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APPLICATION NUMBER:

761035Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	761035
Submission Date(s)	June 27, 2015
Brand Name	EMPLICITI
Generic Name	Elotuzumab
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Team Leader	Gene Williams, Ph.D
Pharmacometrics Reviewer	Justin Earp, Ph.D
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OCP Division (s)	Division of Clinical Pharmacology V Division of Pharmacometrics
OND Division	Division of Hematology Products
Sponsor	Bristol Meyer-Squibb
Relevant IND(s)	IND 100043
Submission Type; Code	NME/ Priority Review/ Breakthrough Therapy
Formulation; Strength(s)	Intravenous, 25 mg/mL reconstituted
Indication	Treatment of patients with multiple myeloma who have received 1 to 3 prior therapies in combination with lenalidomide and dexamethasone (b) (4)

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1 EXECUTIVE SUMMARY

EMPLICITI® (elotuzumab) is a humanized recombinant monoclonal immunoglobulin G1 (IgG1) that binds human Signaling Lymphocyte Activation Molecule F7 (SLAMF7) on the surface of myeloma cells and recruits circulating Natural Killer (NK) cells to the vicinity of the myeloma cell. This BLA submission is in support of the safety and efficacy of elotuzumab in combination with lenalidomide/dexamethasone (b) (4) for the treatment of patients with relapsed multiple myeloma who have received one to three prior therapies. The clinical pharmacology data submitted with this BLA includes data from multiple-dose studies evaluating the efficacy and safety of elotuzumab as a single agent or in combination. The clinical pharmacology submission also includes population PK and exposure-response analyses for efficacy and safety. The population PK model revealed covariate relationships for elotuzumab clearance with baseline M-protein concentrations and body weight. Body weight based dosing is thus justified. Higher M-protein correlated with higher elotuzumab clearance, however the correlation was modest. The exposure-response analysis revealed there was no difference in median PFS between patients with elotuzumab Cavgss in the lowest quartile of elotuzumab exposure (Cavgss < 209 µg/mL) and patients on active control, after controlling for potential confounding factors such as high M-protein, higher B2-microglobulin, ECOG score, and higher LDH levels. Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors. As PFS in patients with Cavgss concentrations less 209 µg/mL was not better than in the control arm, even after adjusting for other risk factors, it appears reasonable to explore options to optimize dose in this subgroup of patients. We are asking for additional analyses to be conducted as a PMC. The results of the ongoing trial CA204006 will be used to conduct exposure-response analyses and determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10 mg/kg).

Recommendation

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in BLA 761035. This BLA is acceptable for approval from a clinical pharmacology perspective.

Signatures

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1.1 Post-marketing Commitments

Conduct elotuzumab exposure-response analyses for efficacy and safety utilizing data from trial CA204006. The results of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have low exposure to elotuzumab at the approved dose (10 mg/kg). Submit a final report of the exposure-response analyses based on CA204004 and CA204006.

1.2 Summary of Important Clinical Pharmacology Findings

This BLA submission is to support the safety and efficacy of elotuzumab in combination with lenalidomide and dexamethasone (b) (4) for the treatment of patients with relapsed multiple myeloma who have received one to three prior therapies. The safety and efficacy of elotuzumab in this population were evaluated in two randomized trials. In the first trial, patients were randomized (1:1) to elotuzumab with lenalidomide plus dexamethasone (ELd) (n=321), or lenalidomide plus dexamethasone (Ld) (n=325). The co-primary endpoints were progression-free survival (PFS) and objective response rate (ORR). In this trial, the improvement in median PFS time between Arm ELd (19.4 months) and Arm Ld (14.9 months) was 4.5 months (p=0.0002 2-sided p-value) and the ORRs were 78.5 vs. 65.5%, respectively. In the second trial, patients were randomized (1:1) to elotuzumab with bortezomib plus dexamethasone (EBd) (n=77), or bortezomib plus dexamethasone (Bd) (n=75). In this trial, the improvement in median PFS time between Arm EBd (9.7 months) and Arm Bd (6.9 months) was 2.8 months (b) (4) (b) (4)

A population PK analysis was submitted by the applicant incorporating data from five clinical studies: two Phase 1 studies (CA204005 and CA204007), two Phase 2 studies (CA204011 and CA204009), and one Phase 3 study (CA204004). The population PK model showed a relationship between total elotuzumab clearance and weight, co-administration of lenalidomide/dexamethasone, co-administration of bortezomib/dexamethasone, and baseline M-protein.

Exposure-response analyses suggest that optimizing the dose in patients with low exposure may offer additional PFS benefit.

- An exposure-response relationship for elotuzuamb Cavg at steady-state and PFS was identified by both Kaplan Meier curves for PFS and the applicant's multivariate Cox proportional hazards model for exposure-response. Using a case control analysis to control for additional confounding factors (M-protein, β2-microglobulin, lactate dehydrogenase, ECOG score, prior immunomodulatory therapy, prior treatment duration, and prior stem cell transplantation) an assessment of PFS in subjects with the lowest quartile of elotuzumab Cavgss was done and compared to that in a subset of the control group with matching patient characteristics. This was also perfomed for the remaining 75% of patients with higher exposure and compared to a matching subset of the control arm.
- The exposure-response analysis revealed there was no difference in median PFS between patients with elotuzumab Cavgss in the lowest quartile of elotuzumab exposure (Cavgss < 209 µg/mL) and patients on active control, after controlling for the potential confounding factors listed above.
- Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors.
- This analysis in conjunction with the higher clearance of elotuzumab with higher M-protein suggests that patients who are at higher risk of PFS and have lower exposure may benefit from a dose increase.

Thus, a post-marketing commitment (PMC) is being recommended to conduct elotuzumab exposure-response analysis for efficacy and safety utilizing data from the ongoing trial CA204006. The results of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10 mg/kg).

The applicant included data on the immunogenicity of elotuzumab. Antibody response was, in general, transient. Its impact on the PK of elotuzumab was confounded by its correlation with baseline M-protein.

APPEARS THIS WAY ON ORIGINAL

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?

- Established name: elotuzumab
- Amino acid sequence: The elotuzumab molecule consists of (b) (4) heavy chain subunits and (b) (4) light chain subunits. (b) (4)
- Molecular Weight: Elotuzumab has a theoretical mass of 148.1 kDa for the intact antibody. (b) (4)
- Structural formula:

(b) (4)

Elotuzumab for injection is a non-pyrogenic lyophilized powder that is white to off-white whole or fragmented cake.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Elotuzumab is a humanized recombinant monoclonal immunoglobulin G1 (IgG1) that binds human Signaling Lymphocyte Activation Molecule F7 (SLAMF7). SLAMF7 is a cell surface glycoprotein expressed on multiple myeloma (MM) cells independent of disease stage or cytogenetic abnormalities. Elotuzumab binds the SLAMF7 on the surface of myeloma cells and recruits circulating NK cells to the vicinity of the myeloma cell. Elotuzumab causes NK-cell activation which kills the myeloma cell via an ADCC mechanism.
The activity of elotuzumab appears to be enhanced by co-administration with the small molecules bortezomib, lenalidomide and pomalidomide, as well as with antibodies that enhance NK cell function.

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

The applicant proposes the following dosages and routes of administration when elotuzumab is given in combination with lenalidomide and dexamethasone (**Table 1**) (b) (4)

Table 1: Applicant's Recommended Dosing Schedule of Elotuzumab in Combination with Lenalidomide and Dexamethasone

Cycle	**28-Day Cycles 1 and 2**				**28-Day Cycles 3+**			
Day of Cycle	1	8	15	22	1	8	15	22
Premedication*	✓	✓	✓	✓	✓		✓	
Elotuzumab (mg/kg) intravenously	10	10	10	10	10		10	
Lenalidomide† (25 mg) orally	Days 1-21				Days 1-21			
Dexamethasone‡ (mg) orally	28	28	28	28	28	40	28	40
Day of Cycle	1	8	15	22	1	8	15	22

* Premedicate with the following 45 to 90 minutes prior to elotuzumab infusion: 8 mg intravenous dexamethasone, H1 blocker: diphenhydramine (25-50 mg orally or intravenously) or equivalent; H2 blocker: ranitidine (50 mg intravenously) or equivalent; acetaminophen (650 - 1000 mg orally).

