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APPLICATION NUMBER:

761036Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

FDA	761036 (IND 100,638)
Submission Date:	6/5/15 and 7/9/15
Brand Name:	Darzalex™
Generic Name:	Daratumumab (JNJ-54767414; HuMax-CD38)
Formulation:	Injection for intravenous infusion: 100 mg/5mL and 400 mg/20 mL single use vial
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products
Sponsor:	Janssen Biotech Inc.
Submission Type; Code:	BLA: 0000, SDN 1, 3, 8, 13, 15, 19
Dosing regimen:	Recommended dose is 16 mg/kg body weight: Weekly Weeks 1 to 8 Every two weeks Weeks 9 to 24 Every four weeks Week 25 onwards until disease progression
Indication:	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 (IMiD) or who are double-refractory to a PI and IMiD.

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1 Executive Summary

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1 κ) human monoclonal antibody (mAb) that specifically binds 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 (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. The proposed dosing regimen is 16 mg/kg weekly on Weeks 1 to 8, every two weeks on Weeks 9 to 24 and every four weeks on Weeks 25 onwards until disease progression.

The key registration trial (MMY2002) was an open-label, single arm, phase 2 trial in which the proposed patient population received 16 mg/kg 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 a statistically significant ORR of 29% (95% confidence interval [CI]: 21%, 39%), with a median time to response of 1 month, and a median duration of response of 7.4 months. Daratumumab efficacy and safety were supported by GEN501, a first-in-human phase 1/2 dose-escalation trial in patients with relapsed or refractory multiple myeloma.

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 ($C_{\text{pre-infusion, max}} \geq 270 \mu\text{g/mL}$). However, this analysis was confounded by baseline risk factors such as disease severity. Given that there is no control arm available in these open-label trials, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. As such, we recommend that the applicant 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 (TEAEs), treatment discontinuation due to TEAE, and death due to TEAE, compared to patients with normal hepatic function. Patients with moderate and severe hepatic impairment were excluded from the clinical trials, and there are no safety data in these patient populations. A PMR is 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. Based on the population PK analysis, 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. Thus, no dose adjustment is needed for these intrinsic factors.

Recommendations

The Office of Clinical Pharmacology (Divisions of Clinical Pharmacology V and Pharmacometrics) have reviewed the information contained in BLA 761036. This BLA is considered acceptable for approval from a clinical pharmacology perspective. The adequacy or inadequacy of specific drug information is provided below:

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pivotal and supportive clinical trials
Proposed dose for general population	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	The proposed dose appears sufficiently efficacious and safe in the proposed patient population with the proposed formulation. Please refer to the clinical reviews for safety and efficacy.
Dose adjustment in specific patients or patients with co-medications	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	<u>PMR studies:</u> Submit a proposal for a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment. <u>General Recommendation:</u> An exposure-response relationship for efficacy was evident for both ORR and PFS, indicating that 30% of patients with the proposed dosing exhibited lower exposures and lower response. Due to the lack of a control arm, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. Therefore, we recommend that the applicant evaluates the possibility of dose optimization in these patients when more data are available from the controlled ongoing clinical trials.
Pivotal bioequivalence studies	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> NA	
Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Post Marketing Requirements

Submit a proposal for a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Comments to the Applicant:

An exposure-response relationship for efficacy was evident for both ORR and PFS, indicating that 30% of patients with the proposed dosing exhibited lower exposures and lower response. Due to the lack of a control arm, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. Therefore, we recommend that the applicant evaluates the possibility of dose optimization in these patients when more data are available from the controlled ongoing clinical trials.

Comment to the Clinical Review Team:

None.

1.3 Summary of Clinical Pharmacology Findings

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1 κ) human monoclonal antibody (mAb) that specifically binds to the CD38 protein expressed on the surface of multiple myeloma tumor cells and other cell types at various levels. In vitro, daratumumab can induce tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. The proposed indication is daratumumab 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 an immunomodulatory agent. The proposed dosing regimen is 16 mg/kg body weight weekly on Weeks 1 to 8, every two weeks on Weeks 9 to 24 and every four weeks on Weeks 25 onwards until disease progression.

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 (9) 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 ($C_{pre-infusion,max} \geq 270$ μ g/mL). Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab $C_{pre-infusion,max} < 270$ μ g/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations > 270 μ 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 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. Patients with moderate and severe hepatic impairment were excluded from the clinical trials, and there are no safety data in these patient populations. 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 is issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1 κ) human monoclonal antibody (mAb) that specifically binds CD38.

The daratumumab final drug product is supplied as a sterile 20 mg/mL liquid concentrate for infusion. Each single use vial contains 100 or 400 mg of daratumumab in a 5 mL (100 mg) or 20 mL (400 mg). The necessary amount of daratumumab drug product must be diluted to the appropriate volume with 0.9% Sodium Chloride prior to intravenous infusion.

- **Established names:** Daratumumab (JNJ-54767414; HuMax-CD38)
- **Molecular Weight of antibody:** 148 kilo Dalton (kDa)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

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. The proposed indication for daratumumab is 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 (IMiD) or who are double-refractory to a PI and IMiD.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed daratumumab dosing regimen is 16 mg/kg body weight administered as an intravenous infusion (to be completed within $\frac{90}{4}$ hours) according to the following dosing schedule:

Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

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 Part 1 patients were randomized to receive 8 mg/kg datatumumub 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.

Table 1 below summarizes the design features of the clinical trials that support the Clinical Pharmacology Section of the BLA.

Table 1. Clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics.

Study Number ^a	Phase	Subject Population	Doses (Number of Subjects Dosed)	Number of Subjects Evaluable for Pharmacokinetic Analysis/Number of Subjects Treated
GEN501	1/2	Subjects with relapsed or refractory multiple myeloma	<p>Part 1:</p> 0.005 mg/kg (1 subject) 0.05 mg/kg (1 subject) 0.1 mg/kg (6 subjects) 0.5 mg/kg (3 subjects) 1 mg/kg (6 subjects) 2 mg/kg (3 subjects) 4 mg/kg (3 subjects) 8 mg/kg (3 subjects) 16 mg/kg (3 subjects) 24 mg/kg (3 subjects)	100/104 (Part 1=32; Part 2=72)
MMY2002	2	Subjects with multiple myeloma (either 3 lines of prior therapy or double refractory to PI and an IMiD)	<p>Part 2:</p> 8 mg/kg (18 subjects) 16 mg/kg (106 subjects)	123/124
MMY1002	1	Japanese subjects with relapsed or refractory multiple myeloma	8 mg/kg (4 subjects) 16 mg/kg (5 subjects)	9/9
Total Subjects Evaluable for Pharmacokinetic Analysis/Total Subjects Treated				232/237

Key: IMiD=immunomodulatory agent; PI= proteasome inhibitor.

Source: Applicant Summary of Clinical Pharmacology Studies.

Applicant Population Pharmacokinetic and Exposure-Response Analysis Report

The pooled population pharmacokinetic analysis and exposure-response analyses included data from trials GEN501 and MMY2002. The population pharmacokinetic dataset included samples from 223 patients (150 patients at the 16 mg/kg dose).

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Trial MMY2002 was the key registration trial to establish the efficacy and safety of daratumumab, with supportive data from trial GEN501. In trial MMY2002, the primary efficacy endpoint of overall response rate (ORR) was calculated as the proportion of subjects who achieved a partial response (PR) or better during treatment or the follow-up phase (as described by the International Myeloma Working Group [IMWG] response criteria). An Independent Review Committee (IRC) reviewed disease assessments over time and were provided the primary data for response and progressive disease evaluations. A statistically-significant and clinically-meaningful improvement in ORR has been the basis for the initial approval of drugs for the treatment of relapsed and/or refractory multiple myeloma.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the clinical pharmacology related studies appropriately analyzed daratumumab serum concentrations by using a validated ELISA method.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

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 (≥ 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). (See 2.2.7 below and Pharmacometrics Review, Appendix 4.1 for details)

2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

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. (See Pharmacometrics Review, Appendix 4.1 for details)

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.

2.2.6 Does this drug prolong the QT or QTc interval?

Because daratumumab as a large targeted protein, it 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 (See QT-IRT review, SDN 1, DARRTs date: 10/19/15).

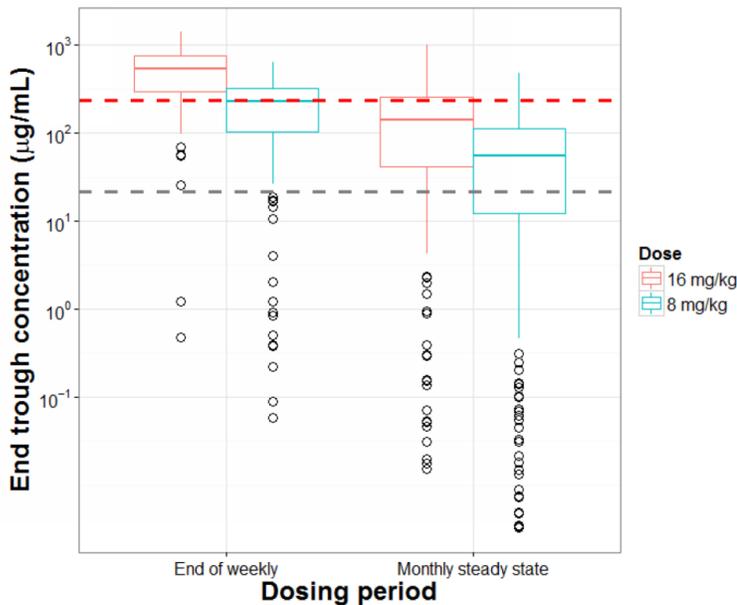
2.2.7 is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. The proposed dosing regimen of daratumumab is generally supported by the following rationale:

- The randomized comparison of 8 mg/kg and 16 mg/kg in trial MMY2002 indicated a clear dose-response with an ORR of 11% in the 8 mg/kg group compared to 29% in the 16 mg/kg group.
- The exposure-response relationship for efficacy utilizing PFS or ORR as the efficacy endpoint indicates that with the proposed dosing regimen, approximately 70% of the patients lie in the flat part of the exposure-response curve. This indicates that an additional increase in daratumumab exposure in these patients will not result in an added benefit.
- From a target engagement perspective, in the majority of subjects (>80%), the recommended dosing regimen is expected to achieve 99% target saturation (EC_{99}^{TAR}) after weekly dosing, and 90% target saturation (EC_{90}^{TAR}) after Q4W (at steady state) dosing. These estimated *in vivo* EC_{99}^{TAR} and EC_{90}^{TAR} values are also consistent with *in vitro* human CD38 cell binding data.
- The proposed more frequent dosing regimen initially, followed by a less frequent dosing regimen later, are supported from a target mediated clearance perspective, such that higher exposures are required initially to counter balance the higher target density.
- There was no apparent exposure-response relationship for safety events, such as infusion reaction, thrombocytopenia, anemia, neutropenia, and lymphopenia.

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 (**Figure 12**). 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.



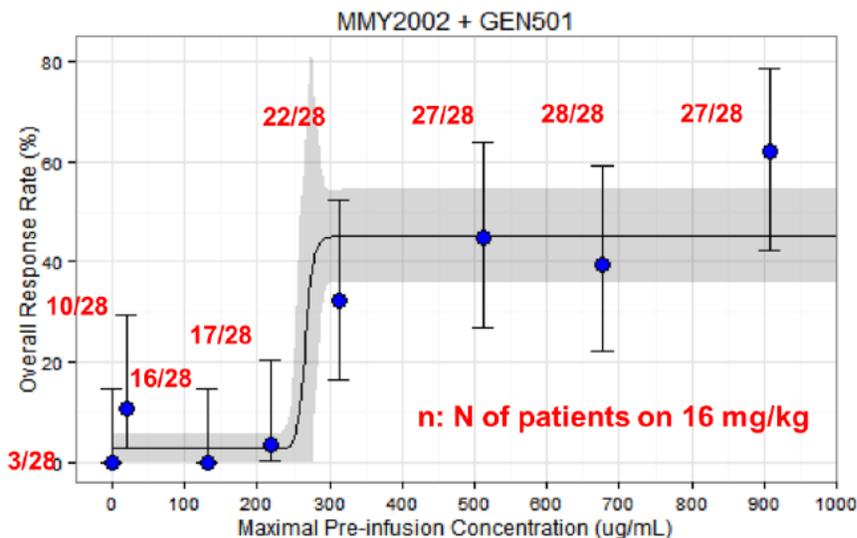
Note: EC_{99}^{TAR} was obtained by solving $\frac{EC_{99}^{TAR}}{K_m + EC_{99}^{TAR}} = 99\%$ and EC_{90}^{TAR} was obtained by solving $\frac{EC_{90}^{TAR}}{K_m + EC_{90}^{TAR}} = 90\%$. The percentages of subjects who achieved >99% target saturation at the end of weekly dosing at 16 mg/kg and 8 mg/kg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

Source: Population PK report, Figure 8.

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 (

Figure 13). Therefore, limited additional benefit in ORR is expected with $C_{pre-infusion,max}$ higher than the predicted $EC_{90}^{ORR} = 274 \mu g/mL$. 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.

Source: Population PK report, Figure 9.

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. (Refer to 2.2.14 below and Pharmacometric review (Appendix 4.1) for more details).

More detailed justification is provided in Pharmacometric Review, Appendix 4.1.

2.2.8 What are the single dose and multiple dose pharmacokinetic (PK) parameters?

Noncompartmental analysis trial GEN501 describing the single dose and multiple dose PK of daratumumab in patients with multiple myeloma:

In trial GEN501, Part 1, 32 subjects provided concentration data for the first full infusion (at Visit 3) and comprised the PK dataset. Of these, 16 also provided concentration data for the last (7th full infusion). Serum PK parameters were estimated using non-compartmental analysis. Blood samples characterizing the single dose and multiple dose daratumumab PK were obtained up to 7 days after dosing, and the AUC_{0-inf} was reported as computed; no cutoff value was employed for evaluating the percent of the AUC which was extrapolated.

No parameters were computed for the 0.005 and 0.05 mg/kg dose groups (N = 1 each), as all concentrations were below the limit of quantitation. The non-compartmental approach used to assess the PK of daratumumab was limited by the sampling period of 7 days, and is unlikely to have captured the complete terminal elimination phase. Therefore information from trial GEN501 should only be used to assess absorption (C_{trough} , C_{max} , T_{max}) and dose proportionality rather than $T_{1/2}$, AUC_{0-inf} , clearance and volume of distribution. Dense PK sampling was only obtained in Part 1 of trial GEN501 in which the phase 2 drug product was administered.

