendation of the Secondary (Clinical Team Leader) Reviewer:** Accelerated Approval.

**2. BACKGROUND:** (This section was derived in part from the review of Barry Miller).

**Multiple Myeloma:** Multiple myeloma (MM) is a plasma cell neoplasm characterized by the proliferation and accumulation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating immunoglobulin and/or free light chains, depressed immunity, and end-organ damage.

Multiple myeloma accounts for an estimated 1.6% of all cancers and 16.6% of hematologic malignancies. An estimated 26,850 new cases of myeloma will occur in the U.S. in 2015 with an estimated 11,240 deaths. The diagnosis is most common in the 6<sup>th</sup> and 7<sup>th</sup> decades of life. Myeloma is more common in men than women (7.9 vs. 5.1 per 100,000 persons per year). African Americans or Blacks are the most affected race and account for twice as many new cases of myeloma than Whites: 12.8 vs. 5.8 per 100,000 persons per year.

With the introduction of chemotherapy, median survival extended to 24 to 30 months from a natural history median survival of 7 months. The introduction of corticosteroids, proteasome inhibitors, immunomodulatory agents, and stem cell transplants has further extended median survival to 5 to 6 years.

**Current Treatment Options in Myeloma:** Treatment of multiple myeloma is typically initiated when symptoms develop. Patients with symptomatic myeloma often respond to

cytotoxic chemotherapy. However, responses are often transient; myeloma is not considered curable with available treatments. 2 lists all FDA approvals for multiple myeloma.

Current treatment regimens tend to be comprised of two to three agents; most all patients receive a proteasome inhibitor (bortezomib or carfilzomib) and an immunomodulatory agent (lenalidomide, pomalidomide, thalidomide) both early and late in the course of treatment of their disease.

Treatment for relapsed and/or refractory myeloma depends on disease- and patient-specific features, initial treatment regimen, and the duration of responses to initial and subsequent treatment. Single drug or combination regimens, stem cell transplant, or clinical trial therapy are all options for patients with relapsed or refractory myeloma. In patients who are refractory or relapsed to both an immunomodulating agent and the proteasome inhibitor bortezomib, ORR ( $\geq$ PR) ranged from 24% to the first therapy to 6% after the 5<sup>th</sup> regimen. The median overall survival of patients with multiple myeloma who have received multiple salvage therapies is 9 months.

Approvals for drugs in multiple myeloma have been supported by improvements in time-to-progression (TTP) or progression-free survival (PFS). Both include objective tumor progression measured in time from randomization; TTP does not include deaths. Accelerated approvals have been supported by overall response rate (ORR) results from single-arm trials.

When compared to dexamethasone alone as a single agent or in combination with dexamethasone, the agents bortezomib, lenalidomide, and thalidomide demonstrated improvements of 2.7 to 16 months in TTP. In trials adding an investigational agent to a known single- or double-agent treatment regimen, differences in median PFS or TTP ranged from 2.8 to 8.7 months.

**Table 2 Currently Available Treatment for Multiple Myeloma**

Drug Name <i>Indication</i>	Trial Type	Approval Date, <i>Type</i>	Approval Basis	Survival Benefit?
Cytosan (cyclophosphamide) <i>For treatment of MM</i>		1959 <i>Regular</i>	Case series	NE
Alkeran tablet (melphalan) <i>For palliative treatment of MM</i>		1964 <i>Regular</i>	Case series	NE
BiCNU (carmustine) <i>For MM, with prednisone</i>		1977 <i>Regular</i>	Case series	NE
Alkeran injection (melphalan) <i>For palliative treatment of MM for whom oral therapy is not appropriate</i>	Alkeran IV injection + pred (n=203) vs. oral melphalan + pred (n=107)	1992 <i>Regular</i>	Response rate at 22 weeks: Oral 44% vs. IV 38%	NE
Velcade (bortezomib) <i>For 3<sup>rd</sup> line MM</i>	Single arm trial (n=256)	2003 <i>Accelerated</i>	ORR 28%	NE
Velcade (bortezomib) <i>For 2<sup>nd</sup> line MM</i>	RCT of Velcade vs. dex (n=669)	2005 <i>Regular</i>	TTP: 6.2 m. vs. 3.5 m. $\Delta$ TTP 2.7 m.	Yes HR 0.57, p<0.05 (median f/u 8.3 m.)

Drug Name Indication	Trial Type	Approval Type	Date,	Approval Basis	Survival Benefit?
Velcade (bortezomib) For untreated MM	RCT of Velcade + melphalan + pred (VMP) vs. melphalan + pred (MP) (n=682)	2008 <i>Regular</i>		PFS: 18.3 m. vs. 14 m. Δ PFS 4.3 m.	Yes HR 0.61, p=0.0078
Revlimid (lenalidomide) For 2 <sup>nd</sup> line MM, with dex	Two RCTs of Revlimid + dex vs. dex (n=341, n=351)	2006 <i>Accelerated</i>		Trial 1 TTP: 8.5 m. vs. 4.6 m. Δ TTP 3.9 m. Trial 2 TTP: NE (Rev+dex) vs. 4.6 m.	No
Thalomid (thalidomide) For newly diagnosed MM	Two RCTs: Thalomid + dex vs. dex (n =207) Thalomid + dex vs. placebo (n=470)	2006 <i>Accelerated</i>		Trial 1 ORR: 52% vs. 36% Trial 2 TTP: 22.5 m. vs. 6.5 m. Δ TTP 16 m.	Difference not statistically significant
Doxil (doxorubicin HCL liposome) For 2 <sup>nd</sup> line MM (no prior Velcade)	RCT of Doxil + bort vs. bort (n=646)	2007 <i>Regular</i>		TTP: 9.3 m. vs. 6.5 m. Δ TTP 2.8 m.	No
Kyprolis (carfilzomib) For 3 <sup>rd</sup> line MM	Single arm trial (n=266)	2012 <i>Accelerated</i>		ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8 m.	NE
Kyprolis (carfilzomib) For 2 <sup>nd</sup> , 3 <sup>rd</sup> , or 4 <sup>th</sup> line MM, with len and dex	Kyprolis + len/dex vs. len/dex (n=792)	2015 <i>Regular</i>		PFS: 26.3 m. vs. 17.6 m. Δ PFS 8.7 m.	Difference not statistically significant
Pomalyst (pomalidomide) For 3 <sup>rd</sup> line MM	Pomalyst + dex vs. Pomalyst (n=221)	2013 <i>Accelerated</i>		PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.	NE
Pomalyst (pomalidomide) For 3 <sup>rd</sup> line MM	Pomalyst + dex vs. Dex (n=455)	2015 <i>Regular</i>		PFS: 3.6 m. vs. 1.8 m. OS: 12.4 m. vs. 5.8m.	Yes HR 0.70, p=0.009
Farydak (panobinostat) For 3 <sup>rd</sup> line MM, with bort and dex	RCT Farydak + bort/dex vs. bort/dex (n=768)	2015 <i>Accelerated</i>		Subgroup: prior tx bort and immunomodulatory agent and median 2 prior therapies (n=193) PFS: 10.6 m. vs. 5.8 m.	Difference not statistically significant

bort = bortezomib, dex = dexamethasone, len = lenalidomide, mDOR = median duration of response, m = months, MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone, RCT = randomized controlled trial, TTP = time to progression, Δ = difference

**3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):** (This section was excerpted from the CMC reviews of Drs. Tura Camilli, Maria Jose Lopez Barragan, Laura Fontan, and Natalia Pripuzova. For details, see the reviews of these individuals.)