† (b) (4)

‡ Oral dexamethasone (28 mg) taken between 3 and 24 hours before elotuzumab infusion.

(b) (4)

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?

Several clinical trials were conducted in cancer patients using elotuzomab as a single agent and in combination to support the proposed indication at the proposed dose as shown in **Table 3**. One single-agent (HuLuc63-1701) and two combination dose-escalation studies (HuLuc63-1702 and HuLuc63-1703) were conducted to assess the dose-response characteristics and dose-limiting toxicities of elotuzumab. The single agent dose escalation trial assessed elotuzumab doses of 0.5, 1, 2.5, 5, 10, and 20 mg/kg (HuLuc63-1701). The combination dose-escalation trials assessed elotuzumab doses of 5, 10 and 20 mg/kg given with lenalidomide/dexamethasone (HuLuc63-1703) (b) (4) .

Population PK and exposure-response analyses for efficacy and safety using data from selected studies described in **Table 3** below were also conducted.

Table 3: Clinical Pharmacology and Clinical trials conducted to support the approval of Elotuzumab

Study Number	Treatment	N	Design of Clinical Pharmacology component of the study	Contribution of the Clinical Pharmacology profile
HuLuc63-1701 Phase 1, dose escalation study in subjects with advanced MM	Subjects received 4 doses of elotuzumab IV every other week of 8 wk (52/56 day) treatment cycle.	34	PK, biomarker/PD, Immunogenicity samples	PK, biomarkers/PD, immunogenicity, PPK

	Dose cohorts: 0.5, 1, 2.5, 5, 10, 20 mg/kg			
HuLuc-63-1702 Phase 1/2, dose-escalation study of elotuzumab and bortezomib in subjects with MM following 1 – 3 prior therapies	Subjects received 4 cycles of IV bortezomib and elotuzumab. Subjects with PD at the end of C2 or C3 (Day 11) also received 20 mg Dex Dosing cohorts: 2.5, 5, 10, or 20 mg/kg.	28	PK, Biomarker/PD, Immunogenicity samples	PK, biomarkers/PD, immunogenicity
HuLuc63-1703 (Phase 1 Portion) Phase 1b/2, dose-escalation study of elotuzumab + Len/ Dex in subjects with RMM	Subjects received elotuzumab IV, lenalidomide PO, and dexamethasone (8 mg Dex IV and 28 mg Dex PO on dosing days) Dosing cohorts: 5, 10, 20 mg/kg	28	PK , biomarker/PD , Immunogenicity samples	PK, Biomarkers/PD, immunogenicity, PPK, E-R analyses
CA204005 Phase 1 multiple ascending dose study of elotuzumab + Len/low-dose Dex in patients with RRMM in Japan	Subjects received elotuzumab IV infusion, or placebo, lenalidomide PO, and dexamethasone Dosing cohorts: 10 or 20 mg/kg	6 (3/ cohort)	PK, Immunogenicity samples	PK, immunogenicity, PPK
CA204007 Phase 1b study of elotuzumab + Len/Dex in subjects with MM and normal renal function, severe renal impairment, or ESRD requiring dialysis	Subjects received lenalidomide/ dexamethasone with elotuzumab Dosing cohorts: elotuzumab 10 mg/kg,	26 (NRF, 8; SRI, 9; ESRD, 9)	PK, Immunogenicity samples:	Effects of SRI and ESRD on PK, immunogenicity, PPK
HuLuc63-1703 (Phase 2 Portion) Phase 1b/2, dose-escalation study of elotuzumab + Len/Dex in subjects with RMM	Subjects received elotuzumab IV infusion, lenalidomide PO QD, and dexamethasone Dosing cohorts:10 or 20 mg/kg	73	PK, Biomarker/PD, Immunogenicity samples	PK, Biomarkers/PD, PGX, Immunogenicity, PPK, E-R analyses
CA204009 Phase 2 study of bortezomib/Dex with or without elotuzumab in subjects with RRMM	Subjects were randomized in a 1:1 ratio and received bortezomib/dexamethasone with or without elotuzumab Dosing cohorts: elotuzumab 10 mg/kg	Control : 75 Investigational arm: 75	PK , Biomarker/PD, Immunogenicity samples:	PK, biomarker/PD, PGX, immunogenicity, PPK, E-R analyses
CA204011 Phase 2 biomarker study of elotuzumab monotherapy to assess the association between NK cell status and efficacy in high risk smoldering myeloma	Subjects received elotuzumab IV infusion on Days 1 and 8 of Cycle 1, and Day 1 of Cycle 2 and beyond (Cohort 1) or weekly for 4 weeks in Cycles 1 and 2 and every other week in Cycles 3 and beyond (Cohort 2) Dosing cohorts: 20 mg/kg (Cohort 1) and 10 mg/kg (Cohort 2)	Cohort 1:15 Cohort 2: 16	PK, Immunogenicity, samples: ECG assessments:	PK, biomarker/PD, immunogenicity, PPK, ECG assessments
CA204004 ELOQUENT-2: Phase 3, randomized trial of lenalidomide/dexamethasone with or without elotuzumab in RRMM	Subjects were randomized 1:1 to receive lenalidomide PO/dexamethasone with or without elotuzumab (10 mg/kg IV) Dosing cohorts: 10 mg/kg,	Control arm: 317 Investigational arm: 318	PK, Immunogenicity samples	PK, PGX, immunogenicity, PPK, E-R analyses, ECG assessments

To demonstrate the clinical efficacy of elotuzumab in combination with lenalidomide/ dexamethasone, a Phase 3, randomized, controlled, open-label, multicenter study in subjects with relapsed/refractory MM who had progressed after 1 to 3 lines of therapies (Study CA204004) was conducted. In this study, subjects (n=646) were randomized to receive elotuzumab (10 mg/kg) in combination with lenalidomide/ dexamethasone (E-Ld) (n=321) or lenalidomide/ dexamethasone alone (Ld) (n=325). Elotuzumab 10 mg/kg was given weekly during Cycles 1 and 2, and every 2 weeks during Cycle 3 and beyond. Lenalidomide 25 mg PO once daily was administered for the first 3 weeks of the 4-week cycle on Days 1 – 21 and dexamethasone was administered weekly as a split dose of 28 mg PO (3 - 24 hours prior to the start of elotuzumab infusion) + dexamethasone 8 mg IV (on the day of elotuzumab infusion at least 45 min prior to the start of infusion, as part of the premedication). Plasma samples for the assessment of the PK of elotuzumab were collected in this study and the study was included in the exposure-response analyses for safety and efficacy.

(b) (4)

(b) (4)

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?

Efficacy Endpoint

In the pivotal phase 3 study for elotuzumab in combination with lenalidomide/dexamethasone (E-Ld), the primary endpoints were progression free survival (PFS) and objective response rate (ORR), as determined by an independent review committee (IRC), in the response evaluable population. A total of 646 subjects (321 in E-Ld and 325 in Ld) were randomized of which 318 were treated with E-Ld and 317 were treated with Ld. The median age was 66 years with 20% of subjects 75 years of age or older. The median duration of MM was 3.5 years prior to entering the trial and 53% of subjects were ISS stage II or III. The median number of prior therapies was 2 (range 1-4) and prior therapy included bortezomib, thalidomide, and lenalidomide in 70%, 48%, and 6%, respectively and were well balanced between the treatment arms. A summary of the results of the study is presented in **Table 4**.