Summary statistics of the single dose serum daratumumab pharmacokinetic parameters for all dose groups and single dose serum daratumumab concentrations vs. time profiles are shown in **Table 2** and **Figure 3**, respectively. The interpatient variability (arithmetic %CVs) after the first full infusion, across the dose range of 1 mg/kg to 24 mg/kg ranged from 16% to 86% for AUC_{0-7days} and from 16% to 29%, for C_{max}. The concentration-time profiles over the 1 mg/kg to 24 mg/kg dose range show an increase in exposure with dose.

Summary statistics of the multiple dose serum daratumumab pharmacokinetic parameters for all dose groups are shown in **Table 3**. The interpatient variability (arithmetic %CVs) after the last (7th) full infusion, across dose (1 mg/kg to 24 mg/kg) ranged from 19% to 114% for AUC_{0-8days} and from 13% to 59% for C_{max}. Based on the elimination half-life after the last (7th) full infusion, it is unlikely subjects in Part 1 had reached steady-state by the last infusion.

Parameter	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16mg/kg	24 mg/kg
C_{trough} (µg/mL)						
N	6	3	3	3	3	3
Mean	0.000	0.000	0.596	3.733	7.023	0.000
SD	0.0000	0.0000	1.0329	6.4663	12.1636	0.0000
CV(%)			173.2	173.2	173.2	
C_{max} (µg/mL)						
N	6	3	3	3	3	3
Mean	20.279	38.139	83.403	153.611	405.754	500.104
SD	5.8662	7.3573	15.9857	40.8315	72.5004	80.4271
CV(%)	28.9	19.3	19.2	26.6	17.9	16.1
T_{max} (h)						
N	6	3	3	3	3	3
Median	6.017	9.667	9.583	9.933	8.000	10.000
Range	5.67 – 8.00	8.42 - 11.00	7.58 - 9.92	9.50 - 11.60	8.00 - 12.17	8.33 - 10.72
AUC_{0-7day} (µg·h/mL)						
N	6	3	3	3	3	3
Mean	Mean 762.755	1936.018	6354.139	14899.574	35613.298	47678.061
SD	656.7838	302.4440	3400.8875	5256.1083	7686.8697	14396.5478
CV(%)	86.1	15.6	53.5	35.3	21.6	30.2
AUC_{0-inf} (µg·h/mL)						
N	5	3	3	3	3	3
Mean	977.236	1927.138	10062.880	27916.416	56893.559	97175.647
SD	758.0958	373.2869	6886.0158	16155.6804	22030.4204	39899.8745
CV(%)	77.6	19.4	68.4	57.9	38.7	41.1
CL (mL/h/kg)						
N	5	3	3	3	3	3
Mean	1.500	1.064	0.726	0.404	0.315	0.287
SD	0.9601	0.2034	0.7459	0.3139	0.1336	0.1487
CV(%)	64.0	19.1	102.7	77.7	42.4	51.7
V (mL/kg)						
N	5	3	3	3	3	3
Mean	44.659	38.240	54.257	56.827	45.220	58.940
SD	5.7036	1.0545	4.0001	6.2621	5.9543	14.1501
CV(%)	12.8	2.8	7.4	11.0	13.2	24.0
T (1/2) (h)						
N	5	3	3	3	3	3
Mean	28.273	25.615	91.492	131.776	109.900	154.651
SD	17.8534	5.6050	59.8914	68.1924	42.0480	36.4843
CV(%)	63.1	21.9	65.5	51.7	38.3	23.6

Key: AUC, area under the curve; C_{max}, the maximum concentration observed after the dose was administered;

C_{trough}, the concentration immediately before a dose is administered; T (1/2), elimination half-life.

Figure 3. Mean Log Serum Daratumumab Concentrations vs. Nominal Time by Dose Group (pre-dose infusion and first full infusion): Pharmacokinetic Analysis Set (Source: Study report GEN501 Part 1).

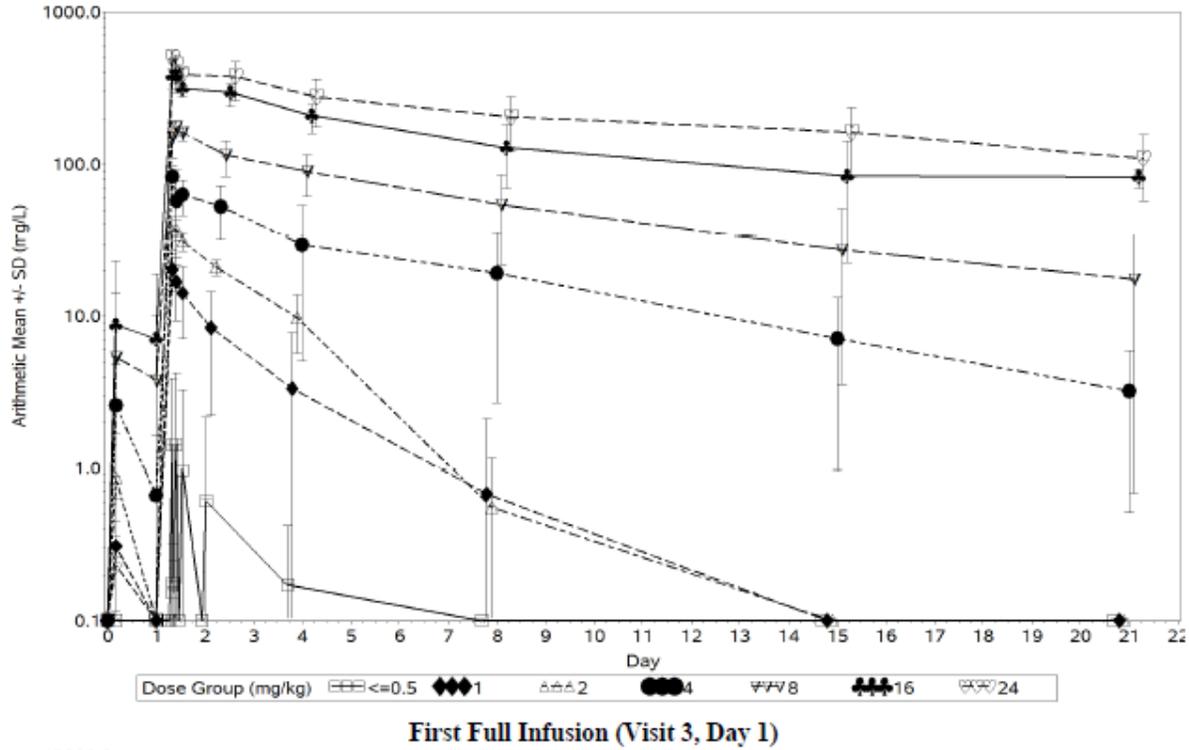


Table 3. Summary of Daratumumab Pharmacokinetic Parameters for the Last (7th) Full Infusion: (Study GEN501 Part 1; phase 2 formulation).

Parameter	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16mg/kg	24 mg/kg
C_{trough} (µg/mL)						
N	2	1	2	3	2	2
Mean	2.679	6.083	123.293	213.853	574.962	753.943
SD	3.7880		86.0259	117.2155	94.6109	387.2286
CV(%)	141.4		69.8	54.8	16.5	51.4
C_{max} (µg/mL)						
N	2	1	2	3	2	2
Mean	20.235	39.279	218.496	426.615	993.648	1163.338
SD	11.9084		101.2563	176.5507	127.0395	333.9474
CV(%)	58.9		46.3	41.4	12.8	28.7
AUC_{0-8day} (µg·h/mL)						
N	2	1	2	2	1	2
Mean	1226.337	3596.853	30832.564	66765.805	171652.702	185591.882
SD	1394.0483		20789.324367	12571.4743		88439.3124
CV(%)	113.7		.4	18.8		47.7
AUC_{0-inf} (µg·h/mL)						
N	2	1	2	2	1	2
Mean	1345.216	4231.701	38149.094	186611.920	371159.322	1018233.501

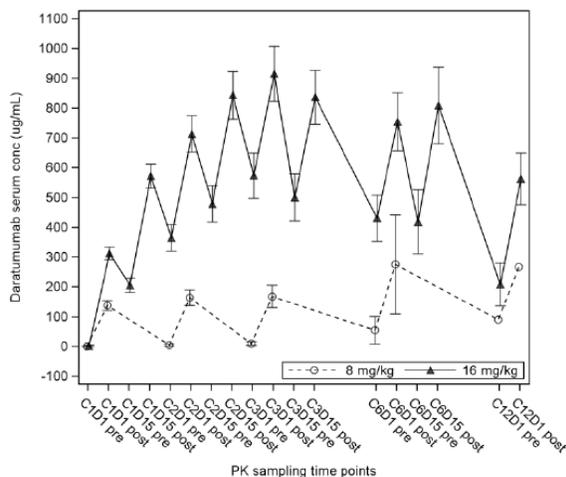
SD	1620.2447		163369.9648	90617.6371		1029108.3627
CV(%)	120.4		118.3	48.6		101.1
CL (mL/h/kg)						
N	2	1	2	3	1	2
Mean	2.315	0.586	0.183	0.189	0.104	0.162
SD	2.6047		0.1182	0.0946		0.0756
CV(%)	112.5		64.7	50.0		46.5
V (mL/kg)						
N	1	1	2	2	1	2
Mean	40.814	58.434	67.374	53.592	31.902	104.767
SD			40.1334	12.3612		43.6716
CV(%)			59.6	23.1		41.7
T (1/2) (h)						
N	2	1	2	2	1	2
Mean	35.684	72.140	396.487	289.499	215.329	586.564
SD	37.5450		408.0819	121.8816		486.8880
CV(%)	105.2		102.9	42.1		83.0

Key: AUC, area under the curve; Cmax, the maximum concentration observed after the dose was administered; T (1/2), elimination half-life; Notes: The last full infusion was received at Visit 14 and was the last of 6 full infusions administered once every 7 days. Although the dosing interval was 7 days, no sample was collected 7 days after starting the last full infusion and the nearest time interval (0 to 8 days) was used to compute AUC.

Trial MMY2002 describing the single and multiple dose peak and trough daratumumab concentrations with the clinically recommended dosing regimen in patients with multiple myeloma:

In trial MMY2002, a total of 105 PK evaluable patients were treated at the 16 mg/kg dose with the proposed dosing schedule (daratumumab Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly for 8 weeks); Days 1 and 15 of Cycles 3 to 6 (biweekly for 16 weeks); and Day 1 of every cycle thereafter (monthly)). In Part 2, at the 16 mg/kg dose, peak (end of infusion) and trough (predose) daratumumab concentrations were obtained for all patients for Cycle 1-12 via sparse PK sampling (**Figure 4**). Under this schedule, accumulation occurred through the first 2 Cycles. The mean \pm SD trough concentration at the end of weekly dosing (Cycle 3 Day 1 predose) was 573.49 ± 331.49 $\mu\text{g/mL}$. At the end of weekly dosing at the recommended dose and schedule, the mean end of infusion concentration was 914.86 ± 410.34 $\mu\text{g/mL}$, approximately 2.9-fold higher than following the first infusion (312.54 ± 106.65 $\mu\text{g/mL}$). After subjects entered Cycle 3, peak and trough concentrations decreased, with mean trough concentrations maintained above 400 $\mu\text{g/mL}$ through Cycle 6. Mean peak and trough concentrations decreased between the last every 2 weeks dose on Cycle 6 Day 15 and the sixth dose in the every 4 week dosing period (Cycle 12 Day 1).

Figure 4. Mean Daratumumab Serum Peak and Trough Concentrations ($\mu\text{g/mL}$) Cycles 1 to 12; Pharmacokinetic Evaluable Analysis Set (source: Study MMY2002; Study report Figure 5).

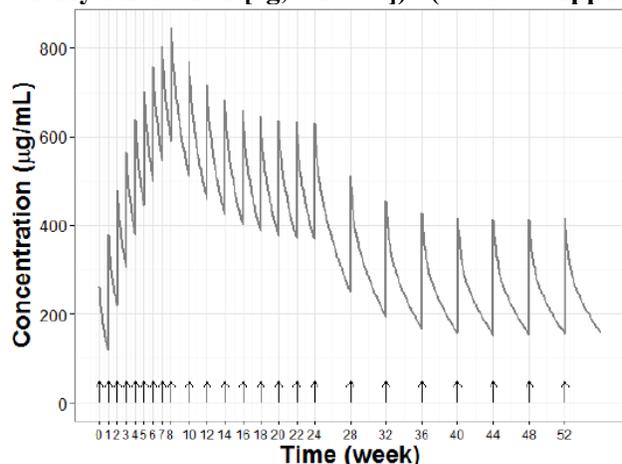


Key: For 16 mg/kg, the schedule is weekly intervals for 8 weeks, then every 2 weeks for an additional 16 weeks, then every 4 weeks (Q4W) thereafter; for 8 mg/kg, the schedule is every 4 weeks throughout. Visit labels: C = Cycle (4 week cycles), D = Day; Pre = pre-infusion; Post = post-infusion. At each timepoint, concentration values are plotted on linear scale, and the error bars are mean \pm 1.96 * standard error (95% CI).

Population PK Analysis with data from trial GEN501 and trial MMY2002:

The population pharmacokinetic analysis was based on pharmacokinetic samples from 223 subjects (150 subjects received 16 mg/kg) enrolled in trials MMY2002 and GEN501. For details see the Pharmacometrics review, Appendix 4.1. The observed concentration-time data of daratumumab were adequately described by a 2-compartment population pharmacokinetic model with parallel linear and nonlinear Michaelis-Menten eliminations. The final population pharmacokinetic model was used to simulate a concentration-time profile for the recommended dose of 16 mg/kg following the recommended schedule (**Figure 5**). It can be seen that the concentration keeps increasing until the 1st dose in the Q2W dosing period. Then, the concentrations started to decrease following the Q2W and Q4W dosing. Apparent steady state is reached by the 21st infusion approximately 5 months into the every 4 week dosing period of the recommended dose and schedule. The ratio of the steady-state peak after every 4 week dosing and the peak after the first dose was 1.6 ± 0.5 (mean \pm SD).

Figure 5. Typical Pharmacokinetic Profile of Daratumumab for the Recommended Dose (16 mg/kg) and Schedule (Weekly for 8 Weeks [8 Doses], Biweekly for 16 Weeks [8 Doses], and Monthly Thereafter [eg, 8 Doses]). (Source: Applicant Population PK report, Figure 15).



2.2.9 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. Daratumumab has not been administered to healthy volunteers.

2.2.10 What are the characteristics of drug absorption?

Not applicable. Daratumumab is administered via IV infusion.

2.2.11 What are the characteristics of drug distribution?

The population PK model-derived mean (\pm SD) central compartment volume of distribution of daratumumab is 4.7 ± 1.3 L.