**3.A. CMC Facilities:** (The section was excerpted from the review of Dr. Laura Fontan. For details, see her review).

Daratumumab is a fully human immunoglobulin G1k monoclonal antibody that binds with high affinity and specificity to the extracellular domain of human CD38 and is a transmembrane glycoprotein. The DP is provided in two strengths, 400 mg/mL and 100 mg/mL.

The subject BLA proposes manufacture of daratumumab drug substance (DS) and drug product (DP) at the facilities listed below. The drug substance is manufactured at two facilities: (b) (4) at Janssen Biologics in Ringaskiddy, Cork County, Ireland (FEI: 3007029098). The drug product is filled

into vials at 100mg/ml and 400 mg/ml strengths. Both strengths are filled at (b) (4). Additionally the 100 mg/vial strength is filled at Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695). Cell banking operations will occur at Janssen Biotech, Inc., Malvern PA (FEI: 3001610451). A complete list of facilities associated with Daratumumab manufacturing is provided below in Tables 3 and 4.

Table 3

Site Name	Address	FEI Number	Responsibilities
(b) (4)	(b) (4)	(b) (4)	-Daratumumab (b) (4) DS manufacture -Process (b) (4) testing
Janssen Biologics (Ireland)	Barnahely Ringaskiddy, Cork, Ireland	3007029098	-Daratumumab (b) (4) manufacture -Process (b) (4) testing -Release testing of drug substance
Janssen Biotech, Inc	200 Great Valley Parkway Malvern, PA	3001610451	-Manufacture of working cell bank -Biological and characterization assays -Release testing of bulk drug substance and drug product
Janssen Biologics B. V.	Einsteinweg 101 23333 CB Leiden Netherlands	3002806632	- Bulk DS stability testing - DP stability and release testing for all tests but CCIT -Mycoplasma and In Vitro Assay for Adventitious Agents
(b) (4)	(b) (4)	(b) (4)	-Mycoplasma and In Vitro Assay for Adventitious Agents
(b) (4)	(b) (4)	(b) (4)	-Mycoplasma and In Vitro Assay for Adventitious Agents

Table 4

Site Name	Address	FEI Number	Responsibilities
Cilag A G.	Hochstrasse 201 8200 Schaffhausen Switzerland	3002806695	-DP-100mg/ vial liquid -DP release and stability testing for CCIT -DP in process testing -DP labelling and packaging
(b) (4)	(b) (4)	(b) (4)	-DP-100mg and 400mg/ vial liquid -Endotoxin and sterility
Janssen Biologics (Ireland)	Barnahely Ringaskiddy, Cork, Ireland	3007029098	-DP release testing
Janssen Biotech, Inc	200 Great Valley Parkway Malvern, PA	3001610451	-Biological and characterization assays
Janssen Biologics B. V.	Einsteinweg 101 23333 CB Leiden Netherlands	3002806632	-DP release and stability testing for all test except CCIT
(b) (4)	(b) (4)	(b) (4)	- (b) (4) only

	(b) (4)	Endotoxin and sterility
		Visual inspection only
		Visual inspection only
		Endotoxin and sterility
		Polysorbate 20 only
		DP labelling and packaging

The facilities for manufacture of daratumumab DS are adequately described above in Table 3. Compliance decisions are pending for the (b) (4) inspection of the (b) (4) (b) (4) DS manufacture, and the 10/5-9/2015 inspection of the Janssen Biologics site (FEI 3007029098) (b) (4) DS manufacture. Both of these sites are currently in acceptable compliance standing. The compliance status of drug product sites, (b) (4) and Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695) are also acceptable compliance standing. Final recommendation for the proposed manufacturing and testing sites is pending final compliance decisions for the DS manufacturing facilities.

**Regulatory Recommendation:** Approval

**3.B. Drug Substance** (This section was excerpted in part from the review of Maria Jose Lopez Barragan, PhD. For details, see the review of that individual).

The facilities listed above in Table 4 are also involved in the manufacture, release testing, and stability testing of daratumumab drug substance.

Daratumumab DS is manufactured (b) (4) formulation. Two facilities are involved in the DS manufacture: (b) (4) and Janssen Biologics in Cork, Ireland. (b) (4)

All aspects of the manufacturing process were found to be satisfactory.

There is one post-marketing commitment:

Provide data demonstrating that the [REDACTED] (b) (4) validation studies of [REDACTED] (b) (4) has the same microbial growth promotion properties than the daratumumab [REDACTED] (b) (4). Sponsor has agreed to complete these studies by 06/30/2016.

**Regulatory Recommendation:** Approval

**3.C. Drug Product Quality Microbiology Review:** (This review is excerpted from the review of Dr. Natalia Pripuzova. For details, see her review).

BLA761036, Module 3, “Quality”, was submitted in electronic format on 09-July- 2015 as a part of the rolling submission to license daratumumab for treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD.

Daratumumab (HuMax-CD38) is a monoclonal antibody which specifically binds an epitope of the CD38 molecule present on the extracellular surface. The concentrated [REDACTED] (b) (4) is manufactured by [REDACTED] (b) (4). The drug substance (DS) is manufactured in Cork, Ireland. The Drug Product (DP) is manufactured by Cilag A.G. in Schaffhausen, Switzerland (100mg/vial) and [REDACTED] (b) (4) (100 and 400 mg/vial).

The daratumumab DP is supplied as a sterile, 20 mg/mL liquid concentrate for infusion in two presentations: 100 mg/vial and 400 mg/vial. It is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride.

All aspects of the manufacturing of the DP that were reviewed by the FDA team were satisfactory.

**Regulatory Recommendation:** Approval

**3.D. Product Quality Review** (This section was excerpted from the review of Dr. Tura Camilli and Dr. Jee Chung. For details, see their reviews)

**I. Primary Reviewer Summary Recommendation:** We recommend approval of this BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of daratumumab is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. There will be a PMR concerning work to be done in the area of the development of an immunogenicity assay.

The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that daratumumab be approved for human use (under conditions specified in the package insert). We recommend an expiration dating period of (b) (4) months for daratumumab concentrated (b) (4) when stored at (b) (4) C. We recommend an expiration dating period of 18 months for daratumumab drug substance when stored at (b) (4) C. We recommend an expiration dating period of 18 months for drug product when stored at 2-8°C protected from light.

## **II. List of Deficiencies To Be Communicated: None**

## **III. List Of Post-Marketing Commitments/Requirements:**

PMR 1: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR 2: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 1 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

PMR 3: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC 1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and 7 confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b) (4) and drug substance long term storage containers.

PMC 3: Re-evaluate (b) (4) lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 6: Provide data to demonstrate that the (b) (4) validation studies of (b) (4) has the same microbial growth promotion properties as daratumumab (b) (4) corresponding to (b) (4). These studies are needed to demonstrate that (b) (4) daratumumab product (b) (4) are adequate to support microbial quality.

**IV. Review Of Common Technical Document-Quality Module 1:** Environmental Assessment or Claim of Categorical Exclusion as specified in 21 CFR 25.15(d), Janssen states that this Biologic License Application qualifies for a categorical exclusion to the environmental assessment requirement under 21CFR 25.31(c), based on consideration of its effects when exposed to the environment. Daratumumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment. The claim of categorical exclusion is acceptable.