Table 4: Summary of elotuzumab efficacy in combination with lenalidomide and dexamethasone (Applicant's analysis)

Efficacy Parameter	E-Ld		Ld
IRC-Assessed PFS (Co-primary Endpoint)			
Number of Events(%)	179 (55.8)		205 (63.1)
Hazard Ratio (E-Ld/Ld)		0.70	
95% CI		(0.57, 0.85)	
97.61% CI		(0.55, 0.88)	
P value		0.0004	
1-year PFS rate (95% CI)	0.68 (0.63, 0.73)		0.57 (0.51, 0.62)
2-year PFS rate (95% CI)	0.41 (0.35, 0.47)		0.27 (0.22, 0.33)
IRC-Assessed ORR (Co-Primary Endpoint)			
Number (%) of Responders	252 (78.5)		213 (65.5)
Exact 95% CI	(73.6, 82.9)		(60.1, 70.7)
Common odds ratio		1.94	
95% CI		(1.36, 2.77)	
99.5% CI		(1.17, 3.23)	
P-value		0.0002	
Difference in ORR		12.6%	
95% CI		(6.1, 19.2)	

In the study evaluating elotuzumab in combination with bortezomib/dexamethasone, the primary endpoint was PFS based on the investigators assessment. Objective response rate (ORR), also based on the investigator's assessment, was considered a secondary endpoint. In this study, 152 patients were randomized, and 150 (75 per treatment group) were treated across 46 sites. The median age was 66 years and 19.1% of subjects were 75 years of age or older. The median duration of MM was 3.7 years (44.7 months) prior to entering the trial. A total of 46.1% of subjects were ISS stage II or III. The median number of prior therapies was 1 (range 1-3) and prior therapy included bortezomib, thalidomide, and lenalidomide in 51.3%, 31.6%, and 52.0%, respectively.

The study met its primary endpoint of PFS. The 1-year PFS rate was 39% and 33% for E-Bd and Bd, respectively. The hazard ratio (HR, E-Bd/Bd) was (b) (4) (b) (4) two-sided stratified log rank

test p-value (b) (4)). Median PFS was 9.7 months (b) (4) (b) (4) in the E-Bd group and 6.9 months (b) (4) (b) (4)) in the Bd group. (b) (4)

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 sponsor collected PK samples from 9 studies (see **Table 3**).

2.2.4 Exposure-response

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

An exposure-response relationship was observed relating progression-free survival (PFS) to the average concentration at steady state (Cssavg) for Study CA204004 where elotuzumab was administered in combination with lenalidomide /dexamethasone and Study CA204009, where elotuzumab was administered in combination with bortezomib/dexamethasone.

As shown in **Table 5**, the final covariates retained in the exposure-response models were C_{avgSS}, LDH, baseline β2 macroglobulin, prior IMiD therapy (Yes:No), prior stem cell transplantation (Yes:No), chromosome abnormality T(4,14) (Yes:No or Unknown), and time from diagnosis (≥ median [3.5 years]: < median [3.5 years]) (b) (4)

Table 5: Summary of Exposure-Response Analysis for Efficacy based on Data from Study CA204004 and CA42009 (Applicant's analysis)

	Study CA204004			Study CA204009		
Predictor (Comparator:Reference)	Coefficient	RSE (%)	Hazard Ratio (95% CI)	Coefficient	RSE (%)	Hazard Ratio (95% CI)
CavgSS [µg/mL]	-0.001497	21.05	0.9985 (0.998-0.999)	(b) (4)		
LDH [time of LDHULN]	0.6491	25.25	1.914 (1.388-2.639)			
β2 microglobulin [mg/L]	0.5925	15.96	1.81 (1.50 - 2.18)			
Time from disease diagnosis (≥ median: < median)	-0.6479	17.4	0.523 (0.420 - 0.653)			
Prior IMiD Therapy (Yes: No)	0.4069	26.01	1.50 (1.22 - 1.85)			
Prior stem cell transplantation (Yes: No)	0.4581	25.16	1.58 (1.26-1.98)			
Chromosomal Abnormality T(4,14) (Yes: No or Unknown)	0.5505	28.97	1.73 (1.27-2.37)			

Exposure response analyses and the mechanism of clearance of the drug suggest that patients with lower exposure of the drug may benefit from an increased dose. As the drug targets tumor cells that are cleared due to its mechanism of action, elotuzumab clearance correlates with a higher tumor burden (Pharmacometrics Review, Appendix 4.2, Section 1.1.1.1). Additionally, Multiple Myeloma (MM) patients in Trial CA204004 with low exposure showed no improvement compared to the active control arm (lenolidamide/dexamethasone), whereas patients with high exposure showed about a 5 month benefit in the median Progression-Free Survival (PFS) duration compared to the active control.

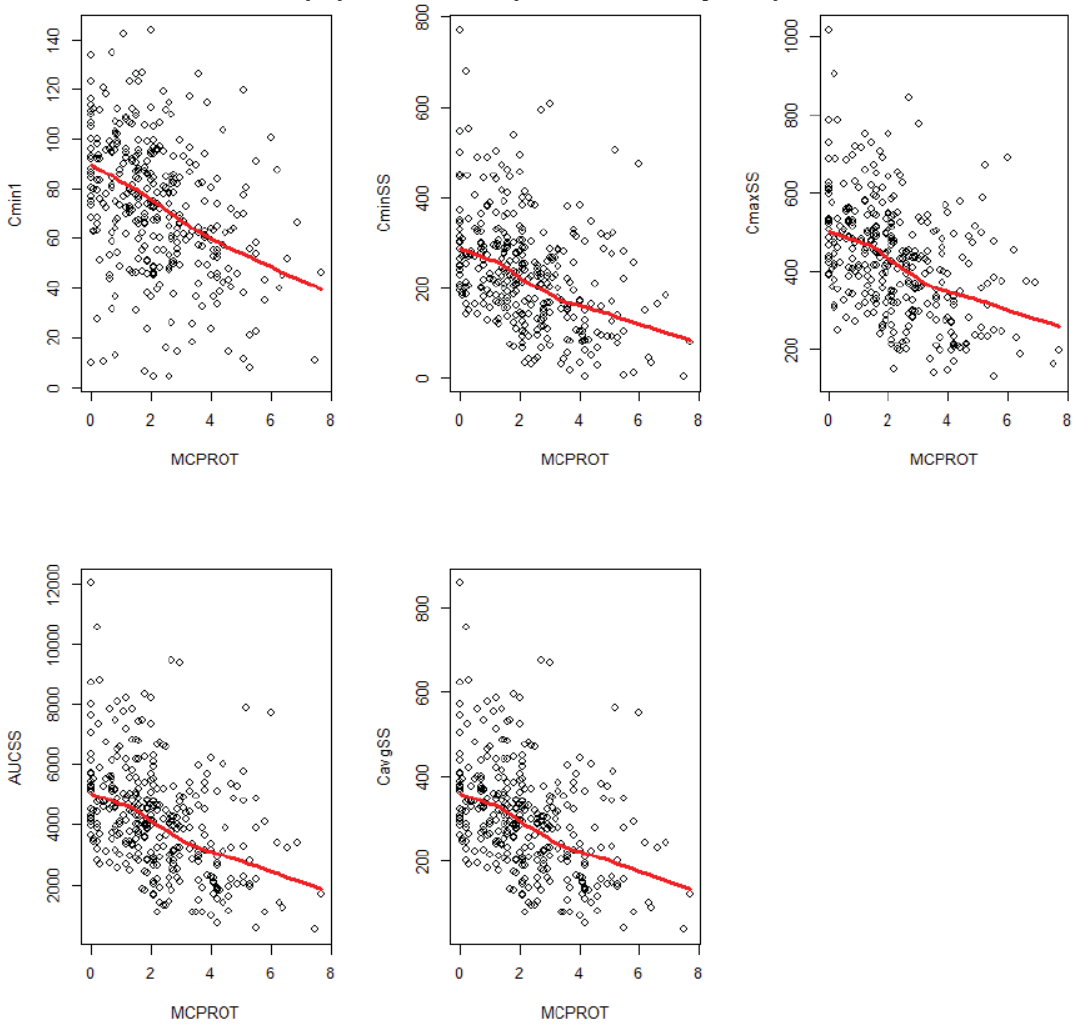
It is worth noting that even though the lack of benefit in patients with lower exposures was based on comparison of two treatments (25% patients with lower exposures in the Elotuzumab arm and matched patients from the LenDex arm) with similar baseline risk factors, the relationship between exposure and