2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance trial was not needed, as daratumumab is a IgG human monoclonal antibody for which renal and hepatic elimination are not important.

2.2.13 What are the characteristics of drug metabolism?

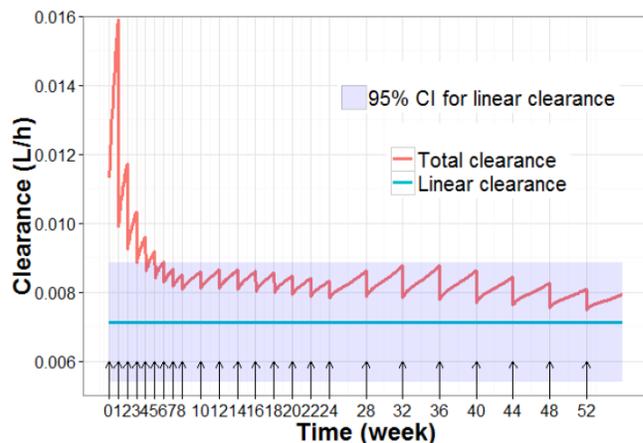
Daratumumab is expected to be biotransformed similarly to other endogenous IgG through degradation into small peptides and amino acids via intracellular catabolic pathways following receptor mediated endocytosis. Renal excretion and hepatic enzyme mediated metabolism of daratumumab are not likely to represent major elimination routes.

2.2.14 What are the characteristics of drug excretion?

Elimination and Clearance

The final population pharmacokinetic model was used to simulate the total clearance profile of daratumumab at the recommended 16 mg/kg dose and schedule (**Figure 6**). For details see the Pharmacometrics review, Appendix 4.1. The presence of target mediated drug disposition was suggested by the initial nonlinear concentration-dependent clearance of daratumumab that was also time-dependent. Approximately 8 weeks after administration of 16 mg/kg daratumumab the total clearance approached the linear clearance, which provides evidence for target-mediated PK drug disposition and saturation of target at the exposure levels of 16 mg/kg. Based on the population PK analysis, the mean linear clearance (SD) of daratumumab is estimated to be 171.4 (95.3) mL/day. The Q2W and Q4W dosing at 16 mg/kg appeared to be adequate to maintain the total clearance close to the nonspecific linear clearance.

Figure 6. Model-Based Simulation of Total Clearance (Red) and Linear Clearance (Blue) Versus Time Profiles in Weekly (QW) for 8 Weeks (8 Doses), Every 2 Weeks (Q2W) for 16 Weeks (8 Doses), and Then Every 4 Weeks (Q4W) Thereafter (e.g., 8 Doses) for the 16 mg/kg Daratumumab Dosing Regimen Based on Typical Values of Final Model Parameters.



Key: Black arrows represent dosing events. Shaded blue area represents 95% confidence interval (CI) for linear clearance.

Half-life

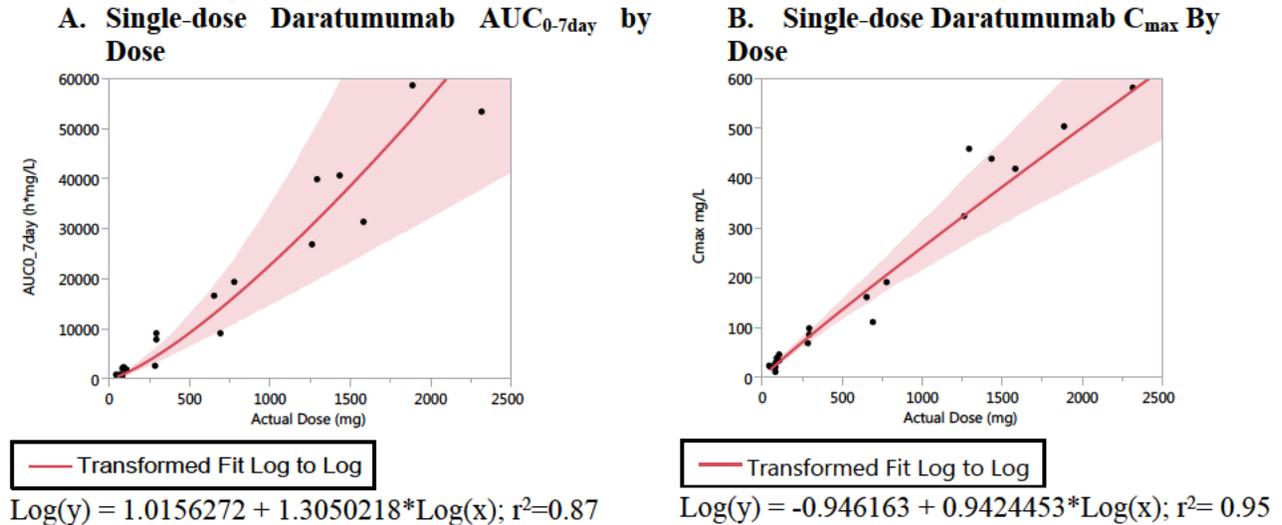
The population PK model-derived half-life associated with linear elimination was approximately 18 ± 9 (mean \pm SD) days in patients with multiple myeloma.

2.2.15 Based on the PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Single Dose:

The single dose noncompartmental analysis estimated $AUC_{0-7\text{day}}$ and C_{max} obtained from trial GEN-501 were used to assess the dose proportionality of daratumumab in serum at 1, 2, 4, 8, 16, 24 mg/kg. Over the dose range from 1 to 24 mg/kg, the slope of the line of the $\log AUC_{0-7\text{day}}$ vs. \log dose plot was 1.3. Over the dose range of 1 to 24 mg/kg, the slope of the line of the $\log C_{\text{max}}$ vs. \log dose plot was 0.94. The analysis shows that the $AUC_{0-7\text{day}}$ increased in a greater than dose-proportional manner following the first infusion over the 1 to 24 mg/kg dose range. There was an approximately dose proportional increase in daratumumab C_{max} following the first infusion over the 1 to 24 mg/kg dose range (**Figure 7**).

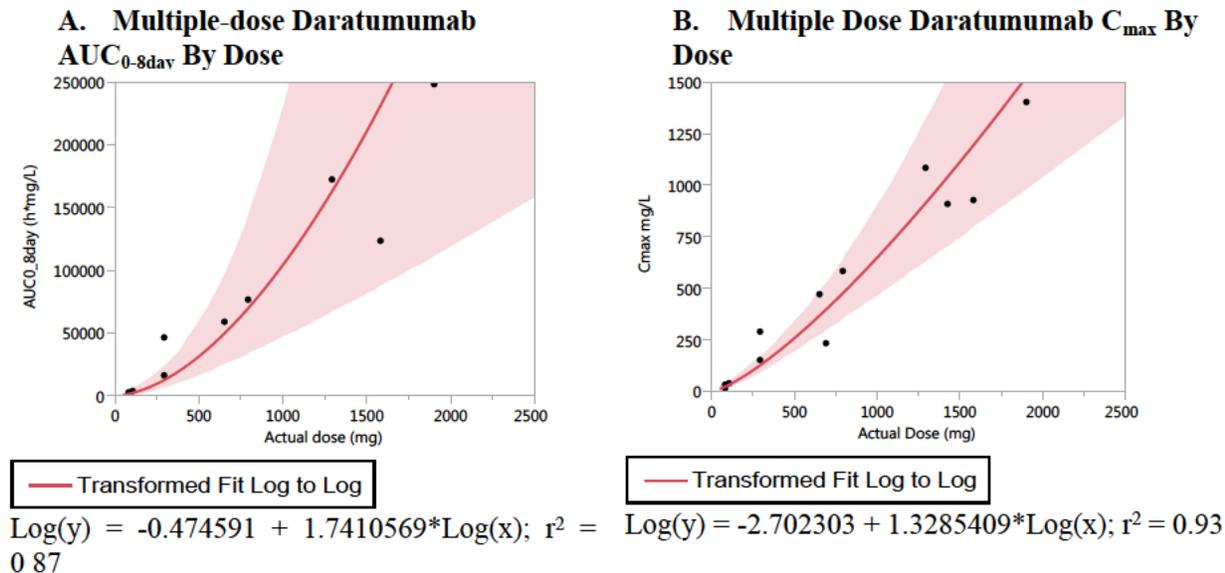
Figure 7. A: Log AUC_{0-7day} vs. Log of Actual Dose and B: Log C_{max} vs. Log of Dose over the 1 to 24 mg/kg dose range, following the first infusion in patients multiple myeloma. The shaded area is the 90% CI of the slope (Trial GEN501).



Multiple-dose:

The multiple-dose (7th full infusion) noncompartmental analysis estimated AUC_{0-8day} and C_{max} obtained from trial GEN501 were used to assess the dose proportionality of daratumumab in serum at 1, 2, 4, 8, 16, 24 mg/kg. Over the dose range from 1 to 24 mg/kg, the slope of the line of the log AUC_{0-8day} vs. log dose plot was 1.7. Over the dose range of 1 to 24 mg/kg, the slope of the line of the log C_{max} vs. log dose plot was 1.3. The analysis shows that the multiple-dose AUC_{0-8day} and C_{max} increased in a greater than dose-proportional manner following the first infusion over the 1 to 24 mg/kg dose range (**Figure 8**).

Figure 8. A: Log AUC_{0-8day} vs. Log of Dose and B: Log C_{max} vs. Log of Dose over the 1 to 24 mg/kg multiple dose range (7th full infusion) in patients with multiple myeloma. The shaded area is the 90% CI of the slope (Trial GEN501).



2.2.16 How do the PK parameters change with time following chronic dosing?

Based on results from trial GEN501, daratumumab exposure increases with repeated dosing in patients with multiple myeloma. At the end of weekly dosing at the recommended dose and schedule, the mean end of infusion daratumumab concentration was approximately 2.9-fold higher than following the first end of infusion concentration (Trial MMY2002). Based on simulations using the sponsor population PK model, the ratio of the steady-state peak daratumumab concentration after every 4 week dosing and the peak after the first dose was 1.6 ± 0.5 (mean \pm SD) (See Appendix 1, Pharmacometrics Review).

The interpatient variability (arithmetic %CVs) after the first full infusion, across the dose range of 1 mg/kg to 24 mg/kg ranged from 16% to 86% for AUC_{0-7days} and from 16% to 29%, for C_{max} (Trial GEN501) (Table 2). The interpatient variability (%CVs) after the last (7th) full infusion, across the dose range of 1 mg/kg to 24 mg/kg ranged from 19% to 114% for AUC_{0-8days} and from 13% to 59% for C_{max} (Trial GEN501) (Table 3).

2.2.17 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

No PK data are available in volunteers. Based on base model of population PK analysis, the inter-subject variability (%CV) was 74.2% for linear clearance, and 36.5% for central volume of distribution. The residual variability (%CV) was estimated to be 32.7%.

Statistically significant covariates on linear clearance were body weight, baseline albumin level, drug product (Phase 2 versus Phase 3 commercial), and type of myeloma (IgG versus non-IgG). Statistically significant covariates on volume of distribution in the central compartment (V₁) were body-weight and sex (See Appendix 4.1, Pharmacometrics Review).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

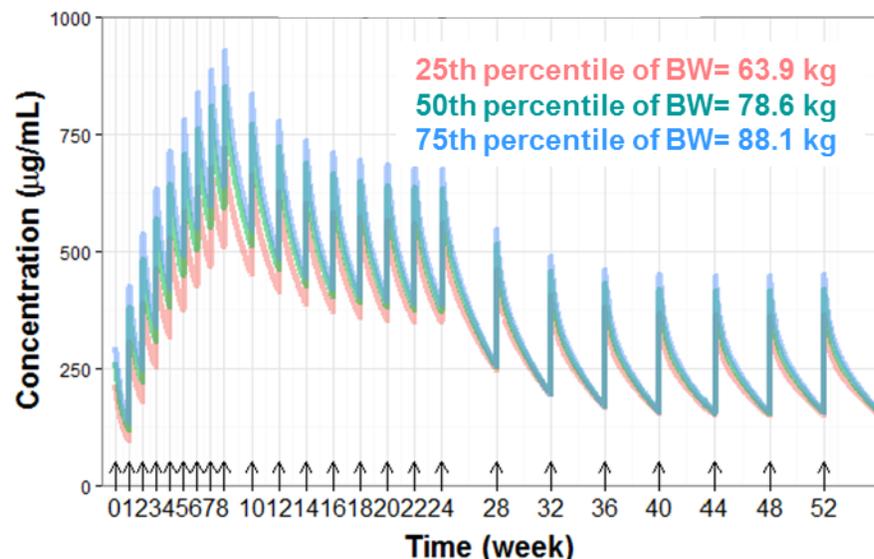
The applicant population PK analysis included data from trials MMY2002 and GEN501, and assessed the influence of the following covariates: albumin levels, type of myeloma (IgG or non IgG), age, gender, body weight, renal impairment and hepatic impairment on the PK of daratumumab.

Baseline albumin levels, type of myeloma, and body weight were significant covariates on clearance while weight and gender were found to be significant covariates for central volume of distribution. Since body weight was a significant covariate for clearance and volume of distribution, body weight-based dosing is justified. The magnitude of effect of albumin on clearance and gender on volume was small and not clinically relevant. Further exposure-response analyses by the applicant demonstrated that baseline albumin levels, type of myeloma and gender covariates had no clinically relevant impact on efficacy (ORR). Additionally, an increase in exposure to daratumumab was generally not associated with an increased rate of adverse events. Based on the population PK and exposure-response analyses conducted by the applicant, the FDA Pharmacometrics reviewer concluded that dose adjustment based on baseline albumin levels, type of myeloma, age, gender, mild to severe renal impairment and mild hepatic impairment is not needed.

Relationship between Weight and Exposure

The results of the population PK analysis indicated a significant effect of body weight on both linear clearance and central volume of distribution (V_1) of daratumumab. Doubling body weight was associated with a 65% and 50% increase in clearance and V_1 , respectively. Simulation showed that the exposure to daratumumab was similar for subjects with different body weight after administration on an mg/kg basis (**Figure 9**), and therefore bodyweight-based dosing is acceptable.

Figure 9. Simulated Typical Daratumumab Pharmacokinetic Profiles Stratified by Body Weight.



Source: Population PK report, Attachment 25.

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 ≥ 90 mL/min, N=71), mild renal impairment (CrCL <90 and ≥ 60 mL/min; n=78), moderate renal impairment (CrCL <60 and ≥ 30 mL/min; n=68) and severe renal impairment (CrCL <30 mL/min and ≥ 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 (See Appendix 4.1, Pharmacometrics Review). 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 type of Myeloma and Exposure

The results of the population PK analysis showed that the linear clearance of daratumumab was higher in IgG multiple myeloma subjects compared with the non-IgG myeloma subjects. However, based on the exposure-response analyses exposures in non- non IgG subjects lie in the flat part of the exposure-response curve. In addition, based on the subgroup analysis conducted by the sponsor, ORR between IgG and non-IgG myeloma subjects was similar. (See Appendix 4.1, Pharmacometrics Review).