**Regulatory Recommendation:** Approval.

**Regulatory Recommendation of the Entire CMC Division:** Approval.

**4. PHARMACOLOGY/TOXICOLOGY:** (This section was derived in part from the reviews of Christopher Sheth, PhD and Emily Place, PhD. For details, see the primary reviews of these individuals.)

According to the Applicant, daratumumab is designed to target CD38 positive plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme involved in the production of nucleotide metabolites. CD38 is expressed in human hematopoietic cells/tissues, and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone. Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or HuMab- 3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). The in vitro studies demonstrated that daratumumab and HuMab-CD38 bound to purified human CD38 with high affinity as shown by KD values in the low nanomolar (nM) range. Both antibodies also bound to several lymphoma cell lines. Daratumumab induced myeloma tumor cell lysis through complement-dependent cytotoxicity (CDC), whereas HuMab-CD38 has far less CDC activity. Daratumumab, HuMab-CD38 and rituximab were shown to elicit similar maximal lysis (approximately 40%) of lymphoma cells in vitro through antibody-dependent cell-mediated cytotoxicity (ADCC), and daratumumab is approximately twice as potent as either HuMab-CD38 or rituximab. Daratumumab and a variant (DARA-K322A) with an altered residue in the Fc region were shown to induce macrophage-mediated phagocytosis (antibody-dependent cellular phagocytosis (ADCP)) in malignancies expressing CD38. Daratumumab also promotes apoptosis through Fc mediated cross-linking, in vitro.

Pharmacology studies also indicate daratumumab modulates CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38, whereas the surrogate HuMab-CD38's ability to inhibit ribosyl cyclase enzyme activity is substrate dependent and it conversely inhibits cADPR hydrolase activity. Importantly, the degrees to which the known mechanisms contribute to the clinical efficacy of daratumumab is still unknown. In vivo pharmacology studies showed that daratumumab reduced tumor growth and burden in human lymphoma xenograft mouse models. Based on the nonclinical data submitted in the BLA and its chemical structure, the Established Pharmacological Class (EPC) of "human CD38-directed monoclonal antibody" was determined to be both clinically meaningful and scientifically valid for daratumumab.

Stand-alone safety pharmacology studies were not conducted with daratumumab. ECG parameters, respiratory rates, body temperatures and pulse rates were assessed during the 6-week repeat-dose toxicology study in chimpanzees and were unremarkable at doses up to 25 mg/kg. ECGs, body temperature and heart rate were assessed during the 2 week repeat dose toxicology study in monkeys and were unremarkable at doses up to 100 mg/kg.

The toxicology data for daratumumab was generated in the chimpanzee (in study that was not designed to be terminal and was not requested by the FDA), and in the monkey using the HuMab-CD38 surrogate antibody. These studies indicated there are no gender differences in exposure in chimpanzees or monkeys. Increases in Cmax and AUC values are greater than dose proportional in the chimpanzee, and approximately dose proportional in monkeys. Daratumumab was slowly eliminated in the blood following intravenous dosing with half-lives of approximately 15.5 to 18.8 days in chimpanzees, and 9 to 63 hours for HuMab-CD38 in the monkey.

The general toxicology studies reviewed were a 6-week repeat-dose toxicity study in chimpanzee and a 2-week repeat dose toxicity study in the monkey. Both repeat-dose toxicity studies utilized IV dosing, which is the intended route of administration for Darzalex. In animals, daratumumab was found to target the hematopoietic and lymphatic systems, in addition to the liver and spinal cord and nervous system. Findings include:

- a. Hematopoietic and lymphatic systems: Increases in red blood cells, hemoglobin, and hematocrit; decreases in white blood cells and platelets (chimpanzee and monkey); lymphoid depletion/atrophy in thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch (monkey only).
- b. Liver: Elevated AST, ALT (chimpanzee only).  
Cytokine response reaction (chimpanzees only): Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest leading to one mortality.
- c. Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.
- d. The Applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. The considerations led to no reproductive and developmental toxicology studies being conducted for daratumumab include: the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); that these studies are not warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9). ICH S9 also outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies were needed.

**Regulatory Recommendation:** The nonclinical studies submitted to this BLA provide sufficient information to support the use of Darzalex for the treatment of patients with multiple myeloma 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 immunomodulatory agent.

**5. CLINICAL PHARMACOLOGY:** (This section was derived in part from the review of Dr. Jeanne Fourie Zirchelbach, PhD. For details, see the primary review of Dr. Fourie Zirchelbach.)

The population pharmacokinetic (PK) analysis included 223 patients with multiple myeloma who received daratumumab (150 subjects received 16 mg/kg). Over the dose range from 1 to 24 mg/kg, AUC increases more than dose-proportionally. Clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the recommended dose and schedule, the  $C_{max}$  at the end of weekly dosing is 2.9-fold higher than following the first infusion.

Daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period and the  $C_{max}$  at steady-state to  $C_{max}$  after the first dose is 1.6. The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day

and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance is approximately 18 days.

Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also show that age (31-84 years), gender, mild to severe renal impairment (15 to 89 mL/min) and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis shows that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations ( $C_{\text{pre-infusion, max}} \geq 270 \mu\text{g/mL}$ ). Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab  $C_{\text{pre-infusion, max}} < 270 \mu\text{g/mL}$  (1.9 month) and longer (6.6 months) in those with daratumumab concentrations  $\geq 270 \mu\text{g/mL}$ . However, this analysis was confounded by baseline risk factors such as disease severity. Patients with lower exposure who did not respond to treatment were also the patients with higher disease burden, worse performance status (Eastern Cooperative Oncology Group [ECOG]), and more advanced disease at baseline.

Given that there is no control arm available in these open-label trials, it is difficult to differentiate the true contribution of exposure from other baseline risk factors on efficacy. As such, we recommend that the applicant should evaluate the possibility of dose optimization in these patients with lower exposure when more data are available from the ongoing controlled clinical trials. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trials MMY2002 and GEN501.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased rates of  $\geq$  grade 3 treatment emergent adverse events (TEAE), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. There are no safety data in patients with moderate and severe hepatic impairment. Recent literature data suggest that CD38 may play roles in normal hepatic function and liver disease. Therefore, patients with hepatic impairment may be sensitized to daratumumab through yet unknown mechanisms involving CD38. Additional data are needed to confirm this potential safety signal, and to characterize the safety of daratumumab in the patient sub-population with baseline hepatic impairment and multiple myeloma for which daratumumab may provide clinical benefit. A PMR was issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Data from three monotherapy trials (trials GEN501, MMY2002 and MMY 2001), in patients with relapsed or refractory multiple myeloma, were included in the pharmacokinetic analyses (N=232). Following the Part 1 dose-escalation portion of trial GEN501, the other trials were conducted at 8 mg/kg and 16 mg/kg daratumumab.

**Trial GEN501:**

Trial GEN501 is entitled “Daratumumab safety study in multiple myeloma – Open-label, dose-escalation followed by open-label, single-arm study”. In Part 1, the first full infusion was followed by a 3-week resting period, and the subsequent 6 full infusions were given at weekly intervals. In Part 2 of trial GEN501, the 8 mg/kg and 16 mg/kg doses were further evaluated. Subjects received the first full infusion with a 3-week resting period, followed by weekly dosing for 7 weeks and then biweekly dosing for 14 additional weeks, and once every four week dosing thereafter for up to 72 weeks until disease progression.