response could still be influenced by the specific distribution of risk factors across the four subgroups. For such an exposure-response relationship to be valid (higher exposure leading to better PFS), one has to make the assumption that this relationship is the same under any combination of those risk factors (because of the unbalanced distributions of the risk factors across these four subgroups). Therefore, it is not possible to conclude with the current data if dose increase in patients with lower exposures would offer additional benefit.

Patients with higher M-protein exhibit higher clearance of elotuzumab.

Based on the applicant's population PK analysis, patients with higher M-protein concentrations clear the drug faster and therefore have lower exposures. **Figure 1** demonstrates the correlation between the applicant's metrics of elotuzumab exposure and the patient's baseline M-protein concentrations. This correlation is consistent with the mechanism of action of the drug, whereas elotuzumab binds the multiple myeloma cells and attracts the natural killer cell to destroy the cell, clearing the drug along with it. Therefore with a higher tumor burden and higher M-protein it might be expected that clearance of the drug is greater.

Figure 1. Elotuzumab exposure versus baseline serum M-protein (g/dL) following 10 mg/kg elotuzumab administered QW for two 28-day cycles followed by Q2W for subsequent cycles.



(Source: Applicant's Population PK Study Report, CA204004, Figure 5.1.5.4-3)

M-protein levels for each group are shown in **Table 6** indicating that M-protein potentially confounds the analysis for PFS. As expected, M-protein is higher in the lowest exposure quartile, but that also leads to

the observation that other PFS risk factors are higher in the lowest exposure quartile. M-protein accounts for roughly 50% of the exposure difference between Q1 and Q2. This is also consistent with the modest correlation between exposure and M-protein such that such that M-protein alone cannot be used to select patients with lower exposures. Additionally, after the case control analysis that matches for M-protein, the exposure benefit appears to remain. Therefore, evaluating a higher dose based on low exposure rather than M-protein may appear to be appropriate.

Table 6: Patient characteristics related to PFS risk and elotuzumab clearance for the active control group and each elotuzumab exposure quartile.

	N	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG score ≥ 2	Prior Treatment duration	Prior Stem Cell
Lenalidomide/Dexamethasone control	316	2.52	4.01	0.85	10%	50%	56%
Elotuzumab Q1	78	3.48	5.65	0.77	12%	45%	44%
Elotuzumab Q2	78	2.28	3.97	0.76	6%	47%	55%
Elotuzumab Q3	79	1.91	3.88	0.82	9%	65%	65%
Elotuzumab Q4	78	1.65	3.41	0.83	3%	46%	47%

Patients with lower exposure and higher risk factors appear to exhibit shorter PFS times.

Figure 2 shows Kaplan Meier (KM) curves for PFS as a univariate exposure-response analysis. As shown in **Figure 2**, patients in the lowest exposure quartile had about an 8 month shorter PFS duration than patients with higher elotuzumab exposure. However, this difference is not only due to exposures alone but also due to an imbalance in baseline risk factors among the four groups of exposure-quartile such that patients in the lowest quartile (Q1) are also sicker patients compared to the patients in Q2 to Q4 (**Table 6**).

Figure 2. Kaplan Meier (KM) curves for PFS by average concentration at steady state (Trial CA204004, ITT population).

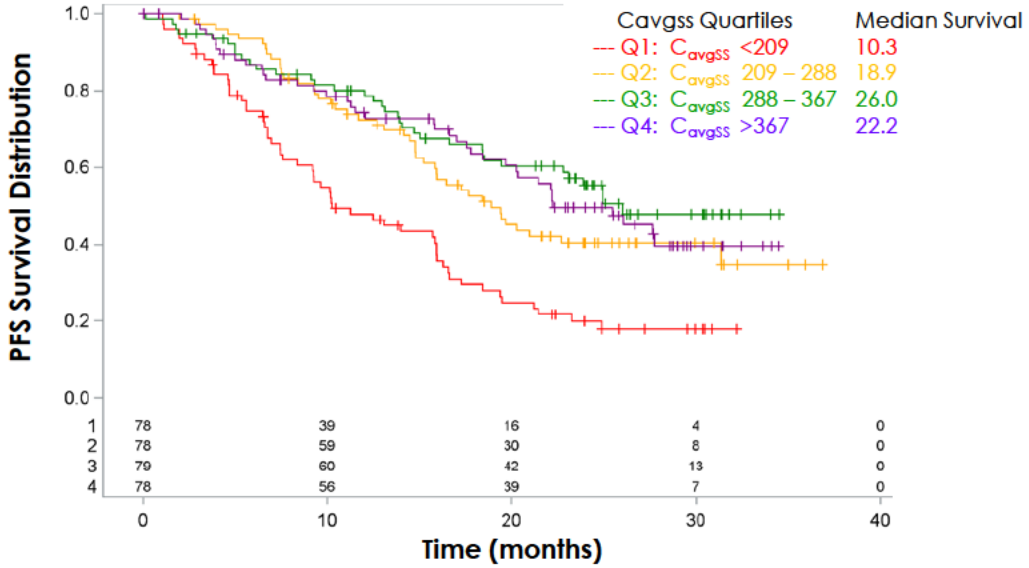
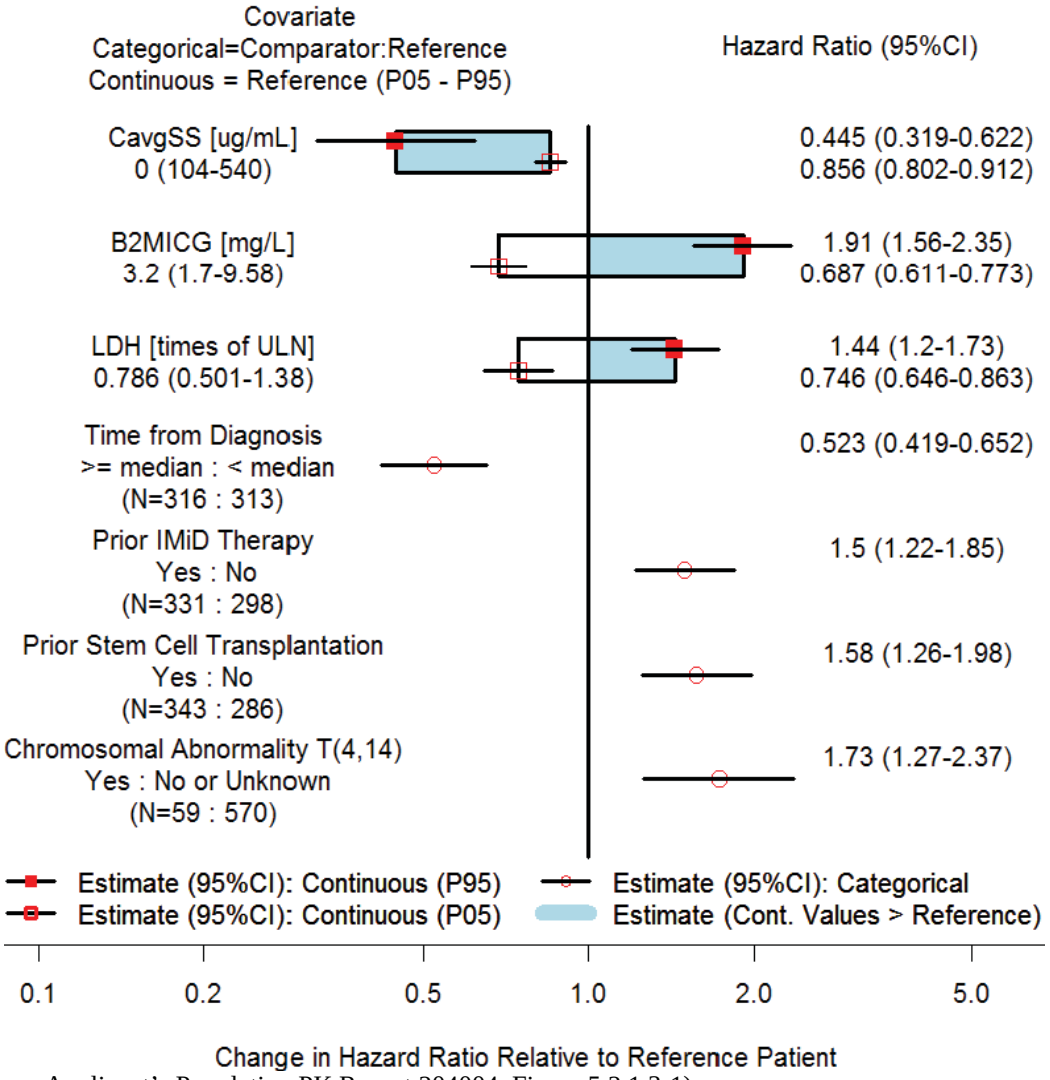