Relationship between Baseline Albumin Levels and Exposure

The results of the population PK analysis showed that baseline albumin concentration was a statistically significant covariate on linear clearance of daratumumab. However, simulations demonstrated that the magnitude of the effect on the exposure to daratumumab was not clinically significant.

Relationship between Gender and Exposure

The results of the population PK analysis in 132 male and 91 female patients with multiple myeloma indicated that there was a statistically significant effect of gender on V_1 . Simulations demonstrated that the magnitude of the effect of sex (male versus female) on the exposure to daratumumab was less than 14%, and therefore not clinically significant.

Relationship between Race and Exposure

It was not possible to assess the effect of race, as nearly all of the subjects enrolled in clinical trials were white (n=197) and there was limited enrollment of races other than Caucasians (n=26).

Relationship between Age and Exposure

Age was not a statistically significant covariate on the pharmacokinetics of daratumumab and no dose adjustment is recommended with respect to age.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Renal Impairment:

No dose adjustments are necessary for patients with mild, moderate and severe renal impairment (CrCL 15-90 mL/min) (Section 2.3.1).

Hepatic Impairment:

No dose adjustments are needed for use in patients with mild hepatic impairment (Section 2.3.1). The effect of moderate or severe hepatic impairment on the PK and safety of daratumumab could not be determined as data were not available.

Adverse Events by Baseline Renal Function

Of the 156 subjects treated with daratumumab 16 mg/kg monotherapy, 95 (61%) had a baseline CrCL of ≥ 60 mL/min, 56 (36%) had a baseline CrCL of 30 to < 60 mL/min, and 5 (3%) had a baseline CrCL of < 30 mL/min. The incidence of treatment-emergent adverse events (TEAEs) in the ≥ 60 mL/min and 30 to < 60 mL/min subgroups was similar to the total 16 mg/kg group; there were too few subjects in the < 30 mL/min group (n=5) to make any meaningful comparisons.

Adverse Events by Baseline Hepatic Function

Hepatic enzyme-mediated metabolism of intact daratumumab is unlikely to represent a major elimination route. As such, variations in hepatic function are not expected to affect the elimination of daratumumab.

Of the subjects (N=156) treated with daratumumab 16 mg/kg monotherapy, 134 (86%) had normal hepatic function at baseline, and 21 (13%) had mild hepatic impairment at baseline. In general, for the 16 mg/kg dose group, the incidence of TEAEs in patients with mild baseline hepatic impairment was higher compared to patients with normal hepatic function (**Table 4**). Subjects with mild hepatic impairment at baseline had a numerically higher incidence of SAEs (9 subjects [43%]), Grade 3 or higher TEAEs (15 subjects [71%]), TEAEs leading to treatment discontinuation (4 subjects [19%]) and death due to TEAEs (2 subjects [9.5%]), compared to subjects with normal hepatic function (40 subjects [30%], 72 subjects [54%], 2 subjects [1.5%] and 1 subject [0.7%]); respectively. *Patients with mild hepatic impairment did not have increased exposure to daratumumab vs. patients with normal hepatic function (See Appendix 4.1, Pharmacometrics Review).*

FDA issued an Information Request on Oct 7, 2015: *“Please provide a comparative analysis to address whether the increased incidence of adverse events in patients with mild hepatic impairment may be associated with a difference in the distribution of any other baseline risk factors. Also provide summary comparative liver function data (normal vs mild hepatic impairment) in graphical and tabular format”*.

The applicant provided a response to the IR (SDN 32; Oct 8, 2015) as follows:

“Data show that baseline risk factors may contribute to more TEAEs in the group with mild hepatic impairment. Specifically, an ECOG score of 1 or higher was recorded in 86% and 68% of patients in the mild hepatic impairment and normal hepatic function cohorts, respectively. In addition, Stage 3 or higher renal impairment was recorded in 52% and 37% of patients in the mild hepatic impairment and normal hepatic function cohorts, respectively”.

The applicant suggests that the cohort with mild hepatic impairment may have a worse performance status, leading to the numerically increased TEAEs versus the cohort with normal hepatic function. However, FDA does not think that the increased incidence of TEAEs has been adequately explained by available data. FDA remains concerned about the numerically higher incidence of serious TEAEs in patients with mild hepatic impairment based on the following rationale:

- The potential safety signal is supported by data from a large patient cohort of 21 patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment were excluded from the clinical trials, and there are no safety data in these patient populations. It is therefore important for the applicant to collect additional data in patients with baseline hepatic impairment in order to fully characterize the safety of daratumumab in this sub population of patients with hepatic impairment and multiple myeloma for which daratumumab may provide clinical benefit.
- Furthermore, recent literature data (summarized below) 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.
 - CD38-mediated Ca²⁺ signaling in hepatocytes contributes to glucagon-induced hepatic gluconeogenesis [PMID: 26038839].
 - Infiltration of inflammatory cells expressing mitochondrial proteins (including CD79a, CD38, CD138 IgM-positive and/or IgG positive plasma cells) may be involved in the pathogenesis of primary biliary cirrhosis [PMID: 24407434].

A PMR is issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Table 4. Subgroup Analysis on Treatment-emergent adverse events (TEAEs) in multiple myeloma patients at the 16 mg/kg dose level (trial MMY2002, GEN501 and MMY1002).

		N	TEAE	Serious TEAE	Grade 3 or Higher TEAE	Treatment Discontinuation due to TEAE ^a	Death due to TEAE ^b
All Subjects		156	154 (98.7%)	50 (32.1%)	88 (56.4%)	6 (3.8%)	3(1.9%)
Renal Impairment (Creatinine Clearance)	≥ 60 mL/min	95	94 (98.9%)	29 (30.5%)	48 (50.5%)	2 (2.1%)	2 (2.1%)
	30 to <60 mL/min	56	56 (100.0%)	19 (33.9%)	37 (66.1%)	4 (7.1%)	1 (1.8%)
	< 30 mL/min	5	4 (80.0%)	2 (40.0%)	3 (60.0%)	0	0
Hepatic Function^c	Normal	134	132 (98.5%)	40 (29.9%)	72 (53.7%)	2 (1.5%)	1 (0.7%)
	Mild Impairment	21	21 (100.0%)	9 (42.9%)	15 (71.4%)	4 (19.0%)	2 (9.5%)

TEAE = treatment-emergent adverse event.

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

A Treatment discontinuation due to adverse event on the end of treatment CRF page.

B Death due to adverse event on the death CRF page.

C Hepatic function is classified into 4 levels per NCI Organ Dysfunction criteria: Normal: total bilirubin ≤ ULN and AST ≤ ULN; Mildly Impaired: (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); Moderately Impaired: 1.5×ULN < total bilirubin ≤ 3×ULN; and Severely Impaired: total bilirubin > 3×ULN.

Pediatric patients

Daratumumab has not been studied in pediatric patients.

2.3.3 What pregnancy and lactation use information is there in the application?

None.

2.3.4 Immunogenicity

2.3.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

None (0%) of the 111 subjects with appropriate immunogenicity samples enrolled in trial MMY2002 were positive for antibodies to daratumumab. See the CMC review for a description of problems with the (b)(4) and Janssen Research & Development (JRD) assays, which lead to potential problems in the accurate determination of ADA levels in samples.

For trial GEN501, the (b)(4) assay tolerance limit was below the levels of daratumumab present in the majority of the serum of samples. *Therefore, an accurate determination of ADA levels in these samples cannot be made, and results from trial GEN501 will not be reported in the package insert.*

Two methods were developed, validated and applied for the detection of anti-daratumumab antibodies in human serum. The original bridging electrochemiluminescent immunoassay (ECLIA) method, validated in 2012 at (b)(4) was used for ADA detection in support of Study GEN501. A second, and improved, bridging ECLIA method (JRD) was developed and validated at Janssen Research & Development (JRD) (Spring House, Pennsylvania, USA) and used for detection of anti-daratumumab antibodies in human serum samples from Study MMY2002.

The JRD method improved the assay drug-tolerance (from 5 µg/mL of daratumumab tolerated (in the detection of 2.5 µg/mL ADA; a 1:2 ratio) in the original (b)(4) assay to 500 µg/mL tolerated (in the detection of 0.250 µg/mL ADA; a 1:2000 ratio) by the JRD assay, a 1000-fold improvement) while not compromising the limit of detection (sensitivity) of the method. Without accepting a substantial loss in method sensitivity, it was not possible for the applicant to further enhance the drug-tolerance.

In trial MMY2002, blood samples for analysis of ADA to daratumumab were assessed from samples taken predose up to 2 hours before the start of the infusion for Cycle 1 Day 1, Cycle 3 Day 1, Cycle 6 Day 1, and Cycle 12 Day 1, as well as Weeks 4 and 8 post last dose using the JRD method. *The sampling scheme appears appropriate.* None (0%) of the 111 subjects with appropriate immunogenicity samples were positive for antibodies to daratumumab. In study MMY2002, 16/16 subjects (100%) with appropriate samples for ADA analysis in the 8 mg/kg treatment group had at least 1 post-treatment ADA sample with <250 µg/mL daratumumab and >85% of subjects with appropriate samples in the 16 mg/kg group had at least 1 post-treatment ADA sample with <500 µg/mL daratumumab. In addition almost 70% of subjects in study MMY2002 had less than 250 µg/mL daratumumab present in their last sample available for ADA assessment. Only a single subject from the 16 mg/kg treatment group had a Week 8 post-treatment ADA sample with >500 µg/mL daratumumab in the sample.

2.3.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

The assessment could not be done as none of the subjects with appropriate immunogenicity samples enrolled in trial MMY2002 were positive for antibodies to daratumumab.

2.3.4.3 Do the anti-product antibodies have neutralizing activity?

The assessment could not be done as none of the subjects with appropriate immunogenicity samples enrolled in trial MMY2002 were positive for antibodies to daratumumab.

2.3.4.4 What is the impact of anti-product antibodies on clinical efficacy?

The assessment could not be done as none of the subjects with appropriate immunogenicity samples enrolled in trial MMY2002 were positive for antibodies to daratumumab.

2.3.4.5 What is the impact of anti-product antibodies on clinical safety (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

The assessment could not be done as none of the subjects with appropriate immunogenicity samples enrolled in trial MMY2002 were positive for antibodies to daratumumab.

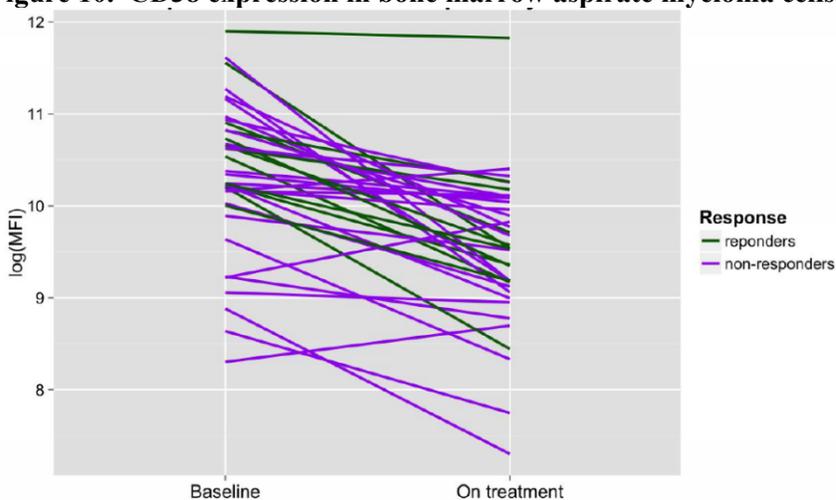
2.3.4 Are baseline levels or on-treatment changes in expression of biomarkers (immune phenotyping, CD38 expression, and cytokines) predictive of clinical response to daratumumab?

Daratumumab's mechanism of action relies on immune effector cells including natural killer (NK) cells, T cells, B cells, monocytes, macrophages, and neutrophils to induce immune-mediated tumor cell lysis. The effect of daratumumab on pharmacodynamic biomarkers related to the immune response was evaluated in the proposed patient population in study 54767414MMY2002 (study report TR2015-T-006). In addition, baseline levels and changes in immune biomarkers in response to therapy were compared between responders and non-responders to determine if these markers could be predictive of response or early indicators of response to daratumumab. The proposed labeling refers to the effect of daratumumab on NK cells and T cells; the other pharmacodynamic biomarkers of immune response are not included in the proposed labeling.

Flow cytometric analysis was used to evaluate natural killer (NK), T cell, B cell, myeloma cells (CD138+), and CD38 expression in peripheral blood and bone marrow aspirate samples. Cytokines were quantified in serum samples using Bio-Plex® suspension array system at baseline and 4 hours post-infusion on Cycle 1 Day 1.

Expression of CD38, the drug target, was observed in all MM cells at varying levels. Median baseline CD38 expression in MM cells was higher in daratumumab responders ($52,332 \pm 36,919$) compared to non-responders ($35,265 \pm 26,822$). However, there was substantial overlap between responders and non-responders (Figure 8), which limits the utility of CD38 expression as a predictor of daratumumab response. CD38 expression in MM cells was reduced following treatment with daratumumab in both responders and non-responders (Figure 10). Soluble CD38 was not detectable in plasma from most patients.

Figure 10. CD38 expression in bone marrow aspirate myeloma cells.

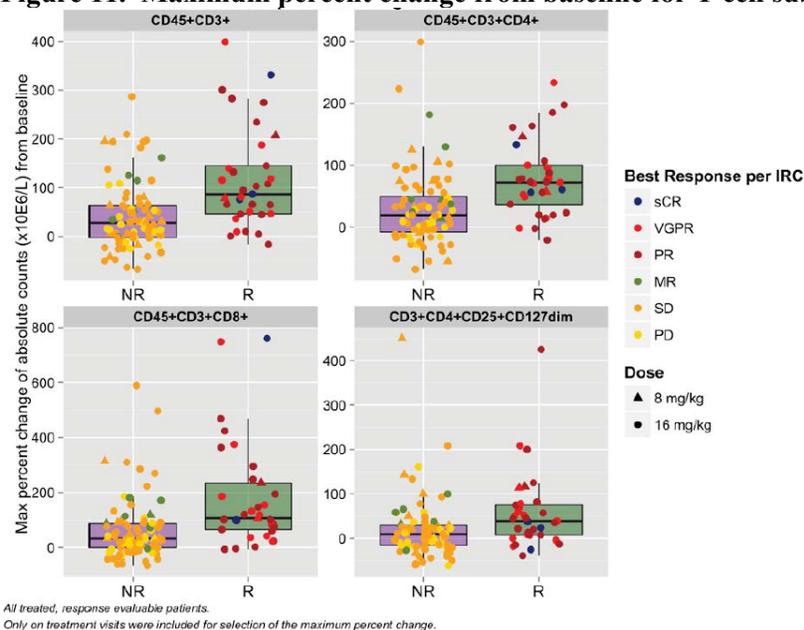


Only subjects with both a baseline and an on treatment measurement are included.
In case of multiple on treatment measurements for a given subject, the last one during treatment was selected.