**Trial MMY2002:**

Trial MMY2002 entitled “An open-label, multicenter, phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a PI and IMiD) or are double refractory to a PI and an IMiD” was conducted in the current proposed patient population. In Study MMY2002, a total of 33 subjects (2 [11%] in the 8 mg/kg group and 31 [29%] in the 16 mg/kg group) out of 124 treated subjects had a PR or better response.

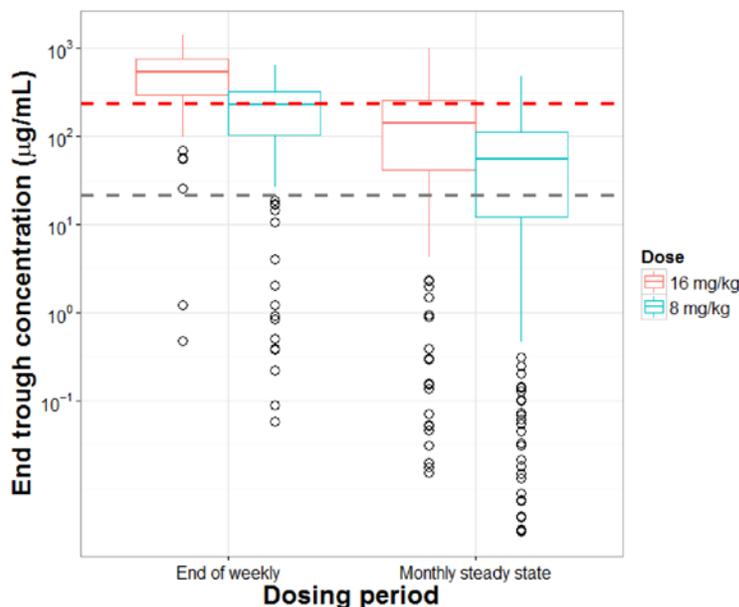
Part 1 patients were randomized to receive 8 mg/kg daratumumab once every 4 weeks, continuously or 16 mg/kg daratumumab with the final recommended dosing schedule. The ORR was 11% and 32% at the 8 mg/kg and 16 mg/kg doses, respectively. In Part 2, a total of 106 patients were treated at 16 mg/kg dose with the recommended dosing schedule (daratumumab weekly for 8 weeks, biweekly for 16 weeks and then once every 4 weeks thereafter until disease progression).

In Study MMY2002, a total of 33 subjects (2 [11%] in the 8 mg/kg group and 31 [29%] in the 16 mg/kg group) out of 124 treated subjects had a PR or better response. Of the 12 subjects in the higher dose groups ( $\geq 4$  mg/kg daratumumab) in Part 1 of GEN501, 4 subjects (33.3%) had a PR. In Part 2 of Study GEN501, 3 subjects in the 8 mg/kg group (out of 30 subjects; 10%) had a PR, while for subjects in 16 mg/kg groups, 15 out of 42 subjects (36%) had a PR or better response. Positive association was consistently observed between daratumumab exposure and efficacy endpoints tested (ORR, PFS).

There was no apparent exposure-response relationship between the predicted first  $C_{max}$  and infusion related reactions (IRR), and the predicted maximal end-of-infusion concentration ( $C_{post-infusion,max}$ ) and thrombocytopenia, anemia, neutropenia, and lymphopenia based on either the data from the pooled analysis of Studies MMY2002 and GEN501 or Study MMY2002 alone. In general, a slightly lower incidence of Grade 3+ AEs was observed in subjects in the high-exposure quartiles (Q3 and Q4) than in subjects in the low-exposure quartiles (Q1 and Q2). Although the event rate of infection appeared to numerically increase with drug exposure, this trend was not observed for Grade 3+ infections. Further analysis demonstrated that there was no significant difference in the rate of infections/infestations between IgG and non-IgG multiple myeloma subjects, although higher exposure was observed in non-IgG multiple myeloma subjects.

Daratumumab exhibits target-mediated drug disposition. Simulations based on the final model further suggested that the 16 mg/kg dose was the lowest tested dose that achieved the  $EC_{99}^{TAR}$  in the majority of the study subjects (>80%) at the end of weekly dosing (see Figure 1 below). Furthermore, this is also supported by *in vitro* data from binding of daratumumab to human CD38 cells, as the estimated  $EC_{90}^{TAR}$  and  $EC_{99}^{TAR}$  *in vivo* are much higher than the *in vitro*  $EC_{99}^{TAR}$  (~1 µg/mL) to human CD38 cells.

**Figure 1.** Box Plot for the Predicted Pre-infusion (Trough) Concentrations at the End of Weekly (QW) and Every 4 Week (Q4W) Steady State Dosing at Dose Levels of 16 mg/kg and 8 mg/kg Daratumumab.

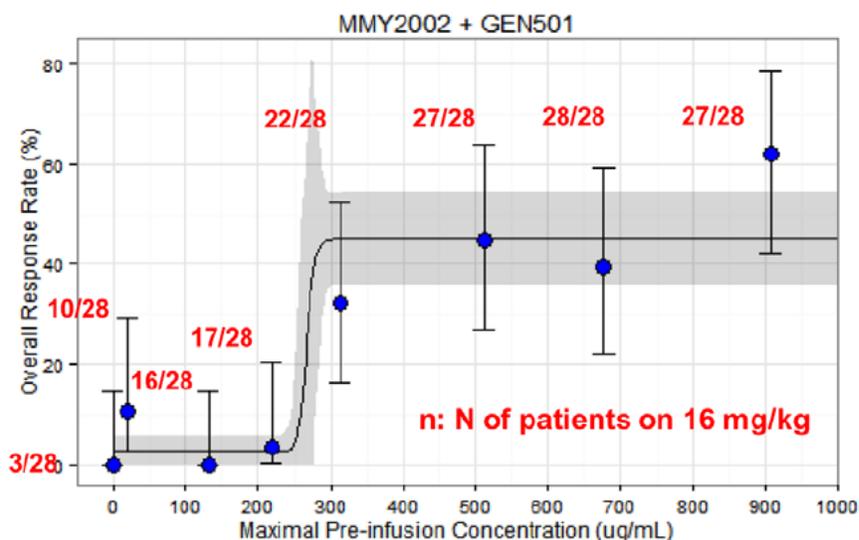


Note:  $EC_{99}^{TAR}$  was obtained by solving  $\frac{EC_{99}^{TAR}}{K_m + EC_{99}^{TAR}} = 99\%$  and  $EC_{90}^{TAR}$  was obtained by solving  $\frac{EC_{90}^{TAR}}{K_m + EC_{90}^{TAR}} = 90\%$ . The percentages of subjects who achieved >99% target saturation at the end of weekly dosing at 16 mg/kg and 8 mg/kg were 83% and 48%, respectively. The percentages of subjects who achieved >90% target saturation at end Q4W dosing for 16 mg/kg and 8 mg/kg were 82% and 67%, respectively.

The applicant conducted the exposure-response analyses based on pooled data from trials MMY2002 and GEN501, which show that ORR significantly increased with daratumumab exposure, and there was an  $E_{max}$  relationship between exposure ( $C_{pre-infusion,max}$ ) and ORR (see Figure 2).