Figure 3 and **Table 5** show the final covariates and their impact on the PFS hazard ratio for the applicant's Cox proportional hazards model for PFS. Their multivariate analysis identified six factors in addition to elotuzumab exposure (β2-microglobulin, lactate dehydrogenase, prior treatment duration, prior immunomodulatory therapy, stem cell transplantation, and chromosomal abnormality) that need to be considered when evaluating the exposure response relationship for PFS. In **Figure 3**, for the continuous covariates, a box was used to connect the point estimates for the hazard ratios based on the 5th and 95th percentiles of the particular covariate. The shading in the box indicates a change from better to worse when compared to the reference.

Figure 3. Covariates identified by the applicant from their final exposure-PFS model that impact the hazard ratio for PFS



(Source: Applicant's Population PK Report 204004, Figure 5.2.1.3-1)

Figure 4 depicts the KM curves for the active control group and the lowest exposure quartile (elotuzumab Q1). Without matching the patient demographics, the PFS curve for the elotuzumab treated arm appears to do worse than for the active control. However, this is explained by the imbalance in the PFS risk factors identified in the applicant's multivariate model. Because of these imbalances, two case control analyses were performed to 1) subset the active control arm to match the demographics of the lowest exposure quartile and 2) to match the demographic characteristics of the highest three quartiles of exposure. **Table 7** and **Table 8** show the demographics before and after the match for both comparisons.

Figure 4. Kaplan-Meir Curves for Progression Free Survival for patients with low elotuzumab exposure (Q1) and patients in the Lenalidomide/Dexamethasone Arm.

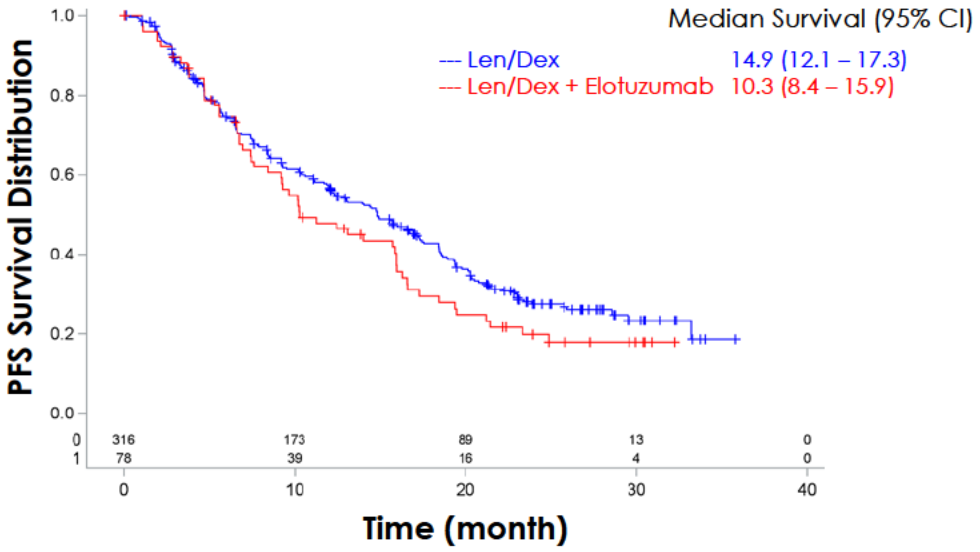


Table 7. Summary of risk factors for patients administered Lenalidomide/dexamethasone and Q1 elotuzumab exposure before and after matching for the case control analysis.

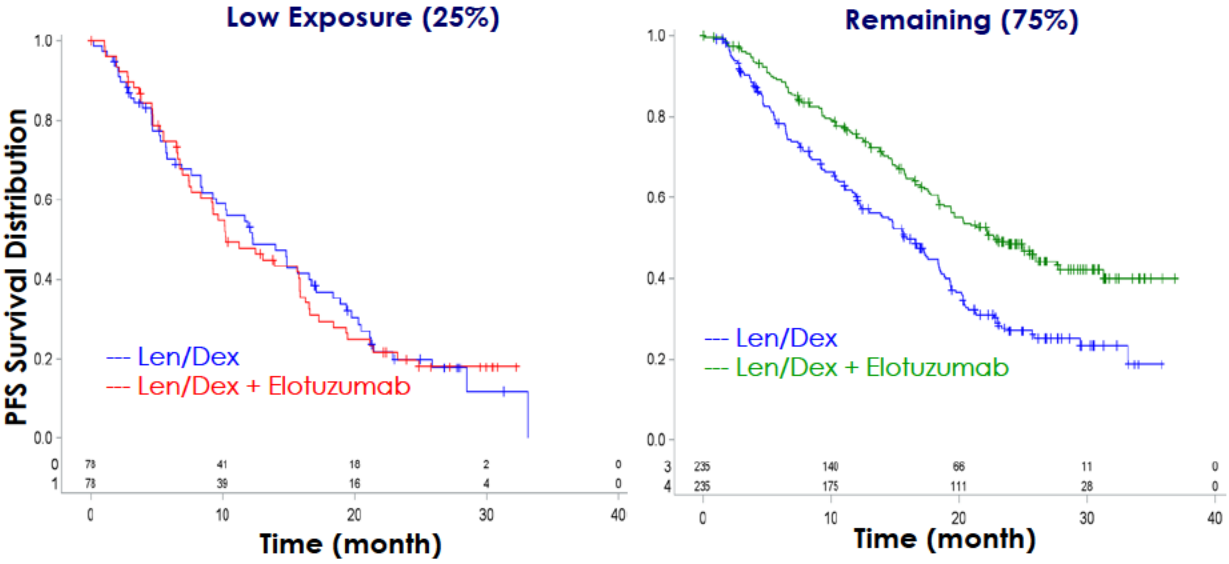
	N	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG score ≥ 2	Prior Treatment duration	Prior IMiD Therapy	Prior Stem Cell
Before Matching								
Lenalidomide/Dexamethasone control	316	2.52	4.01	0.85	10%	50%	54%	56%
Elotuzumab Q1	78	3.48	5.65	0.77	12%	45%	54%	44%
After matching								
Lenalidomide/Dexamethasone control	78	3.34	5.35	0.77	10%	44%	54%	42%
Elotuzumab Q1	78	3.48	5.65	0.77	12%	45%	54%	44%

Table 8. Summary of risk factors for patients administered Lenalidomide/dexamethasone and Q2 to Q4 elotuzumab exposure before and after matching for the case control analysis.