Source: Applicant's Figure 1; Study Report TR2015-T-006.

In response to daratumumab, total (CD16+CD56+) and activated (CD16+CD56^{dim}) NK cells decreased in both blood and bone marrow. Changes in total and activated NK cells did not differ between responders and non-responders. Baseline total and activated NK cells were not different between responders and non-responders in bone marrow or peripheral blood. B cells slightly increased in peripheral blood, but did not change in bone marrow samples, following daratumumab treatment. Baseline B cell counts were similar in responders and non-responders to daratumumab in both bone marrow peripheral blood. T cells showed a larger increase from baseline compared to B cells in both peripheral blood and bone marrow in response to daratumumab. Moreover, T cell receptor sequencing was performed in a subset of patients (n=17) and showed that T cell clonality was significantly increased with daratumumab treatment, indicating that daratumumab induces immune modulatory effects. There were no significant differences in T cell counts at baseline between responders and non-responders. **Figure 11** shows that responders had a higher maximum increase in T cells from baseline compared to non-responders when treated with daratumumab (CD3+ 118.91 ± 104.07 vs. 43.02 ± 69.55, p=3.2993e-05; CD4+ 77.74 ± 60.99 vs. 29.36 ± 59.58, p=3.486e-05; CD8+ 180.81 ± 192.37 vs. 63.96 ± 112.44, p=2.7172e-05; regulatory T cell 57.68 ± 87.47 vs. 19.31 ± 69.32, p=0.002). However, changes in T cell subpopulations were highly variable and therefore are unlikely to be useful for monitoring response to daratumumab. No differences in baseline levels or changes from baseline during daratumumab treatment were observed between responders and non-responders for the cytokines IFN- γ , IL-1 β , IL-6 or TNF α . However, baseline levels of tryptase were slightly higher in responders (6.67 ± 3.06) compared to non-responders (5.78 ± 3.39; p=0.032).

Figure 11. Maximum percent change from baseline for T cell subsets.



Source: Applicant's Figure 15; Study Report TR2015-T-006. Abbreviations: NR, non-responder; R, responder; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effect of drug product (phase 2 or phase 3 commercial drug product) on the dose-exposure and exposure-response for daratumumab were assessed in the applicant population PK and exposure-response analyses, and included data from trial MMY2002 and GEN501.

Relationship between Drug Product and Exposure

Drug product was a statistically significant covariate on linear clearance. The applicant conducted simulations which demonstrated that the Phase 2 drug product (N=137) had approximately 24% (95% CI: 3%, 40%) lower exposure (maximal pre-infusion concentration) than Phase 3 commercial drug product (N=86). However, based on the applicant exposure-response analyses, the difference in daratumumab exposure between the phase 2 and phase 3 drug products was not clinically relevant and did not affect the ORR. Furthermore, an increase in exposure to daratumumab was generally not associated with an increased rate of adverse events. Based on the exposure-response analyses, the FDA pharmacometrics reviewer concluded that dose adjustment based on drug product is not needed.

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

No, given daratumumab is a therapeutic monoclonal antibody. It is expected to be catabolized into amino acids by general protein degradation processes. As daratumumab is not considered a cytokine modulator, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction.

2.4.3 Is the drug a substrate of CYP enzymes?

No, see response to Section 2.4.2.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No, see response to Section 2.4.2.

2.4.5 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

No, see response to Section 2.4.2.

2.4.6 Are other metabolic/transporter pathways important?

No, daratumumab is expected to be degraded into amino acids which will be recycled into other protein synthesis pathways.

2.4.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, daratumumab is proposed as a monotherapy in the current submission.

2.4.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No, see response to Section 2.4.7.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the composition of the to-be-marketed formulation?

The daratumumab final product is supplied as a sterile, 20 mg/mL liquid concentrate for infusion. Each vial contains 100 or 400 mg of daratumumab in a 5 mL (100 mg) or 20 mL (400 mg) in a glass vial. The drug product contains no preservative and is for single-use only. The formulation composition selected for the Phase 3 commercial drug product was 20 mg/mL daratumumab in (b) (4) acetate, (b) (4) mannitol, (b) (4) sodium chloride, and (b) (4) % (w/v) PS 20, at a target pH of (b) (4). The drug product is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride.

2.5.3 What moieties should be assessed in bioequivalence studies?

Not applicable.

2.5.4 is the to-be-marketed formulation the same as the clinical trial formulation and if not, is there bioequivalence data to support the to-be marketed formulation?

Use of the phase 3 commercial drug product is supported by clinical data, the applicant population PK analysis, the applicant exposure response analysis and the CMC drug product comparability program.

During development, the phase 2 drug product was replaced by the phase 3 commercial drug product, and the phase 3 commercial drug product was subsequently evaluated in both the MMY2002 and GEN501 trials at the 16 mg/kg dose level (Table 5). The two drug products differ in the (b) (4) content. Based on the applicant population PK analysis, the phase 3 commercial product has a 24% increased exposure (maximal pre-infusion concentration) compared to the phase 2 drug product. The drug product associated effect on daratumumab exposure did not appear to have a significant effect on ORR.

Table 5. Summary of Drug Product Use at the 16 mg/kg dose in Trials GEN501 and MMY2002.

Drug Product Administered	GEN501 (n)	MMY2002 (n)
Phase 2 drug product	20	41
Phase 3 (commercial) drug product	22	65
n: Number of subjects		

2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, serum concentrations of the active parent, daratumumab were measured in the clinical pharmacology and biopharmaceutics studies.

2.6.2 Which metabolites have been selected for analysis and why?

Not applicable.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Yes, serum concentrations of the active parent, daratumumab were measured in the clinical pharmacology and biopharmaceutics studies.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>)

An enzyme-linked immunosorbent assay (ELISA) method was developed, validated, and applied for the analysis of daratumumab concentration in human serum samples in Study GEN501. It was validated by (b) (4) in 2009 and subsequently transferred from (b) (4) to JRD in 2014. A partial validation was successfully conducted to ensure reproducibility of the validated method at the 2 laboratories using criteria established in the FDA Guidance for Industry: "Bioanalytical Method Validation" (May 2001). The transferred ELISA method was used by JRD (JRD ELISA Method) to determine concentration of daratumumab in human serum samples from subsequent analyses in trials MMY2002 and MMY1002.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

ELISA Method to determine daratumumab serum concentrations:

For the standard curve range, 4 ng/mL lower limit of quantification (LLOQ) to 100 ng/mL upper limit of quantification (ULOQ) defined the standard curve limits of quantification, with anchor points at 2 ng/mL and 150 ng/mL. The minimum required dilution was 1:50. The lowest quantifiable sample concentration for the assay was 200 ng/mL (LLOQ x minimum required dilution). Dilutional linearity was demonstrated in the quantification range of the calibration curve. Incurred sample reproducibility was demonstrated with samples from study GEN501. The intra-assay and Inter-assay accuracy and precision are summarized below (Table 6 and Table 7).

Table 6. Intra-Assay Accuracy and Precision.

Target (ng/mL)	QC85	QC60	QC30	QC6
Mean	74.20	53.63	27.44	5.21
SD	5.47	2.76	2.08	0.59
%CV	7.4	5.1	7.6	11.2
%Recovery	87.3	89.4	91.5	86.9

Table 7. Inter-Assay Accuracy and Precision.

Target (ng/mL)	QC85	QC60	QC30	QC6
Mean	73.93	56.24	29.19	5.77
SD	9.15	5.50	2.39	0.34
%CV	12.4	9.8	8.2	6.0
%Recovery	87.0	93.7	97.3	96.2

2.6.6 What is the QC sample plan?

See Section 2.6.5.

3 DETAILED LABELING RECOMMENDATIONS

The summary of changes to the clinical pharmacology information in the package insert is below.

6.2 Immunogenicity – Excluded data from Trial GEN501 due to CMC identified issues with assay.

8.6 Renal Impairment – Editorial changes.

8.7 Hepatic Impairment – Editorial changes.

12.2 Pharmacodynamics – Added cardiac electrophysiology information.

12.3 Pharmacokinetics – Editorial changes.

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

Office of Clinical Pharmacology:

Pharmacometric Review

1 SUMMARY OF FINDINGS

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

1.1.1 Do the dose/exposure-response relationship for efficacy & safety, and the target saturation data support the proposed dosing regimen of daratumumab (16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter)?

Yes. The proposed dosing regimen of daratumumab is generally supported by the following rationale:

- Randomized comparison of 8 mg/kg and 16 mg/kg in study MMY2002 indicated a clear dose-response with an ORR of 11% in the 8 mg/kg group compared to 29% in the 16 mg/kg group.
- Exposure-response relationship for efficacy utilizing PFS or ORR as the efficacy endpoint indicates that with the proposed dosing regimen, approximately 70% of the patients lie in the flat part of the exposure-response curve indicating that additional increase of exposures in these patients will not result in added benefit.
- From a target engagement perspective, in majority of subjects (>80%), the recommended dosing regimen is expected to achieve 99% target saturation (EC_{99}^{TAR}) after weekly dosing, and 90% target saturation (EC_{90}^{TAR}) after Q4W (at steady state) dosing. These estimated *in vivo* EC_{99}^{TAR} and EC_{90}^{TAR} are also consistent with *in vitro* human CD38 cells binding data.
- More frequent dosing regimen initially followed by a less frequent dosing regimen later is supported from a target mediated clearance perspective such that higher exposures are required initially to counter balance higher target expression.
- There was no apparent exposure-response relationship in safety events, such as infusion reaction, thrombocytopenia, anemia, neutropenia, and lymphopenia.

More detailed justification is provided below:

Dose-Response for Efficacy

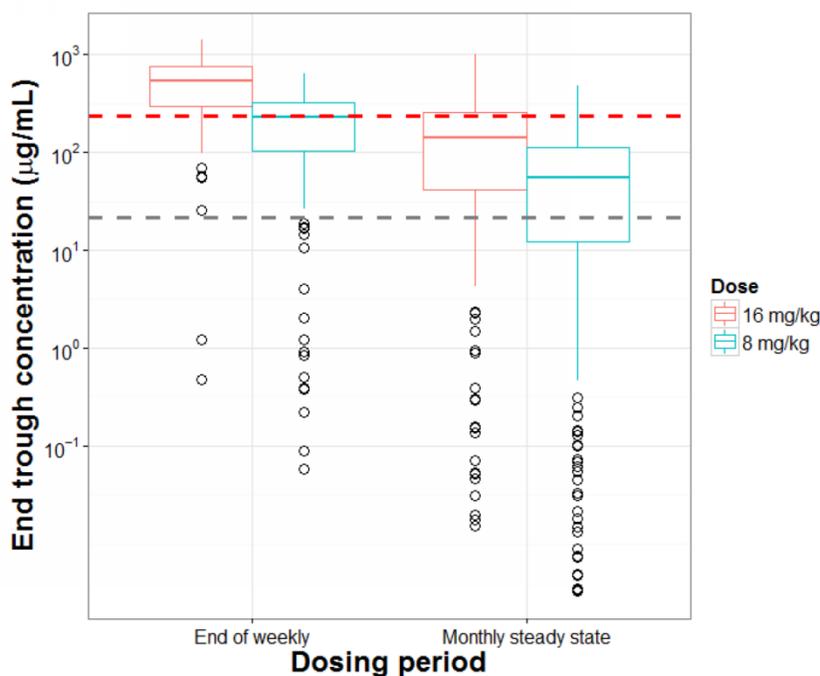
In Study MMY2002, a total of 33 subjects (2 [11%] in the 8 mg/kg group and 31 [29%] in the 16 mg/kg group) out of 124 treated subjects had a PR or better response. Of the 12 subjects in the higher dose groups (≥ 4 mg/kg daratumumab) in Part 1 of GEN501, 4 subjects (33.3%) had a PR. In Part 2 of Study 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.

Evidence from *In Vivo* and *In Vitro* Target Saturation Data

Daratumumab exhibits target-mediated drug disposition. Based on a population PK analysis (see Section 2.1) including 223 subjects (150 subjects received 16 mg/kg), the concentrations needed to achieve 90%

and 99% target saturation were estimated to be 21.4 (EC_{90}^{TAR}) and 236 $\mu\text{g/mL}$ (EC_{99}^{TAR}), respectively. Simulations based on the final model further suggested that the 16 mg/kg dose was the lowest tested dose that achieved EC_{99}^{TAR} in majority of the study subjects (>80%) at the end of weekly dosing. In contrast, approximately 50% of subjects may achieve EC_{99}^{TAR} after the weekly dosing of 8 mg/kg daratumumab (Figure 12). 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 $\mu\text{g/mL}$) to human CD38 cells.

Figure 12. 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.

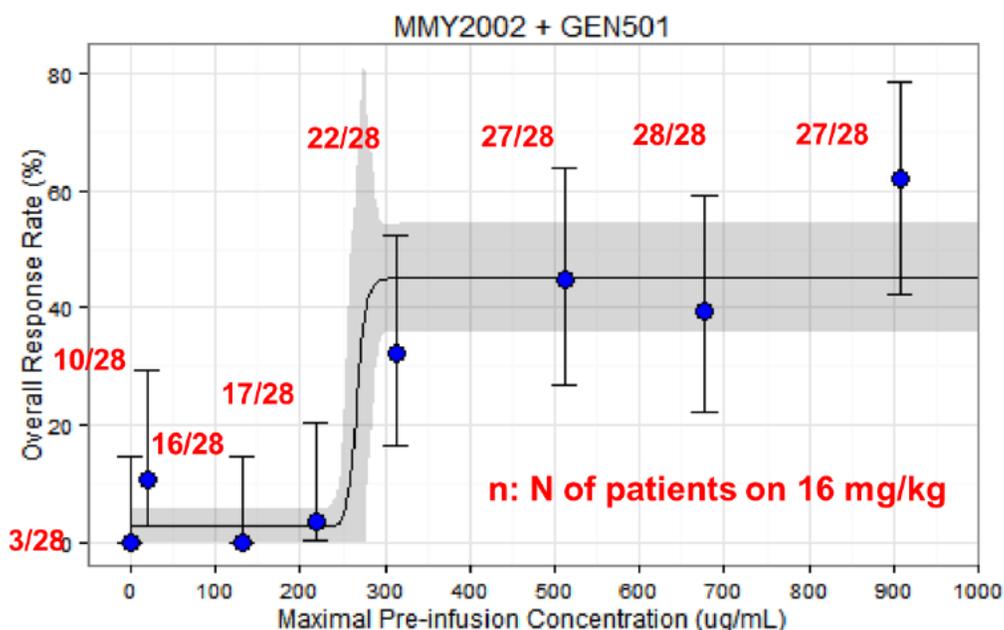
Source: Population PK report, Figure 8.