Therefore, limited additional benefit in ORR is expected with  $C_{pre-infusion,max}$  higher than the predicted  $EC_{90}^{ORR} = 274 \mu\text{g/mL}$ . At an individual level, 70% (104/150) of patients after weekly administration of 16 mg/kg achieved  $C_{pre-infusion,max}$  over the estimated  $EC_{90}^{ORR}$  and reached the plateau part of the exposure-response curve.

**Figure 2.** Logistic Regression Analysis between Overall Response Rate and Predicted Maximal Pre-infusion (Trough) Concentration Using an  $E_{max}$  Model.



Key: Solid blue dots represent the proportion of responders grouped by 8-quantile of maximal pre-infusion concentration and plotted at the geometric mean for each group. The bar represents the 95% confidence interval for the proportion in each group. Centered curves and shaded areas represent predicted values and 95% confidence intervals of model-predicted response rate, respectively.

Furthermore, with respect to the proposed dosing regimen, the population PK analyses suggest that the total clearance of daratumumab decreased over time, most likely due to the saturation of the target (CD38). The intensive weekly dosing at the beginning of the treatment was selected to overcome the high clearance initially, and establish efficacious concentrations in a timely manner.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis showed that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations ( $C_{pre-infusion, max} > 270 \mu\text{g/mL}$ ).

Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab  $C_{pre-infusion, max} < 270 \mu\text{g/mL}$  (1.9 month) and longer (6.6 months) in those with daratumumab concentrations of  $> 270 \mu\text{g/mL}$ .

However, this analysis was confounded by baseline risk factors such as disease severity. Patients with lower exposure who did not respond well were also the patients with higher disease burden, worse performance status (Eastern Cooperative Oncology Group [ECOG]), and more advanced disease at baseline.

Given that there is no control arm available in these open-label trials, it is difficult to differentiate the true contribution of exposure from other baseline risk factors on efficacy. As such, we recommend sponsor to evaluate the possibility of dose optimization in these patients with lower exposure when more data is available from the controlled ongoing trials. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trial

MMY2002 and GEN501.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased incidences of  $\geq$  grade 3 treatment emergent adverse events (TEAEs), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. There are no safety data in patients with moderate and severe hepatic impairment. A PMR was issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Population pharmacokinetic analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Other intrinsic factors, including age, gender, mild to severe renal impairment and mild hepatic impairment do not have clinically important effect on the pharmacokinetics of daratumumab.

**Relationship between Renal Impairment and Exposure:** Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild, moderate and severe renal impairment. The CrCL was calculated by the Cockcroft and Gault equation, and the CL was estimated for each individual in the PK data set, i.e. normal renal function (CrCL  $\geq$  90 mL/min, N=71), mild renal impairment (CrCL  $<$ 90 and  $\geq$ 60 mL/min; n=78), moderate renal impairment (CrCL  $<$ 60 and  $\geq$ 30 mL/min; n=68) and severe renal impairment (CrCL  $<$ 30 mL/min and  $\geq$  15 mL/min; n=5). CrCL was not a significant covariate on daratumumab clearance, and there is no need for dose adjustment in patients with renal impairment (see Appendix 4.1, Pharmacometrics Review). This is consistent with renal elimination not being a significant clearance pathway of daratumumab. The potential effect of end-stage renal disease on daratumumab pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient.

**Relationship between Hepatic Impairment and Exposure:** Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild hepatic impairment. There were no available PK data to assess the effect of moderate or severe hepatic impairment on daratumumab PK.

The effect of hepatic impairment on the clearance of daratumumab was evaluated in subjects who had mild hepatic impairment (total bilirubin 1.0 $\times$  to 1.5 $\times$  upper limit of normal [ULN] or AST  $>$ ULN as defined using the National Cancer Institute - Organ Dysfunction Working Group (NCI-ODWG) criteria; n=34) compared with subjects who had normal hepatic function (total bilirubin and AST  $\leq$ ULN; n=189) in the population pharmacokinetic analysis. Mild hepatic impairment was not a significant covariate based on the model-based covariate analysis. No clinically important differences in the exposure to daratumumab were observed between subjects with mild hepatic impairment and those with normal hepatic function. Daratumumab has not been studied in subjects with moderate (total bilirubin  $>$ 1.5 $\times$  to 3 $\times$  ULN and any AST) or severe (total bilirubin  $>$ 3 $\times$  ULN and any AST) hepatic impairment.

**Relationship between Renal Impairment and Exposure:** Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild, moderate and severe renal impairment. The CrCL was

calculated by the Cockcroft and Gault equation, and the CL was estimated for each individual in the PK data set, i.e. normal renal function (CrCL  $\geq$  90 mL/min, N=71), mild renal impairment (CrCL  $<$ 90 and  $\geq$ 60 mL/min; n=78), moderate renal impairment (CrCL  $<$ 60 and  $\geq$ 30 mL/min; n=68) and severe renal impairment (CrCL  $<$ 30 mL/min and  $\geq$  15 mL/min; n=5). CrCL was not a significant covariate on daratumumab clearance, and there is no need for dose adjustment in patients with renal impairment. This is consistent with renal elimination not being a significant clearance pathway of daratumumab. The potential effect of end-stage renal disease on daratumumab pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient.

**Relationship between Hepatic Impairment and Exposure:** Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild hepatic impairment. There were no available PK data to assess the effect of moderate or severe hepatic impairment on daratumumab PK.

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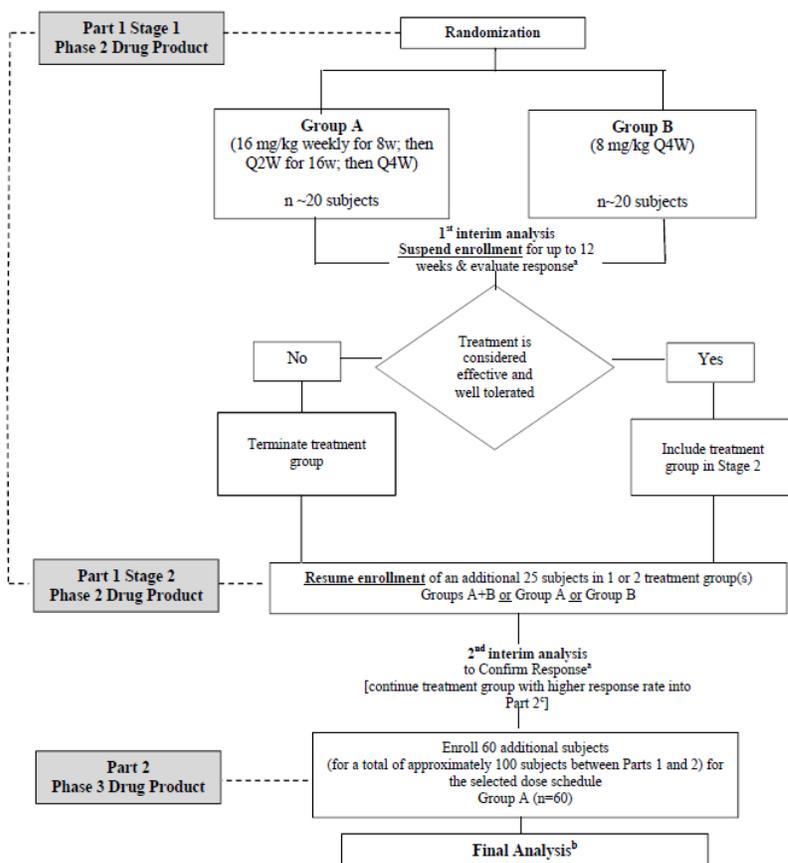
**Regulatory Recommendation of Clinical Pharmacology Team:** Approval

**6. EFFICACY:** (This section is excerpted from the reviews of Dr. Yaping Wang and Barry Miller. For details, please see the primary review of these individuals)

**Trial MMY2002:** Trial MMY2002 is an open-label, multicenter, phase 2, two-part trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose and schedule randomization and expansion cohorts using the early and final drug products. The primary objective of Part 1 was to select the optimal dose and schedule; for Part 2, overall response rate (ORR) was the primary efficacy endpoint. The secondary objectives were to evaluate: safety and tolerability of daratumumab, duration of response, TTR, TTP, PFS, OS, exploration of biomarkers, and predictive of response to daratumumab.