	N	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG score ≥ 2	Prior Treatment duration	Prior IMiD Therapy	Prior Stem Cell
Before Matching								
Lenalidomide/Dexamethasone control	316	2.52	4.01	0.85	10%	50%	54%	56%
Elotuzumab Q2 to Q4	235	1.95	3.75	0.80	6%	53%	51%	56%
After matching								
Lenalidomide/Dexamethasone control	235	2.16	3.68	0.81	7%	53%	52%	58%
Elotuzumab Q2 to Q4	235	1.95	3.75	0.80	6%	53%	51%	56%

After matching, the Kaplan Meier curves for the active control group are shown against the elotuzumab treated groups for the low exposure (**Figure 5**, left panel) and higher exposure (**Figure 5**, right panel) groups. At a sufficiently low exposure, it appears there is no treatment benefit. However in the highest three exposure groups there is about a 5 month difference between the two PFS curves.

Figure 5. Kaplan Meier curves for the active control group and the Q1 and Q2 to Q4 elotuzumab treated groups after case control analysis



As there is an inherent correlation between low exposure and high tumor burden/PFS risk factors, it is not possible to ascertain whether patients will benefit from a higher dose, from these data alone.
More details regarding the exposure-response analysis for efficacy are provided in the Pharmacometrics review in **Appendix 4.2.**

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

Exposure-response relationships for safety were evaluated relating C_{avgSS} to Grade 3+AE and AE leading to discontinuation or Death in Study CA204004. A Cox proportional hazard model did not find that an increase in Grade 3+ AE was related to increasing exposures. However, C_{avgSS} was related to AE leading to discontinuation/death in a counter-intuitive fashion. The model showed that an increase in C_{avgSS} resulted in a decrease in AE resulting to discontinuation or death.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The applicant evaluated the effects of elotuzumab on electrocardiogram (ECG) intervals, including corrected QT (QTc) intervals at doses of 10 and 20 mg/kg in Study CA204011. The applicant showed that the elotuzumab at 10 mg/kg or 20 mg/kg is unlikely to cause QTc prolongations. Refer to QT IRT Review in DARRTS (J. EARP 10/09/2015).

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

The dose selected was consistent with the known exposure-response relationship observed *in vitro* and in the Phase 2 studies. It is important to note that the exposure-response relationship showed that patients with elotuzumab exposures in the lower quartile of the exposures evaluated in Study CA204004, (C_{ssavg} < 209 µg/mL) performed as well as those that did not receive elotuzumab and worse than patients that had C_{ssavg} concentrations that fell in the first 3 quartiles. This relationship is confounded by baseline M-protein concentrations, but it is possible that patients with high protein levels and low exposures may benefit from higher exposures. Please see the Pharmacometrics review in **Appendix 4.2** for more details. A post-marketing commitment is recommended to address this issue (see **1.1 Post-marketing Commitments**)

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Elotuzumab PK data were obtained for doses ranging from 0.5 to 20 mg/kg. The PK parameters of elotuzumab after a single dose and after multiple doses are shown in **Table 9**.

Table 9: Summary of elotuzumab PK on after a Single Dose on Cycle 1 Day 1

Dose (mg/kg)		PK Parameters on Cycle 1 Day1					PK Parameters on Cycle 1 Day 28			
		Cmax (mg/L)	Tmax (hr)	AUClast (mg*L/hr)	T 1/2 (hrs)	AUC_{INF} (mg*L/hr)	Cmax (mg/L)	Tmax (hr)	AUClast (mg*L/hr)	Accumulation Index
0.5	N	3	3	2	2	2	2	2	2	2
0.5	Geometric mean	11.1	1.8	635.1	2.4	684.8	7.3	2.7	472.7	0.7
0.5	Mean	11.3	1.9	647.1	2.4	692.6	7.5	3.3	482.2	0.7
0.5	%CV	26.4	47.2	27.1	10.4	21.2	33.8	79.8	27.9	0.8
1	N	4	4	4	3	3	3	3	3	3
1	Geometric mean	17	1.5	1799.1	3.6	1425	21.5	1.9	2256.1	1.1
1	Mean	17.6	1.5	2036.8	3.8	1437.6	25.7	2	4153.3	1.3
1	%CV	27.5	1.1	63.7	43.1	15.8	77.3	40.9	128.6	82.3
2.5	N	6	6	6	6	6	3	3	3	3
2.5	Geometric mean	43.7	2.6	4725.2	4	5316.6	50.1	2.3	6881.3	1.2
2.5	Mean	45.2	2.7	5385.1	4.3	6347.3	50.1	2.7	7378.2	1.2
2.5	%CV	26.8	35.5	52.6	44.4	61.8	2.1	77.4	48.1	30.6
5	N	4	4	3	1	1	3	3	2	2
5	Geometric mean	86.9	4	14041.4	6.6	13730.3	154.1	3.7	24226.4	1.7
5	Mean	90.5	4.4	14422.4	6.6	13730.3	160.7	4.2	29522.7	1.8
5	%CV	30	38.3	28.4	NC	NC	36.7	50.2	80.8	49.7
10	N	2	3	3	2	2	2	2	2	2
10	Geometric mean	334.1	3.5	34442	4.6	27196.2	215	4.7	35325.1	1.5
10	Mean	337.4	4.1	40701.4	4.6	28540.9	216.6	4.8	36803.9	1.5
10	%CV	19.5	54.7	70.6	1.4	42.9	17.2	29.3	39.7	1.9
20	N	14	14	5	2	2	8	8	4	4
20	Geometric mean	404.9	5.6	64559.8	7.7	84204	553.3	4	124300.4	1.8
20	Mean	415.3	6.8	67092.8	7.8	86311.7	563	4.2	129264	1.8
20	%CV	21.7	93.3	30.2	4.2	31.1	20	33.9	32.1	20.5

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

All of the submitted PK data were collected in patients with cancer, therefore a PK comparison between healthy volunteers and patients cannot be conducted.

2.2.5.3 What are the characteristics of drug absorption?

Elotuzumab is formulated for intravenous administration.

2.2.5.4 What are the characteristics of drug distribution? (Include protein binding.)

The volume of distribution of elotuzumab after a single dose ranged from 3.0 to 5.9 L (**Table 9**). This volume is similar to the plasma volume in humans. Given elotuzumab's large size and hydrophilic nature, distribution to tissue and protein binding are unlikely.

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

Given that this is a monoclonal antibody, mass balance assessment was not conducted.

2.2.5.6 What are the characteristics of drug metabolism?

Elotuzumab is likely not metabolized via the hepatic pathway. For molecules with an Fc domain (including elotuzumab), binding of the Fc domain to Fc gamma-receptors typically results in the internalization and subsequent degradation of the molecule.