Exposure-Response Analysis for Efficacy

Sponsor conducted the exposure-response analyses based on pooled data of studies MMY2002 and GEN501 (see Section 2.2) show that ORR significantly increased with daratumumab exposure, and there was an E_{max} relationship between exposure ($C_{pre-infusion,max}$) and ORR (Figure 13). The estimated half-maximal effect $C_{pre-infusion,max}$ (EC_{50}^{ORR}) was 261 $\mu\text{g/mL}$, and 90% maximal effect $C_{pre-infusion,max}$ (EC_{90}^{ORR}) was 274 $\mu\text{g/mL}$ (Table 8). Therefore, limited additional benefit in ORR is expected with $C_{pre-infusion,max}$ higher than predicted EC_{90}^{ORR} .

At an individual level, 70% (104/150) patients after weekly administration of 16 mg/kg achieved $C_{pre-infusion,max}$ over the estimated EC_{90}^{ORR} and reach the plateau part of the exposure-response curve. However, as depicted in Figure 13, there are still 30% (46/150) of patients on the 16 mg/kg dose with lower exposure at the end of weekly administration who do not respond well.

Figure 13. 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.

Source: Population PK report, Figure 9.

Table 8. Parameter Estimates (% Relative Standard Error) of E_{max} Model for Overall Response Rate: Sensitivity Analysis (1) Pooled Data from Studies MMY2002 and GEN501; (2) Subjects Who Completed at Least 8 Doses in Pooled Data; (3) Study MMY2002; (4) Subjects Who Completed at Least 8 Doses in Study MMY2002.

Analysis	E_0	E_{max}	EC_{50}^{ORR} ($\mu\text{g/mL}$)	Slope	EC_{90}^{ORR} ($\mu\text{g/mL}$)
Pooled	-3.6 (-16.6)	3.4 (18.5)	261 (4.8)	45.3 (191.4)	274
Pooled (≥ 8 Infusions)	-3.6 (-28.3)	3.6 (29.3)	261 (4.8)	42.1 (177.4)	275
MMY2002	-3.2 (-23.9)	2.9 (27.6)	260 (14.1)	20.3 (154.5)	289
MMY2002 (≥ 8 Infusions)	-3.1 (-39.4)	3.0 (42.1)	256 (18.2)	14.5 (143)	298

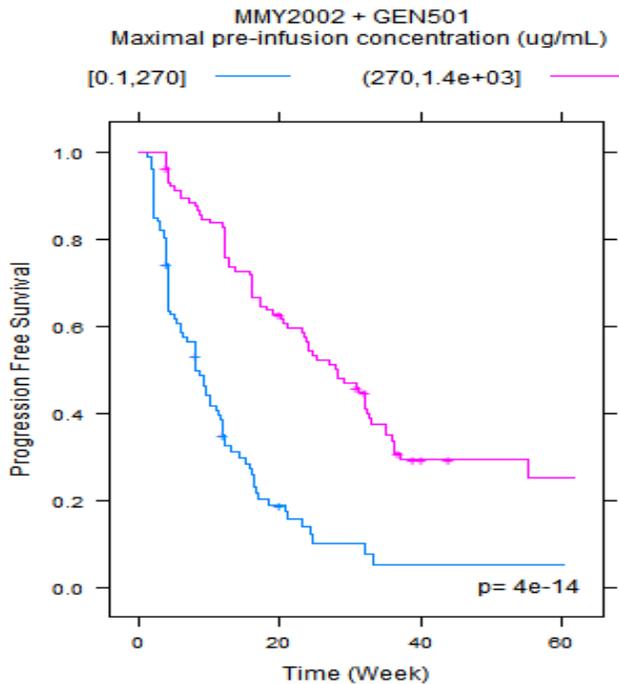
Key: E_0 =baseline log odds when concentration=0; E_{max} =maximum drug effect; EC_{50}^{ORR} =half-maximal drug effect concentration; slope=slope factor for E_{max} models; EC_{90}^{ORR} =90% maximal drug effect concentration

Note: Predicted maximal pre-infusion concentration ($C_{pre-infusion,max}$) was used to fit the models.

Source: Population PK report, Table 9.

A trend of increasing efficacy was also observed in progression free survival (PFS) with higher exposure thus indicating internal consistency with the exposure-response with ORR. The relationship was most distinctive when comparing the subjects with a $C_{pre-infusion,max} > 270 \mu\text{g/mL}$ to those with $C_{pre-infusion,max} < 270 \mu\text{g/mL}$, where the higher exposure group show longer PFS (Figure 14). The cutoff concentration of 270 $\mu\text{g/mL}$ was the median $C_{pre-infusion,max}$ among all subjects included and was similar to the EC_{90}^{ORR} (274 $\mu\text{g/mL}$) and the predicted EC_{99}^{TAR} (236 $\mu\text{g/mL}$).

Figure 14. Kaplan–Meier Curves of Progression-free Survival for the Median-Divided Groups of Predicted Maximal Pre-infusion Concentration Based on Pooled Data From Studies MMY2002 and GEN501.

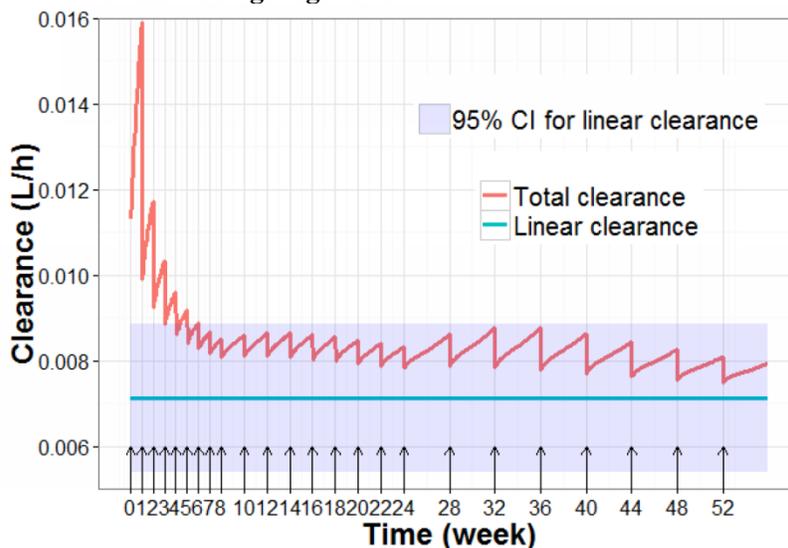


Source: Population PK report, Attachment 33

Dosing schedule

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 the efficacious concentration in a timely manner. Clinical data demonstrate that the median time to best response was around 1.9 months, suggesting that 8 weekly infusions may be needed initially to achieve the best response. Thereafter, the Q2W and Q4W dosing at 16 mg/kg appeared to be adequate to saturate the target and maintain the total clearance close to the non-specific linear clearance (**Figure 15**).

Figure 15. Model-Based Simulation of Total Clearance and Linear Clearance Versus Time Profiles for the proposed Daratumumab Dosing Regimen.



Key: Black arrows represent dosing events. Shaded blue area represents 95% confidence interval (CI) for linear clearance

Source: Population PK report, Figure 7.

1.1.2 Are there any other risk factors associated with the patients (~30% on 16 mg/kg dose) with lower exposures and responses/shorter PFS?

–Is there a possibility of dose optimization in these patients?

Yes, the distribution of baseline risk factors showed an imbalance between the lower and higher exposure group (Table 9). In addition, lack of control group makes it difficult to determine if the lower response in these 30% patients is due to lower exposures or worst baseline risk factors. Thus there are no recommendations of dose optimization in these patients at this time.

Patients with maximum Cpre-infusion lower than 270 µg/mL were also associated with higher M-protein level, worse Eastern Cooperative Oncology Group (ECOG) status, and higher risk stages based on International Staging System (ISS) at baseline, indicating that these poor responders were sicker patients to begin with.

Table 9. Distribution of baseline risk factors for the median-divided groups of predicted maximal pre-infusion concentration based on pooled data from studies MMY2002 and GEN501.

Baseline Risk Factors	Maximum Cpre-infusion	
	< 270 µg/mL (N=45)	> 270 µg/mL (N=105)
M-protein (g/L)	29.6	13.2
ECOG status = 1 or 2	86.7%	64.7%
ISS = 3	51.2%	29.9%

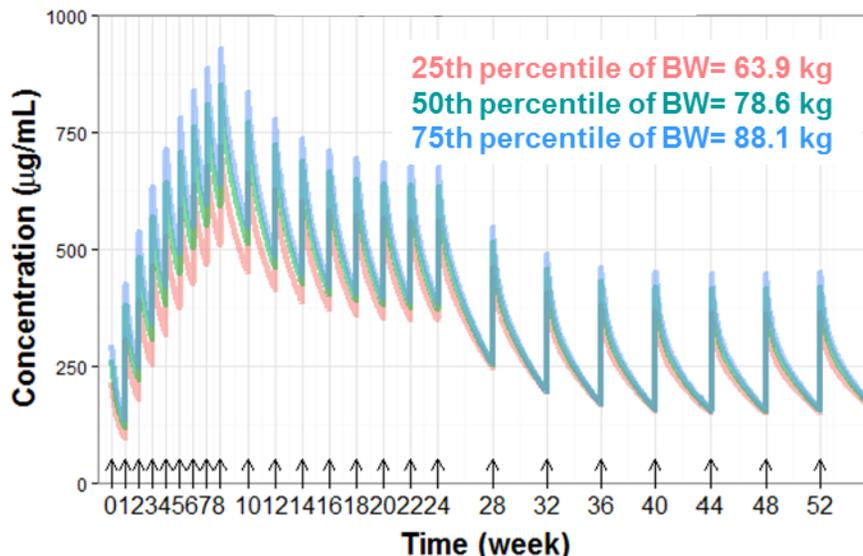
These confounding factors may be of similar or greater significance on the efficacy of daratumumab than exposure. Given that there is no control arm available in these open-label trials, it is difficult to

differentiate the contribution of exposure from other baseline risk factors on efficacy. As such, there are no current recommendations for dose optimization in these patients at this time, though the need for dose regimen optimization should continue to be evaluated as additional data from ongoing controlled phase 3 trials of daratumumab in multiple myeloma patients becomes available.

1.1.3 Is the body weight based dosing appropriate?

Yes, the body weight-based dosing for daratumumab is supported by the population PK and exposure-response analyses. The central volume of distribution and linear clearance of daratumumab significantly increased with increasing body weight. Simulation based on the final model of population PK showed that the exposure to daratumumab was similar for subjects with different body weight after administration on an mg/kg basis (**Figure 16**). Based on the exposure-response analyses, 16 mg/kg can provide exposure to achieve near maximal effect (above EC_{90}^{ORR}) across the body weight range for subjects. In addition, body weight was not significantly associated with ORR before or after adjusting for exposure.

Figure 16. Simulated Typical Daratumumab Pharmacokinetic Profiles Stratified by Body Weight.



Source: Population PK report, Attachment 25.

1.1.4 Is there a need for dose adjustment in patients with mild hepatic impairment or in patients with mild, moderate, or severe renal impairment?

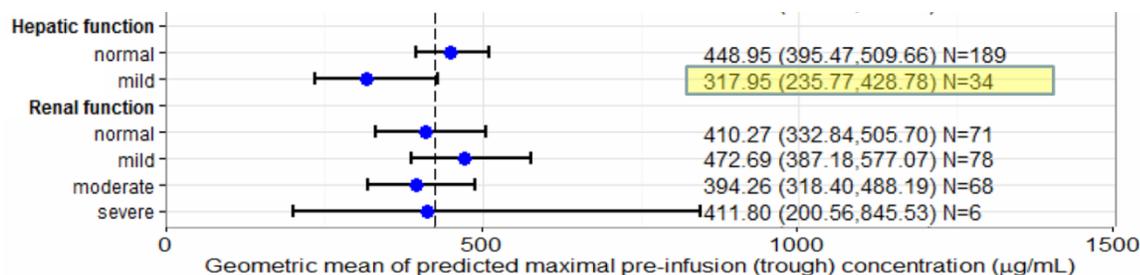
No. Based on population PK analysis, no dose adjustment is needed in patients with mild hepatic impairment or in patients with mild, moderate, or severe renal impairment. This is consistent with physiological understanding that as an IgG_{1k} mAb, renal or hepatic elimination should not be a significant clearance pathway.

Renal Impairment

There was no dedicated renal impairment study conducted for daratumumab. The population PK analysis

included 71 patients with normal renal function (creatinine clearance [CrCL] ≥ 90 mL/min), 78 patients with mild renal impairment (CrCL < 90 and ≥ 60 mL/min), 68 patients with moderate renal impairment (CrCL < 60 and ≥ 30 mL/min), and 5 patients with severe renal impairment (CrCL < 30 mL/min and ≥ 15 mL/min). CrCL was not a significant covariate on the pharmacokinetics of daratumumab. No clinically meaningful differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function (Figure 17).

Figure 17. Forest Plot of Predicted Maximal Pre-infusion (Trough) Concentration of Daratumumab in various Hepatic/Renal Function groups.



Hepatic Impairment

There was no dedicated hepatic impairment study conducted for daratumumab. The population PK analysis included 189 patients with normal hepatic function (TB and AST \leq ULN) and 34 with mild hepatic impairment (TB 1.0 \times to 1.5 \times ULN or AST $>$ ULN) patients. Mild hepatic impairment was not a significant covariate based on the model-based covariate analysis. Even though mild hepatic impairment patients showed $\sim 30\%$ lower exposure, the overall range (235 to 429 $\mu\text{g/mL}$) are still within the flat part of the exposure-response curve of ORR (Figure 17) and ORR was similar between mild hepatic and normal patients. Therefore, the differences in the exposure between patients with mild hepatic impairment and those with normal hepatic function were not considered clinically meaningful. Reason of this low exposure in mild hepatic impairment group, however, is not fully understood according to sponsor's response to our information request.

Daratumumab has not been studied in patients with moderate (TB $> 1.5\times$ to $3\times$ ULN and any AST) or severe (TB $> 3\times$ ULN and any AST) hepatic impairment.