**Trial Design:** The key eligibility criteria was for up to 150 patients with multiple myeloma who had received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulating agent, or whose disease was double refractory to agents in both of these classes. Refractory disease was defined as nonresponse while on therapy or progression of disease within 60 days of stopping therapy for patients who achieved a minimal response (MR)

or better. After the screening period (a maximum 21 days), treatment started and was continued until disease progression, for unacceptable toxicity, or for other reasons listed in the protocol. After treatment, follow-up was to continue until death, consent withdrawal, loss of contact/lost to follow-up, or the end of study. The planned study design (from the protocol) is shown in 3. Patients were centrally randomized to Group A or B. Group A received the dose regimen of 16mg/kg weekly for 8 weeks, 16mg/kg every 2 weeks for 16 weeks, then 16mg/kg every 4 weeks. This dose was selected as it appeared to maximally saturate the target of CD38 for all time points in a majority of patients. Patients in Group B received 8mg/kg every 4 weeks. This dose was selected to better determine the dose response relationship while maintaining near complete CD38 suppression.



<sup>a</sup> Response will be assessed by the Sponsor based on available data (eg. pharmacodynamics, efficacy, safety, biomarkers).

<sup>b</sup> Confirmation of response by the IRC is required.

<sup>c</sup> If only 1 treatment group proceeded to Part 1 Stage 2, this will be the dose that is used in Part 2 of the study.

Q2W=every 2 weeks; Q4W=every 4 weeks; w=week(s)

### Figure 3 Trial MMY2002 Schematic

**Eligibility:** Diagnostic criteria and the definition of need for treatment included in the eligibility criteria are consistent with the target population in the U.S. Patients were required to have documented multiple myeloma as defined by the criteria below and evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

- Prior documentation of monoclonal plasma cells in the bone marrow  $\geq 10\%$  or presence of a biopsy-proven plasmacytoma.
- Presence of measurable disease at baseline as defined by any of the following:
  - Serum M-protein level  $\geq 1.0$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours; or
  - IgA multiple myeloma: Serum M-protein level  $\geq 0.5$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours; or
  - Light chain multiple myeloma: Serum immunoglobulin free light chain (FLC)  $\geq 10$  mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.
- Evidence of response (i.e., achieved  $\geq 25\%$  reduction in M-protein for  $\geq 6$  weeks [MR]) to at least 1 of their prior treatment regimens.

The expectations for prior treatments received are also consistent with contemporary treatment of multiple myeloma in the U.S. Patients were required to have received an alkylating agent ( $\geq 2$  cycles or 2 months) either alone or in combination with other myeloma treatments. One course of an alkylating agent for autologous stem cell transplantation alone or in combination was acceptable. Patients must have also:

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

OR

- Disease was double refractory to a PI and an IA. For subjects who received more than 1 type of PI, their disease was to be refractory to the most recent one. Similarly, for those who received more than 1 type of IA, their disease was to be refractory to the most recent one.

A single line of therapy could consist of 1 or more agents, and could include induction, hematopoietic stem cell transplantation, and maintenance therapy (specified in protocol). Radiotherapy, bisphosphonate, or a single short course of steroids (i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

Only patients 18 years of age and older were allowed to enter the trial. This is appropriate as multiple myeloma does not occur in children and is rare in adults less than 30 years of age. An ECOG performance status of 0, 1, or 2 was required.

Key exclusion criteria were:

- Previous daratumumab or other anti-CD38 therapies
- Anti-myeloma treatment within 2 weeks before Cycle 1, Day 1
- Non-secretory multiple myeloma based upon standard M-component criteria (i.e., measurable serum/urine M-component) unless the baseline serum FLC level was elevated
- Allogeneic stem cell transplant or ASCT within 12 weeks before Cycle 1, Day 1
- Cumulative corticosteroids more than the equivalent of  $\geq 140$  mg of prednisone within the 2-week period before Cycle 1, Day 1
- History of other malignancy within 5 years before Cycle 1, Day 1 (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or

malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, was considered cured with minimal risk of recurrence)

- Clinical signs of meningeal involvement of multiple myeloma

Excluded were patients with the following comorbidities:

- Chronic obstructive pulmonary disease
- Hepatitis B, hepatitis C, or HIV
- Clinically significant cardiac disease
  - Myocardial infarction within one year
  - Unstable or uncontrolled angina or heart failure NYHA Class III-IV
  - Arrhythmias requiring treatment or intervention
  - Prolonged QT interval at screening (QTcF >470msec)

**Study Endpoints:** The primary endpoint was ORR, defined as the proportion of patients who achieve a partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) based on the International Myeloma Workshop Consensus Panel 1 criteria (Rajkumar, Harousseau, et al. 2011) using results from a central laboratory. Investigator-determined response was made on an ongoing basis while the sponsor used a computerized algorithm to derive response and progressive disease assessment. An independent review committee (IRC) was established to review data and assess response of all patients on trial.

Secondary endpoints included:

- Clinical benefit rate, which included minimal response, PR, VGPR, CR, and sCR
- Time to disease progression defined as the number of days from the start of daratumumab to the date of progressive disease
- Progression-free survival defined as the time from the start of daratumumab to disease progression or death
- Time to response defined as the time from the start of daratumumab to response of PR or better
- Duration of response defined as the interval from an initial response of PR or better to disease progression
- Overall survival defined from the start of daratumumab to death
- Serum/urine M-protein or FLC reduction
- Change in the percentage of bone marrow plasma cells
- Overall safety of daratumumab by evaluation of the incidence of treatment emergent adverse events, death, laboratory results, vital signs, physical examination findings, and ECG results.

**Efficacy Results – Primary Endpoint:** The primary analysis population consisted of data from patients enrolled to part 1 and part 2 combined. The objective response rate (ORR) which included partial response or better, among all patients treated with 16 mg/kg was 29%, including 3 stringent complete responses and 10 very good partial responses (VGPR); i.e., VGPR or better was observed in 13 of 106 (12%) patients treated with 16 mg/kg. The ORR among patients treated with 8 mg/kg daratumumab was 11%, which did not meet the protocol specified criteria for continuation of this dose.

None of the complete responses in this trial were impacted with the interference of daratumumab on serum protein electrophoresis and immunofixation assays used. Two of the three patients with stringent complete responses had IgA myeloma disease and one had free light chain only disease; none had IgG kappa myeloma protein disease.