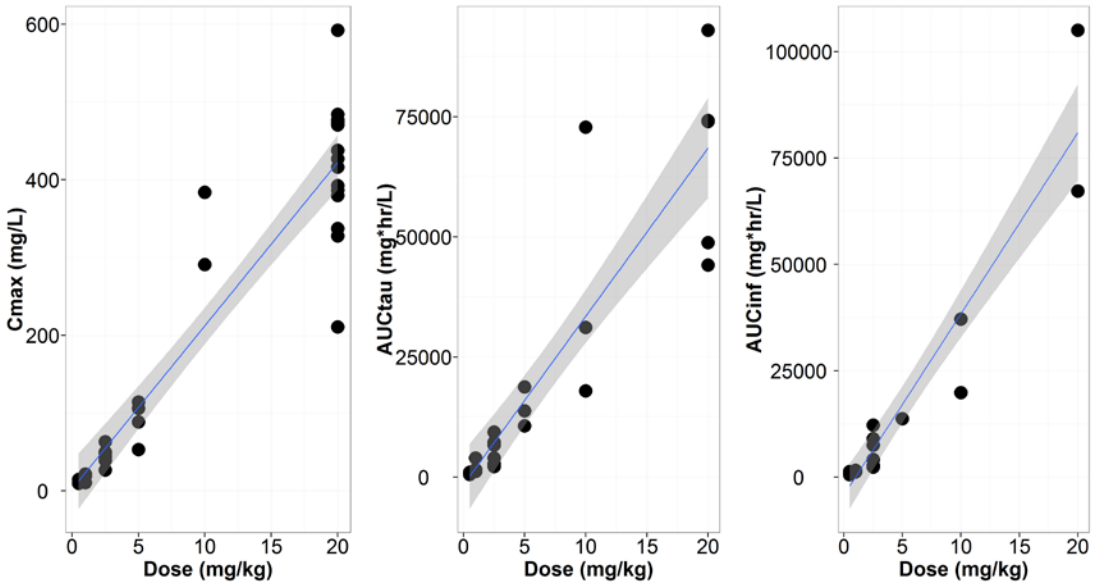
2.2.5.7 What are the characteristics of drug excretion?

Given that this is a monoclonal antibody, assessment of excretion was not conducted.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

After a single dose, there is a dose-proportional increase in Cmax over the range of doses studied (0.5 mg/kg to 20 mg/kg). The slope (95% CI) of the power model used to assess the dose-linearity for Cmax was 1.03 (0.955, 1.11). However, consistent with non-linear elimination observed with monoclonal antibodies and a saturation of the target-mediated elimination process, there was a greater than proportional increase in AUC and AUCinf across the doses evaluated. The estimate exponents (CI) for the power model used to evaluate dose-linearity were 1.23 (1.09, 1.38) for AUCtau and 1.25 (1.06, 1.44) for AUCinf. The relationships between dose and Cmax, AUCtau, and AUCinf are shown in **Figure 6** with the fitted power functions through the data.

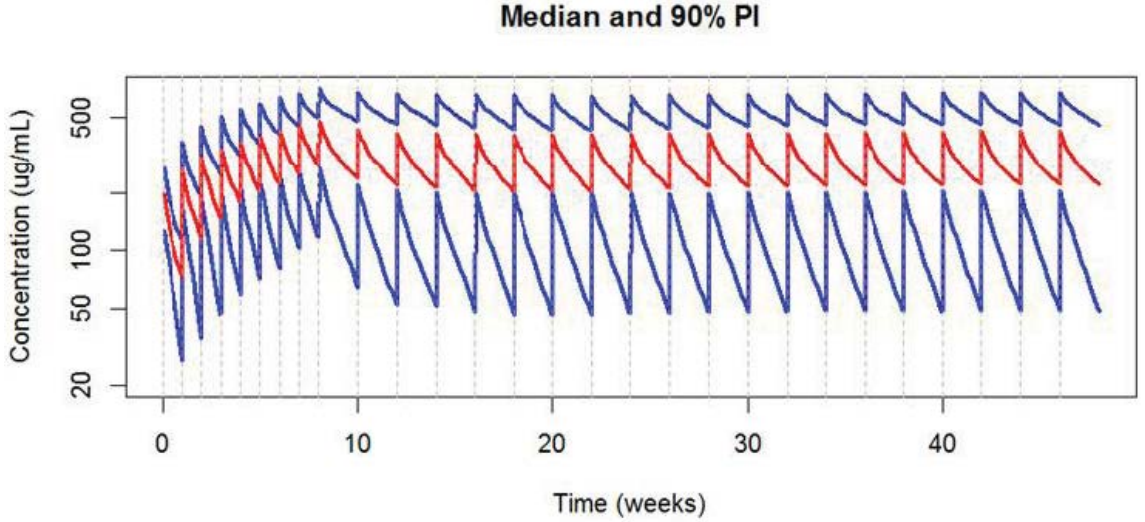
Figure 6. Relationship between Dose and Cmax, AUC_{tau}, and AUC_{inf} with the fitted power function through the data



2.2.5.9 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)

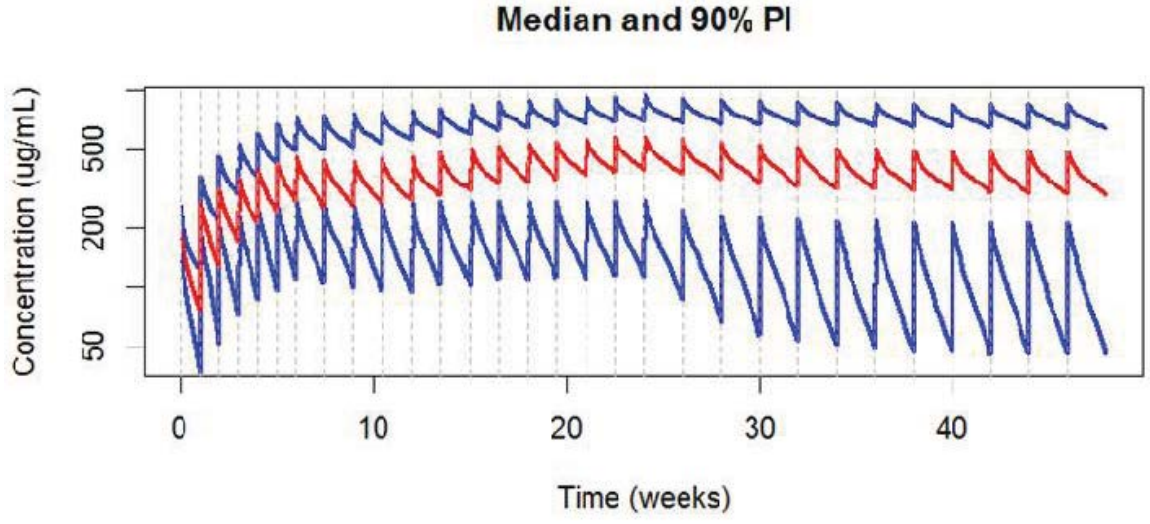
Given that elotuzumab undergoes target mediated clearance, the time to steady-state is dependent on the dose administered. As shown in **Figure 7**, simulations conducted using the population PK model and the dosing regimen evaluated in Study CA204004, (Elotuzumab 10 mg/kg QW for two 28-day cycles followed by Q2W administration) resulted in increasing drug concentrations for approximately 8 weeks after the start of elotuzumab dosing. As expected, drug concentrations decrease to steady state levels 2 to 4 weeks after switching to Q2W dosing.

Figure 7. Predicted Elotuzumab Concentration-Time Course Following 10 mg/kg Elotuzumab Administered QW for Two 28-day Cycles Followed by Q2W for Subsequent Cycles (Applicant's Analysis)



For patients dosed using the regimen evaluated in Study CA204009, (10 mg/kg QW for two 21-day Cycles followed by QW followed by Q10days for six 21-day cycles followed by Q2W for 28 Day cycles), simulations (**Figure 8**) predict that the more intensive initial dosing results in increasing drug concentrations for approximately 15 weeks after start of elotuzumab dosing as shown in **Figure 8**. While concentrations continue to rise slowly for another 9 weeks of Q10D dosing, as expected, the concentrations decrease back to values attained at 15 weeks after switching to Q2W dosing.