1.2 RECOMMENDATIONS

Division of Pharmacometrics/Office of Clinical Pharmacology has reviewed the information provided in the submission and considers that the data are acceptable for supporting the approval and labeling of daratumumab for the indicated patient population.

We have one recommendation for the sponsor:

Exposure-response of efficacy was evident for both ORR and PFS indicating 30% of patients with the proposed dosing exhibited lower exposures and lower response. Due to the lack of a control arm, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. Therefore, we recommend that the applicant evaluates the possibility of dose optimization in these patients when more data is available from the controlled ongoing clinical trials.

1.3 LABEL STATEMENTS

Please refer to clinical pharmacology QBR for detailed labeling recommendations.

2 RESULTS OF SPONSOR'S ANALYSIS

The applicant conducted population PK analyses to characterize the PK of daratumumab and to evaluate the impact of intrinsic and extrinsic factors on daratumumab exposure. In addition, exposure-response analyses for efficacy and safety were performed using exposure metrics derived from the population PK model. The population PK and exposure-response analyses included data from 2 daratumumab studies: Study GEN501 and Study MMY2002. This section summarizes the methods and main conclusions of these analyses.

2.1 POPULATION PHARMACOKINETIC ANALYSIS

The population PK data set contains 2572 measurable PK samples from 223 subjects (150 subjects received 16 mg/kg). Five subjects were excluded from the population PK analysis because they had no measurable concentrations of daratumumab: one subject from Study MMY2002 received only one dose at 16 mg/kg and 4 subjects from Study GEN501 received ≤ 0.1 mg/kg daratumumab.

The population PK models were fitted using NONMEM 7.2 with first order conditional estimation with interaction (METHOD = 1 INTER) method. The PK of daratumumab was best characterized by a 2-compartment population PK model with parallel linear and Michaelis-Menten elimination pathways. The linear clearance represents the non-specific clearance for IgG and the Michaelis-Menten elimination represents the saturable target-mediated clearance. Due to the treatment effect of daratumumab, the total target (CD38) number may decrease over time. This was investigated using an empirical function: $TDVM = V_{max} \cdot \exp(-K_{des} \cdot t)$, in which $TDVM$ represents the time-dependent maximum capacity of the saturable clearance and K_{des} represents first-order rate constant, describing the decrease of V_{max} over time (t). Covariate analysis was conducted in a step-wise fashion to evaluate the effect of demographic factors (body weight, gender, race and age), as well as of creatinine clearance at baseline, liver function, type of MM and form of formulation on both volume and clearance of daratumumab. The parameter estimates of the final model resulting from covariate analysis are provided in **Table 10**. Goodness-of-fit plots and VPC plots for the final model are shown in **Figure 18** and **Figure 19**.

Table 10. Parameter estimates from the final three-compartment and the base model.

Parameter, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
CL (L/h)	0.00714	12.4	55.6	6.55	24.8
ALB on CL	-1.49	35.0			
WT on CL	0.719	25.7			
FORM on CL	-0.36	26.4			
TPMM on CL	0.862	19.1			
V ₁ (L)	4.72	6.23	28.7	11.7	18.7
WT on V ₁	0.584	24.2			
Sex on V ₁	-0.186	38.7			
V ₂ (L)	2.44	7.09			
Q (L/h)	0.0267	19.4			
V _{max} (mg/h)	1.1	13.7	77.4	10.2	20.2
K _{DES} (1/h)	0.000228	32.9	136	12.3	47.6
K _m (µg/mL)	2.38	24.1			
ADD ERR (%CV)	32.7	9.67			9.98

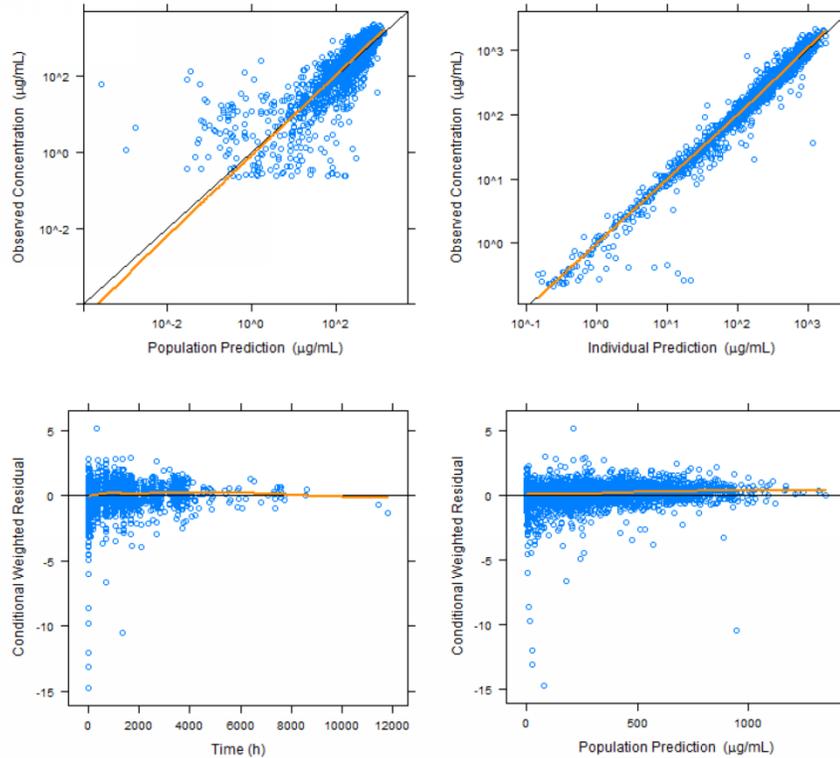
ALB=serum albumin concentration; ADD ERR=additive error term on the log-scale; CL=linear clearance; CV=coefficient of variation; FORM=Phase 2 pre-change/Phase 3 post-change drug product; IIV=interindividual variability; K_m=Michaelis-Menten constant; K_{DES}=first-order rate for decrease of V_{max}; Q=inter-compartmental clearance; RSE=relative standard error; TPMM=type of myeloma, IgG versus non-IgG; V₁=volume of distribution in the central compartment; V₂=volume of distribution in the peripheral compartment; V_{max}=maximum velocity of the saturable clearance process; WT=body weight

Note: The objective function value=-1775.0. Conditional number=193.4. Conditional number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate.

Note: For IIV, RSE% is given for %CV and is an approximate value.

Source: Population PK report, Table 5-2.

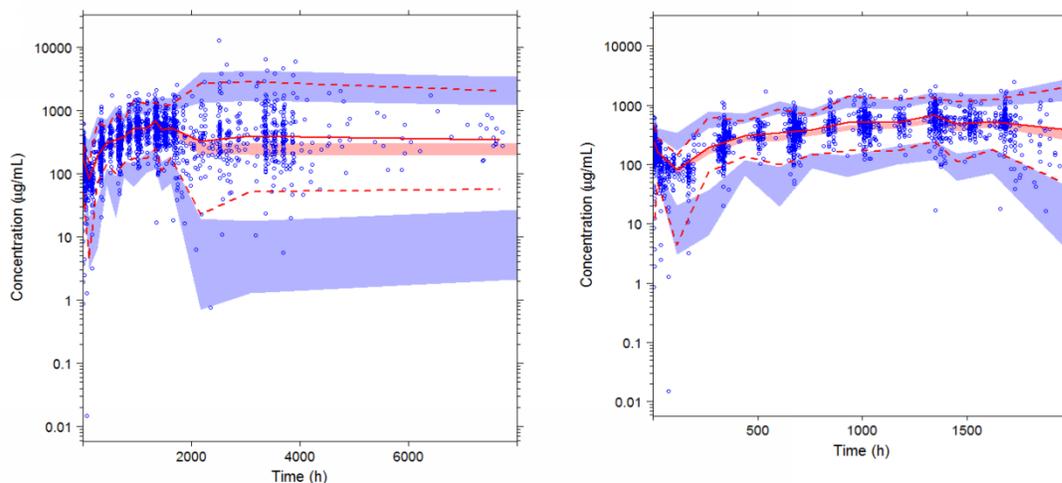
Figure 18. Goodness-of-Fit Plots for the Final Pharmacokinetic Model.



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

Source: Population PK report, Attachment 11.

Figure 19. Visual Predictive Check of the Final Model.



Key: The left panel shows the plot in the time range up to 8000 hours. The right panel zooms in the time range up to 2000 hours. Blue circle represents observation. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.

Source: Population PK report, Attachment 18.

The linear clearance and central volume of distribution (V_1) of daratumumab was 0.00714 L/d (55.6% CV) and 4.72 L (28.7%) in a typical multiple myeloma patient weighing 78.6 kg. Clearance and V_1 both vary with body weight in an allometric relationship. Doubling body weight was associated with a 65% and 50% increase in clearance and V_1 , respectively.

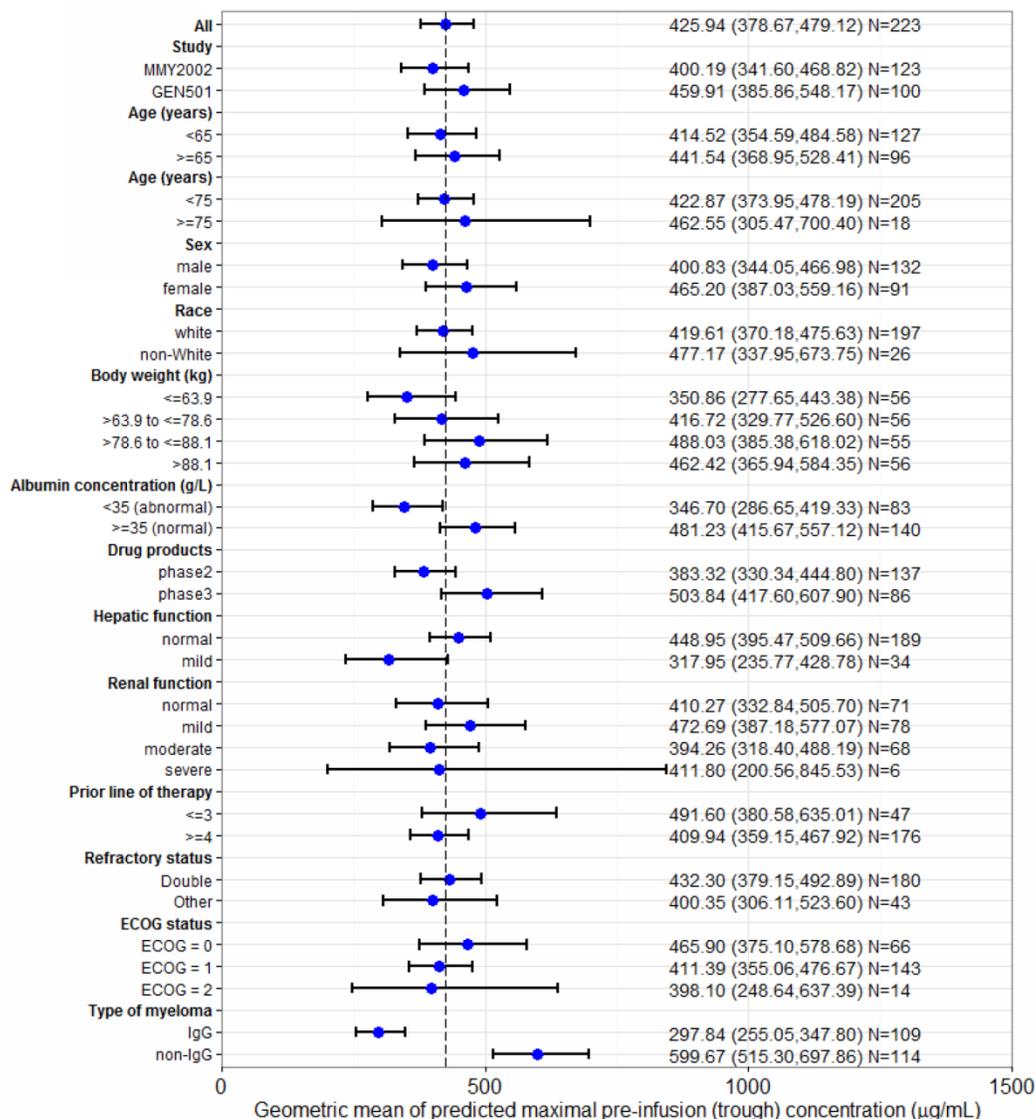
For the nonlinear clearance, the estimated K_m was 2.38 mg/mL, which is of the same magnitude as the in vitro dissociation constant for purified human CD38 (~0.65 mg/mL). Based on the estimated K_m value, concentrations needed to achieve 90% and 99% model-predicted target saturation were calculated to be 21.4 (EC_{90}^{TAR}) and 236 µg/mL (EC_{99}^{TAR}), respectively.

The final model was used to simulate individual PK profiles under recommended dosing regimens and to compare the 8 and 16 mg/kg doses following the recommended schedule. The percentage of subjects that would achieve 90% and 99% target saturation at the end of the QW and Q4W dosing period was calculated. The simulations demonstrated that the majority of subjects (>80%) may achieve EC_{99}^{TAR} after weekly dosing, and EC_{90}^{TAR} after Q4W (at steady state) dosing at 16 mg/kg. However, in comparison, only approximately 50% of subjects may achieve EC_{99}^{TAR} after the QW dosing of 8 mg/kg daratumumab, and approximately 70% of subjects may achieve EC_{90}^{TAR} at 8 mg/kg daratumumab after the Q4W dosing (Figure 12).

Besides body weight, the model-based covariate analysis identified the following statistically significant covariates on linear clearance: baseline albumin level, drug product (Phase 2 formulating vs Phase 3 formulation), and type of myeloma (IgG vs non-IgG), and sex as statistically significant covariate on central volume of distribution. However, further exposure-response analyses on efficacy and safety show that the effects of these covariates were not clinically relevant.

Comparison of daratumumab exposure in subpopulations was based on simulation assuming that all subjects in Studies MMY2002 and GEN501 received 16 mg/kg QW for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and then Q4W thereafter. Figure 20 shows the forest plots of subgroup analyses on exposure metrics of predicted maximal pre-infusion concentrations (at the end of the QW dosing period). This metrics was chosen because it shows the strongest correlation with the efficacy endpoints among other exposure metrics. No clinically important differences in the exposure to daratumumab were observed between subjects with mild hepatic impairment and those with normal hepatic function, or between subjects with renal impairment and those with normal renal function.

Figure 20. Forest Plot of Predicted Maximal Pre-infusion (Trough) Concentration in various subgroups.