Patients on trial who had a best response of VGPR and persistent positive immunofixation or SPEP were tested using an assay under development by the Applicant. This assay has been validated for clinical trial use only. None of the other responses tested demonstrated interference with daratumumab, meaning VGPR was confirmed to be the best response.

**Regulatory Recommendation:** Approval.

**7. SAFETY:** (This section was derived in part from the review of Barry Miller. For details, please see his review).

Safety data were available for 331 patients treated with various doses and schedules of daratumumab. Data from the three monotherapy studies were pooled to provide an integrated safety data base of 237 patients. Of these, 156 patients received the proposed dose of 16mg/kg. Data from two studies of daratumumab with other agents were pooled for 94 patients; 84 of these patients received 16mg/kg (see Tables 5-7 below for additional information).

**Table 5 Safety Population, Size and Denominators**

Safety Database for the Study Drug <sup>1</sup> Individuals exposed to the study drug in this development program for the indication under review n=331				
Clinical Trial Groups	Trial	New Drug (n=331)	Active Control (n=0)	Placebo (n=0)
Normal Volunteers		0	0	0
Controlled trials conducted for this indication <sup>2</sup>		0	0	0
All other than controlled trials conducted for this indication <sup>3</sup>		237	0	0
Controlled trials conducted for other indications <sup>4</sup>		94	0	0

<sup>1</sup> *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

<sup>2</sup> to be used in product's labeling

<sup>3</sup> if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

<sup>4</sup> include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

**Table 6 Duration of Exposure**

	All doses n=237		≤4 mg/kg n=23		8 mg/kg n=55		16 mg/kg n=156		24 mg/kg n=3	
Month(s)										
	n	%	n	%	n	%	n	%	N	%
<1	44	18.6	7	30.4	14	25.5	22	14.1	1	33.3
1 to <3	92	38.8	16	69.6	21	38.2	53	34.0	2	66.7
3 to <6	36	15.2	0	0	9	16.4	27	17.3	0	0
6 to <9	27	11.4	0	0	5	9.1	22	14.1	0	0
9 to <12	11	4.6	0	0	2	3.6	9	5.8	0	0
≥12	27	11.4	0	0	4	7.3	23	14.7	0	0
Total dose mg/kg										
Mean	158		7		77		209		144	
Median	141		4		70		177		170	
Range	0; 528		0; 30		8; 232		2; 528		81; 182	
Total infusions										
Mean	11.4		5		9		13		6	
Median	10		5		9		12		7	
Range	1; 33		1; 7		1; 26		1; 33		3; 7	

**Table 7 Demographics of Safety Population**

	All doses n=237		16mg/kg n=156	
	n	%	n	%
<b>Sex</b>				
Male	139	58.6	84	53.8
Female	98	41.4	72	46.2
<b>Age</b>				
Mean years (SD)	62.4 (9.33)		62.9 (9.50)	
Median (years)	63		63	
Min, max (years)	31, 84		31, 84	
<b>Age Group</b>				
18 - < 65 years	133	56.1	86	55.1
> 65 - < 75 years	84	35.4	54	34.6
≥ 75 years	20	8.4	16	10.3
<b>Race</b>				
White	180	75.9	119	76.3
Black or African American	17	7.2	16	10.3
Asian	13	5.5	9	5.8
Other, Unknown, or Not Reported	27	11.4	12	7.7
<b>Ethnicity</b>				
Hispanic or Latino	10	4.2	10	6.4
Not Hispanic or Latino	173	73.0	135	86.5
Unknown	54	22.8	11	7.1

<b>Region</b>				
United States	110	46.4	89	57.1
Canada	22	9.3	22	14.1
Europe	96	40.5	40	25.6
Japan	9	3.8	5	3.2
<b>ECOG Performance Status</b>				
0	74	31.2	46	29.5
1	149	62.9	100	64.1
2	14	5.9	10	6.4
<b>Weight Groups</b>				
<55 kg	24	23.2	20	12.8
55-100 kg	190	80.2	119	76.3
100 kg	23	9.7	17	10.9
<b>Renal Dysfunction</b>				
≥90 mL/min	71	30.0	44	28.2
60-<90 mL/min	86	36.3	51	32.7
30-<60 mL/min	73	30.8	56	35.9
15-<30 mL/min	6	2.5	4	2.6
<15 mL/min	1	0.4	1	0.6
<b>Hepatic Dysfunction</b>				
Normal	197	83.5	134	86.5
Mildly impaired <sup>1</sup>	39	16.5	21	13.5

<sup>1</sup> (total bilirubin ≤ULN and AST>ULN) or (total bilirubin 1-1.5xULN)

**Deaths:** Of the 237 patients treated with daratumumab in the development program, 56 (24%) died. Most deaths (41 patients, 17%) occurred more than 30 days after the last dose of daratumumab (see Table 8 below).

**Table 8 Deaths**

	All doses n=237		16mg/kg n=156	
	n	%	n	%
All	56	23.6	40	25.3
Within 30 days of last dose of daratumumab	15	6.3	14	9.0

Within 30 days of the last dose of daratumumab, 1 patient who received 8mg/kg died, and 14 patients who received 16mg/kg died. FDA reviewed all narratives to confirm the cause of deaths. FDA considered the cause of death to be the primary malignancy when supported by objective evidence of disease progression. The majority of deaths were due to multiple myeloma (11 patients, 5%).

**Serious Adverse Events:** An SAE occurring within 30 days of the last dose of daratumumab was reported for 74 (31%) of the 237 patients treated on all clinical trials of single-agent daratumumab. In the group of 156 patients treated with daratumumab 16mg/kg, 51 (33%) experienced a serious adverse event (see Table 9 below).

**Table 9 Serious Adverse Events**

System Organ Class	All doses n=237		16mg/kg n=156	
	n	%	n	%
Infections and infestations	25	10.55	20	12.82
General disorders and administration site conditions	13	5.49	13	8.33
Musculoskeletal and connective tissue disorders	8	3.38	6	3.85
Blood and lymphatic system disorders	7	2.95	3	1.92
Renal and urinary disorders	7	2.95	3	1.92
Gastrointestinal disorders	6	2.53	5	3.21
Investigations	6	2.53	4	2.56
Metabolism and nutrition disorders	6	2.53	6	3.85
Respiratory, thoracic and mediastinal disorders	6	2.53	4	2.56
Injury, poisoning and procedural complications	5	2.11	3	1.92
Nervous system disorders	5	2.11	3	1.92
Cardiac disorders	3	1.27	3	1.92
Psychiatric disorders	2	0.84	2	1.28
Vascular disorders	2	0.84	2	1.28
Hepatobiliary disorders	1	0.42	1	0.64
Immune system disorders	1	0.42	0	0
Neoplasms benign, malignant and unspecified	1	0.42	0	0
Reproductive system and breast disorders	1	0.42	0	0

There were 128 SAEs occurring on treatment or within 30 days of follow-up. SAEs considered at least possible related to daratumumab were reported for 21 (9%) patients in the group of all patients treated with single agent daratumumab.

There were 95 SAEs occurring in the subgroup of patients receiving daratumumab 16mg/kg. The most common ( $\geq 2\%$ ) were pneumonia (6%), general physical health deterioration (3%), pyrexia (3%), hypercalcemia (3%), crossmatch incompatible (2%), and herpes zoster (2%).

Of these, 15 (10%) were reported to be at least possible related to daratumumab. The most common ( $\geq 2\%$ ) related SAEs were pneumonia (3%), herpes zoster (2%), and crossmatch incompatible (2%).

**Treatment Emergent Adverse Events and Adverse Reactions:** Treatment emergent adverse events were assessed through 30 days after the last dose of daratumumab. The number of patients with a TEAE are shown in 10 by SOC in decreasing order of incidence in the entire safety population.

**Table 10 Treatment Emergent Adverse Events by SOC**

System Organ Class	All doses n=237		16mg/kg n=156	
	n	%	N	%
General disorders and administration site conditions	152	64.14	106	67.95
Respiratory, thoracic and mediastinal disorders	136	57.38	96	61.54
Musculoskeletal and connective tissue disorders	126	53.16	95	60.9
Infections and infestations	124	52.32	91	58.33
Gastrointestinal disorders	122	51.48	87	55.77
Blood and lymphatic system disorders	106	44.73	80	51.28
Metabolism and nutrition disorders	82	34.6	65	41.67
Nervous system disorders	81	34.18	56	35.9
Skin and subcutaneous tissue disorders	54	22.78	37	23.72
Renal and urinary disorders	52	21.94	26	16.67
Vascular disorders	48	20.25	29	18.59
Investigations	37	15.61	22	14.1
Psychiatric disorders	37	15.61	29	18.59
Injury, poisoning and procedural complications	32	13.5	29	18.59
Eye disorders	24	10.13	17	10.9
Cardiac disorders	17	7.17	13	8.33
Hepatobiliary disorders	13	5.49	8	5.13
Neoplasms benign, malignant and unspecified	10	4.22	9	5.77
Ear and labyrinth disorders	8	3.38	6	3.85
Immune system disorders	8	3.38	3	1.92
Reproductive system and breast disorders	8	3.38	5	3.21
Congenital, familial and genetic disorders	1	0.42	1	0.64

A TEAE was reported in 155 patients who received daratumumab at 16mg/kg. The numbers of patients with common ( $\geq 10\%$ ) TEAE are shown in Table 11 below.

**Table 11 Treatment Emergent Adverse Events by PT**

Preferred Term	16mg/kg n=156			
	All Grade		Grade 3-4	
	n	%	N	%
Fatigue	61	39.10	3	1.92
Anemia	42	26.92	27	17.31
Nausea	42	26.92	0	0.00
Back pain	36	23.08	3	1.92
Neutropenia	35	22.44	19	12.18
Pyrexia	33	21.15	2	1.28
Cough	33	21.15	0	0.00
Thrombocytopenia	31	19.87	22	14.10
Upper respiratory tract infection	31	19.87	1	0.64
Arthralgia	26	16.67	0	0.00
Nasal congestion	26	16.67	0	0.00
Diarrhea	25	16.03	1	0.64
Nasopharyngitis	24	15.38	0	0.00
Dyspnea	24	15.38	1	0.64
Constipation	23	14.74	0	0.00
Decreased appetite	23	14.74	1	0.64
Pain in extremity	23	14.74	1	0.64
Vomiting	21	13.46	0	0.00
Musculoskeletal chest pain	19	12.18	2	1.28
Headache	19	12.18	2	1.28
Hypercalcemia	18	11.54	5	3.21
Pneumonia <sup>1</sup>	17	10.90	9	5.77
Chills	16	10.26	0	0.00

<sup>1</sup> Pneumonia included the Preferred Terms: Lobar pneumonia, Pneumonia, Pneumonia streptococcal

**Laboratory Findings:** Approximately 3% of the results were not graded by the applicant. There was insufficient information to apply grades to the missing test results (see Table 12 below).

**Table 12 Maximum Laboratory Abnormalities**

<b>Preferred Term</b>	16mg/kg n=156			
	All Grade		Grade 3-4	
	n	%	n	%
<b><i>Hematology</i></b>				
Lymphopenia	112	71.79	61	39.10
Neutropenia	93	59.62	31	19.87
Leukopenia	89	57.05	29	18.59
Thrombocytopenia	75	48.08	28	17.95
Anemia	70	44.87	30	19.23
Lymphocytes increased	5	3.21	1	0.64
<b><i>Chemistry</i></b>				
Hypoalbuminemia	62	39.74	5	3.21
Hypercalcemia	49	31.41	11	7.05
Hypocalcemia	48	30.77	0	0.00
Hyponatremia	45	28.85	6	3.85
Creatinine increased	33	21.15	3	1.92
Aspartate aminotransferase (AST) increased	32	20.51	2	1.28
Hypokalemia	30	19.23	5	3.21
Hyperuricemia	26	16.67	6	3.85
Alanine aminotransferase (ALT) increased	23	14.74	1	0.64
Alkaline phosphatase increased	20	12.82	1	0.64
Hypoglycemia	19	12.18	1	0.64
Hypomagnesemia	17	10.90	0	0.00
Hypophosphatemia	17	10.90	6	3.85
Hyperkalemia	13	8.33	4	2.56
Hypoalbuminemia	12	7.69	0	0.00
Bilirubin increased	11	7.05	1	0.64
Hyperglycemia	9	5.77	0	0.00
Hypernatremia	8	5.13	0	0.00
Creatine phosphokinase (CPK) increased	6	3.85	2	1.28
Hypermagnesemia	5	3.21	1	0.64
Cholesterol increased	3	1.92	0	0.00
Hypertriglyceridemia	1	0.64	0	0.00

**Regulatory Recommendation for Safety:** Approval.

**8. ADVISORY COMMITTEE MEETING:** No Advisory Committee meeting.

**9. POSTMARKETING REQUIREMENTS:**

Clinical PMR 1: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3003, a Phase 3, 2-arm, randomized, parallel-group trial of lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

Clinical PMR 2: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3004, a Phase 3, 2-arm, randomized, parallel-group trial of bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

Clinical Pharmacology PMR 3: Conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Immunogenicity PMR 4: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

Immunogenicity PMR 5: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

Immunogenicity PMR 6: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

**10. POSTMARKETING COMMITMENTS:**

Product Quality PMC 1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

Product Quality PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b) (4) and drug substance long term storage containers.

Product Quality PMC 3: Re-evaluate (b) (4) lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 6: Provide data to demonstrate that the (b) (4) validation studies of (b) (4) has the same microbial growth promotion properties as daratumumab (b) (4) corresponding to (b) (4). These studies are needed to demonstrate that (b) (4) for daratumumab product (b) (4) are adequate to support microbial quality.

## 11. OTHER REGULATORY ISSUES:

**11.A. Labelling:** Under negotiation between the Agency and the Applicant.

**11.B. Addition of Information about Interference with Blood Testing and with Determination of Complete Response to Patient Counseling Information and Patient Information:** Review of materials and educational plan developed by Applicant about interference by daratumumab with ascertainment of Complete Response and with Blood Testing has been deemed satisfactory by the clinical reviewer, Barry Miller.

**11.C. REMS:** DRISK review has established that there is no need for a REMS.

**12. REGULATORY RECOMMENDATION OF THE SECONDARY (CLINICAL TEAM LEADER) REVIEWER:** Approval.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALBERT B DEISSEROTH  
10/26/2015