Key: Solid blue circle represents geometric mean and error bar represents 95% confidence interval. Dashed line represents the geometric mean value (ie, 425.94) of all subjects. Numbers represent geometric mean, confidence interval, and number of subjects in each subgroup.

Note: Analyses assumed that all subjects in Studies MMY2002 and GEN501 received 16 mg/kg weekly for 8 weeks (8 doses), every 2 weeks for 16 weeks (8 doses), and then every 4 weeks thereafter. Maximal pre-infusion (trough) concentration was derived as the pre-infusion concentration of the 1st dose of the every 2 weeks dosing period.

Source: Population PK report, Figure 5.

The applicant also conducted simulation on total clearance and linear clearance based on typical values of final model parameters. As shown in **Figure 15**, the total clearance decreased over time and approached the non-specific linear clearance after about 8 weeks. The decrease of total clearance is considered likely due to the decrease of the tumor burden or target, which was induced by daratumumab.

Reviewer's Comments: In general, the applicant's population PK analysis is reasonable. The reviewer's independent assessment using the same methodology resulted in identification of the same model structure and similar covariates. However, Shrinkage (%) of random effects (η_{CL} : 24.9%, η_{VI} : 8.7%, η_{Vmax} : 20.2%, η_{Kdes} : 47.6%, $\eta_{additive}$: 9.98%) indicates diagnostic plots should be interpreted with caution, especially with individual prediction of the decline rate of clearance (higher shrinkage with K_{des}). The VPC plots show mild mischaracterization beginning at around 12 weeks (2000 hours), which may also indicate poor estimation of K_{des} . Given that the key exposure metrics selected for covariate evaluation and exposure-response analyses were maximal pre-infusion concentrations at the end of the 8-week QW dosing period (1512 hours), the observed deviation at 2000 hours does not affect our recommendations. In addition, large conditional weighted residuals at some earlier time points (Figure 18) were observed.

2.2 EXPOSURE-RESPONSE ANALYSES FOR EFFICACY

The applicant conducted exposure-efficacy analyses for overall response rate (ORR, the primary efficacy endpoint in Study MMY2002), and other secondary endpoints (duration of response [DOR], time to progression [TTP], time to response [TTR], overall survival [OS], progression free survival [PFS], and maximal reduction in paraprotein [M-protein]).

Different exposure metrics were derived using estimated individual PK parameters based on the population PK model and actual dosing information for each subject, and tested for the exposure-efficacy analyses. The exposure metrics included (1) maximal pre-infusion (trough) concentration ($C_{pre-infusion,max}$), (2) maximal end-of-infusion concentration ($C_{post-infusion,max}$), (3) pre-infusion concentration before the last dose received, (4) end-of-infusion concentration after the last dose received, and (5) average concentration during the treatment. $C_{pre-infusion,max}$ was selected as the exposure metrics as it had the strongest correlation with ORR.

For the 5 subjects without measurable concentrations and excluded from the population PK analysis, the concentrations were set to half of the lower limit of the quantification (0.1 $\mu\text{g/mL}$) either because they received very low doses (≤ 0.1 mg/kg) and could not establish measurable concentrations or because they discontinued treatment after 1 dose without establishing measurable daratumumab concentrations.

The relationship between exposure and ORR was analyzed with logistic regression. For PFS, Cox proportional hazard's regression models were used and the distribution of PFS according to quartiles of the daratumumab exposure was estimated using Kaplan-Meier method.

The results show that ORR significantly increased with daratumumab systemic exposure, and there was a maximum effect (E_{max}) relationship between daratumumab exposure and ORR (**Figure 13**). The estimated half-maximal effect $C_{pre-infusion,max}$ (EC_{50}^{ORR}) was 261 $\mu\text{g/mL}$, and 90% maximal effect $C_{pre-infusion,max}$ (EC_{90}^{ORR}) was 274 $\mu\text{g/mL}$ (**Table 8**). Therefore, limited additional benefit in ORR would be obtained with $C_{pre-infusion,max}$ above the predicted EC_{90}^{ORR} . The applicant further conducted sensitivity analyses based on (1) data from Study MMY2002, (2) subjects who completed at least 8 doses in the pooled GEN501/MMY2002 dataset, and (3) subjects who completed at least 8 doses in Study MMY2002 alone. The results of sensitivity analyses were consistent (**Table 8**).

The clinical relevance of the statistically significant covariates identified from the population PK analysis was evaluated by studying the covariate effects on ORR before (univariate analysis) and after (multivariate analysis), adjusting for drug exposure. The estimated odds ratios (representing the effect size) of body weight, albumin, sex, and drug product were generally similar before and after adjusting for exposure to daratumumab. In addition, the odds ratios for these 4 covariates appeared not significantly different than one since the 95% confidence intervals included 1 before and after adjusting for the drug exposure, suggesting effects of these covariates on ORR were small.

The odds ratio was close to 1 when comparing subjects with IgG multiple myeloma to those with non-IgG myeloma before adjusting for the drug exposure. After adjusting for exposure, the odds ratio of the IgG effect appeared to be significantly greater than 1, indicating that IgG multiple myeloma subjects responded better to the treatment than non-IgG multiple myeloma subjects. Further analysis showed that the estimated EC_{50}^{ORR} in non-IgG multiple myeloma subjects almost doubled that in the IgG multiple myeloma subjects (**Table 11**). This explains why the ORR in IgG multiple myeloma subjects appeared to be similar to that in non-IgG multiple myeloma subjects despite of 50% lower drug exposure for the subjects with IgG multiple myeloma. Therefore, the effects of the covariate (IgG versus non-IgG multiple myeloma) on the drug exposure and efficacy were cancelled out by each other.

Table 11. Different EC_{50} Estimates for Subjects with IgG Multiple Myeloma and Non-IgG Multiple Myeloma.

Parameters	Estimate (% RSE)
E_0	-3.2 (-18.4)
E_{max}	4.6 (31.4)
EC_{50}^{ORR} (non-IgG) ($\mu\text{g/mL}$)	611.7 (20.6)
EC_{50}^{ORR} (IgG) ($\mu\text{g/mL}$)	311.2 (24.6)
Slope	2.9 (60.3)
ΔOFV	6.8
p-value	0.01

Source: Population PK report, Attachment 33

For PFS, a significant separation was observed for subject groups divided according to quartiles of daratumumab exposures. The difference in PFS was particularly apparent when comparing the subjects with a $C_{\text{pre-infusion,max}} > 270 \mu\text{g/mL}$ to those with $C_{\text{pre-infusion,max}} < 270 \mu\text{g/mL}$ (**Figure 14**). This observation was consistent with the EC_{90}^{ORR} (274 $\mu\text{g/mL}$) and the predicted EC_{99}^{TAR} (236 $\mu\text{g/mL}$). The median PFS according to the median of $C_{\text{pre-infusion,max}}$ for subjects in the lower ($\leq 270 \mu\text{g/mL}$) and upper half ($> 270 \mu\text{g/mL}$) of $C_{\text{pre-infusion,max}}$ was 1.9 months and 6.6 months, respectively. The positive association with daratumumab exposures was also observed for other efficacy endpoints tested (TTP, DOR, TTR and paraprotein).

2.3 EXPOSURE-RESPONSE ANALYSES FOR SAFETY

Exposure-response safety analyses were conducted for selected AEs, including IRRs, thrombocytopenia, anemia, neutropenia, lymphopenia, and infections. The predicted end-of-infusion concentrations after the first infusion (C_{max} after first dose, $C_{\text{max,1st}}$) was explored for IRRs because the majority of IRRs occurred after the first dose, while the predicted maximal end-of-infusion concentration (multiple-dose C_{max} , $C_{\text{post-infusion,max}}$) was investigated for the other AEs. The incidence rates of AEs were analyzed using logistic regression models according to quartiles of the exposure metrics. The estimated incidence rate (along with its 95% CI) for each exposure quartile was reported.

There was no apparent exposure-response relationship between predicted $C_{\text{max,1st}}$ and IRR, and predicted $C_{\text{post-infusion,max}}$ 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 (**Table 12**). 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.

Table 12. Comparison of Adverse Event Rate (95% CI) Between Predicted Daratumumab Exposure Quartiles Based on Pooled Data From Studies MMY2002 and GEN501 and Data From Study MMY2002 Alone.

Adverse Event	Exposure Quartiles			
	Q1	Q2	Q3	Q4
	MMY2002 + GEN501			
Infusion-related Reaction	63.2% (50.3%-74.9%)	56.1% (43.2%-68.5%)	50.9% (38.1%-63.6%)	47.4% (34.7%-60.2%)
Thrombocytopenia	19.3% (10.5%-30.8%)	22.8% (13.3%-34.7%)	17.5% (9.2%-28.7%)	14% (6.7%-24.6%)
Neutropenia	7% (2.2%-15.6%)	15.8% (7.9%-26.7%)	19.3% (10.5%-30.8%)	12.3% (5.5%-22.4%)
Anemia	24.6% (14.7%-36.7%)	36.8% (25.1%-49.7%)	15.8% (7.9%-26.7%)	15.8% (7.9%-26.7%)
Lymphopenia	8.8% (3.2%-17.9%)	0% (NE)	3.5% (0.6%-10.4%)	3.5% (0.6%-10.4%)
Infections	40.4% (28.2%-53.3%)	54.4% (41.5%-66.9%)	56.1% (43.2%-68.5%)	61.4% (48.5%-73.3%)
	MMY2002 + GEN501			
Grade 3+ Infusion-related Reaction	8.8% (3.2%-17.9%)	3.5% (0.6%-10.4%)	1.8% (0.1%-7.5%)	3.5% (0.6%-10.4%)
Grade 3+ Thrombocytopenia	15.8% (7.9%-26.7%)	14% (6.7%-24.6%)	12.3% (5.5%-22.4%)	10.5% (4.3%-20.2%)
Grade 3+ Neutropenia	7% (2.2%-15.6%)	8.8% (3.2%-17.9%)	10.5% (4.3%-20.2%)	3.5% (0.6%-10.4%)
Grade 3+ Anemia	15.8% (7.9%-26.7%)	24.6% (14.7%-36.7%)	7% (2.2%-15.6%)	8.8% (3.2%-17.9%)
Grade 3+ Lymphopenia	5.3% (1.3%-13.1%)	0% (NE)	3.5% (0.6%-10.4%)	3.5% (0.6%-10.4%)
Grade 3+ Infections	5.3% (1.3%-13.1%)	12.3% (5.5%-22.4%)	12.3% (5.5%-22.4%)	5.3% (1.3%-13.1%)
	MMY2002			
Infusion-related Reaction	51.6% (34.4%-68.5%)	35.5% (20.3%-53%)	41.9% (25.7%-59.4%)	41.9% (25.7%-59.4%)
Thrombocytopenia	35.5% (20.3%-53%)	25.8% (12.7%-42.7%)	22.6% (10.4%-39.1%)	22.6% (10.4%-39.1%)
Neutropenia	16.1% (6.1%-31.5%)	25.8% (12.7%-42.7%)	25.8% (12.7%-42.7%)	12.9% (4.2%-27.5%)
Anemia	54.8% (37.5%-71.4%)	41.9% (25.7%-59.4%)	32.3% (17.7%-49.7%)	12.9% (4.2%-27.5%)
Lymphopenia	9.7% (2.5%-23.2%)	3.2% (0.2%-13.4%)	6.5% (1.1%-18.6%)	3.2% (0.2%-13.4%)
Infections	38.7% (23%-56.2%)	58.1% (40.6%-74.3%)	48.4% (31.5%-65.6%)	54.8% (37.5%-71.4%)
Grade 3+ Infusion-related Reaction	12.9% (4.2%-27.5%)	3.2% (0.2%-13.4%)	3.2% (0.2%-13.4%)	3.2% (0.2%-13.4%)
Grade 3+ Thrombocytopenia	25.8% (12.7%-42.7%)	22.6% (10.4%-39.1%)	12.9% (4.2%-27.5%)	16.1% (6.1%-31.5%)
Grade 3+ Neutropenia	16.1% (6.1%-31.5%)	12.9% (4.2%-27.5%)	12.9% (4.2%-27.5%)	3.2% (0.2%-13.4%)
Grade 3+ Anemia	38.7% (23%-56.2%)	29% (15.2%-46.2%)	22.6% (10.4%-39.1%)	3.2% (0.2%-13.4%)
Grade 3+ Lymphopenia	9.7% (2.5%-23.2%)	3.2% (0.2%-13.4%)	6.5% (1.1%-18.6%)	3.2% (0.2%-13.4%)
Grade 3+ Infections	6.5% (1.1%-18.6%)	16.1% (6.1%-31.5%)	9.7% (2.5%-23.2%)	6.5% (1.1%-18.6%)

Key: NE=not evaluable; Q1-4=Quartiles 1-4.

Note: End-of-infusion concentration after the first infusion ($C_{max,1st}$) was used as the exposure measure for analyses on infusion-related reactions, while maximal post-infusion concentration ($C_{post-infusion,max}$) was used as the exposure measure for analyses on other adverse events.

The quartiles for $C_{max,1st}$ are: Q1 (≤ 134 $\mu\text{g/mL}$), Q2 (134–245 $\mu\text{g/mL}$), Q3 (245–310 $\mu\text{g/mL}$), and Q4 (310–470 $\mu\text{g/mL}$).

The quartiles for $C_{post-infusion,max}$ are: Q1 (≤ 270 $\mu\text{g/mL}$), Q2 (270–511 $\mu\text{g/mL}$), Q3 (511–907 $\mu\text{g/mL}$), and Q4 (907–1840 $\mu\text{g/mL}$).

The quartiles for $C_{max,1st}$ from MMY2002 are: Q1 (≤ 225 $\mu\text{g/mL}$), Q2 (225–277 $\mu\text{g/mL}$), Q3 (277–335 $\mu\text{g/mL}$), and Q4 (335–470 $\mu\text{g/mL}$).

The quartiles for $C_{post-infusion,max}$ from MMY2002 are: Q1 (≤ 418 $\mu\text{g/mL}$), Q2 (418–652 $\mu\text{g/mL}$), Q3 (652–993 $\mu\text{g/mL}$), and Q4 (993–1840 $\mu\text{g/mL}$).

Source: Summary of Clinical Pharmacology Studies, Table 10

Reviewer's Comments: The applicant has conducted adequate exposure-response analyses to explore the relationships for efficacy and safety. However, lack of a control arm makes it difficult to make inferences about the contribution of exposures vs. other baseline risk factors on efficacy. Given the number of confounding factors, additional data from forthcoming controlled trials will help in evaluating the need for dose regimen optimization in patients with poor efficacy due to lower exposures.

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/s/

JEANNE FOURIE ZIRKELBACH
10/22/2015

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NAM ATIQUR RAHMAN
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I concur.