Figure 8. Predicted Elotuzumab Concentration-Time Course Following 10 mg/kg QW for two 21-day Cycles followed by Q10days for six 21-day cycles followed by Q2W for 28 Day cycles (Applicant's Analysis)



Using the population PK model, the elotuzumab concentration-time curve was simulated for a typical patient as a single agent, with lenalidomide/dexamethasone, and with bortezomib/dexamethasone, to compute the effective half-life and accumulation ratio, for 10 mg/kg QW dosing regimen. For patients given elotuzumab with lenalidomide/dexamethasone, AUC accumulation ratio was estimated to be 7.42, with the corresponding effective half-life of 33.5 days. For patients given elotuzumab with bortezomib/ dexamethasone, AUC accumulation ratio was estimated to be 9.41, with the corresponding effective half-life of 43.2 days. For elotuzumab monotherapy, the corresponding values were predicted to be 5.32 and 23.3 days, respectively. Effective half-life and accumulation ratio are similar for the combination regimens, and greater than for monotherapy. Data to confirm the hypothesis are lacking, but the induction of elotuzumab clearance by dexamethasone would explain the observed relationships.

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

The PK of elotuzumab was described using a two compartment model with zero order IV infusion, parallel linear and Michaelis-Menten elimination from the central compartment, and additional target-mediated elimination from the peripheral compartment. Distribution and non-specific linear elimination, with concomitant lenalidomide/ dexamethasone administration) were characterized by a rapid distribution phase with a typical distribution half-life of 1.4 days and a slow linear elimination phase with a typical elimination half-life of 49.3 days. The population PK parameter estimates and associated inter- and intra-individual PK variability are summarized in **Table 10**.

Table 10: Summary of Elotuzumab Population PK Results (Applicant's analysis)

Parameter		Value	% RSE	95% CI[a]	CV[b]	Shrinkage
Structural Parameters						
CL_{REF} (L/day)	$\exp(\theta_1)$	0.086	3.52	0.0803 - 0.0921	NA	NA
$V_{C, REF}$ (L)	$\exp(\theta_2)$	4.04	1.83	3.9 - 4.19	NA	NA
Q_{REF} (L/day)	$\exp(\theta_3)$	0.666	7.76	0.572 - 0.775	NA	NA
$V_{P, REF}$ (L)	$\exp(\theta_4)$	2.21	5.65	1.98 - 2.47	NA	NA
R_{MAX} (µg/mL)	$\exp(\theta_5)$	816	8.97	685 - 973	NA	NA
k_{int} (10^{-3}/day/(µg/mL))	$\exp(\theta_6)$	0.169	9.60	0.14 - 0.204	NA	NA
$V_{MAX, REF}$ (µg/mL/day)	$\exp(\theta_7)$	9.22	1.9	8.89 - 9.57	NA	NA
K_M (µg/mL)	$\exp(\theta_8)$	227	7.15	198 - 262	NA	NA
Covariate Effects Parameters						
CL_{WT}	θ_9	1.21	10.2	0.968 - 1.45	NA	NA
CL_{LenDex}	$\exp(\theta_{20})$	0.65	7.96	0.556 - 0.76	NA	NA
CL_{BorDex}	$\exp(\theta_{22})$	0.499	9.57	0.413 - 0.602	NA	NA
$V_{C,WT}$	θ_{10}	0.37	15.3	0.259 - 0.481	NA	NA
$V_{C,female}$	$\exp(\theta_{17})$	0.808	2.49	0.769 - 0.848	NA	NA
$V_{C,ASIAN}$	$\exp(\theta_{18})$	0.864	3.79	0.802 - 0.931	NA	NA
$V_{C,B2MICG>3.5}$	$\exp(\theta_{19})$	1.12	2.25	1.07 - 1.17	NA	NA
Q_{WT}	θ_{11}	0.75		Fixed	NA	NA
$V_{P,WT}$	θ_{12}	0.716	16.6	0.483 - 0.948	NA	NA
$V_{MAX,MCPROT}$ $(g/dL)^{-1}$	θ_{21}	0.178	2.82	0.168 - 0.187	NA	NA
Inter-individual Variability (IIV) Parameters						
ω^2_{CL}	$\Omega(1;1)$	0.0999	14.3	0.0719 - 0.128	31.6%	41.0%
ω^2_{VC}	$\Omega(2;2)$	0.0413	10.1	0.0331 - 0.0494	20.3%	12.4%
ω^2_{Q}	$\Omega(3;3)$	0.519	14.8	0.369 - 0.67	72.1%	36.1%
ω^2_{VP}	$\Omega(4;4)$	0.12	14.3	0.0862 - 0.153	34.6%	32.2%
ω^2_{RMAX}	$\Omega(5;5)$	0.174	23.3	0.0945 - 0.253	41.7%	45.3%
ω^2_{KINT}	$\Omega(6;6)$	1.78	12.9	1.33 - 2.22	133.3%	16.3%

Parameter		Value	% RSE	95% CI[a]	CV[b]	Shrinkage
ω^2_{VMAX}	Ω(7;7)	0.0001	NA	Fixed	1%	NA
ω^2_{KM}	Ω(8;8)	0.985	10.3	0.786 - 1.18	99.3%	16.3%
ω^2_{ε}	Ω(9;9)	0.191	8.83	0.158 - 0.224	43.7%	4.8%
Intra-individual Variability Model Parameters						
SD_L	θ_{13}	2.13	21.9	1.21 - 3.04	NA	NA
SD_H	θ_{14}	0.0981	7.07	0.0845 - 0.112	NA	NA
SD_{50} (μg/mL)	θ_{15}	8.23	28.5	3.63 - 12.8	NA	NA
$SD_{phase1,2}$	θ_{16}	0.703	5.7	0.624 - 0.782	NA	NA

Covariates (in addition to body weight) that reduced the inter-individual variability on clearance (CL) and central volume of distribution (VC) were incorporated into the final model. Body weight and the co-administration of lenalidomide and dexamethasone or bortezomib and dexamethasone were the main source of variability on the linear component of clearance (CL). Baseline body weight, female gender, Asian race, and baseline β2-microglobilin > 3.5 influenced the VC. These factors did not remarkably affect the overall exposure of elotuzumab. However, baseline serum M-protein level influenced the maximum rate of elimination from the central compartment (V_{MAX}) thus affecting elotuzumab exposure.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, 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 conducted a population PK analysis using data from 449 patients who were given elotuzumab as a single agent or in combination with lenalidomide and dexamethasone. The population PK model evaluated the impact of various intrinsic factors on the PK of elotuzumab. Patient covariates such as body weight, sex, age, race (Asian versus all other races), baseline values of albumin, eGFR, LDH, hepatic impairment, ECOG score, baseline β2-microglobilin, concomitant administration of lenalidomide/ dexamethasone, and concomitant administration of bortezomib/dexamethasone were evaluated in the model. As discussed in **Section 2.2.5.10**, baseline body weight influenced the linear component of clearance, the distributional clearance and volume of distribution of elotuzumab. This impact justifies the weight-based dosing proposed in the label. The administration of dexamethasone plus lenalidomide or bortezomib also decreased the linear component of clearance of elotuzumab resulting in higher exposures compared to when elotuzumab is administered alone. Given that elotuzumab is intended to be given with the combination of lenalidomide plus dexamethasone, and the efficacy studies were conducted as such, no impact on the safety and efficacy of elotuzumab is expected.

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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments are recommended for any specific populations.

2.3.2.1 Elderly

In the population PK analysis, age (range: 25 to 88 years) was did not significantly influence the disposition of elotuzumab.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The applicant has not conducted clinical studies with elotuzumab in pediatric patients and is exempt given that it received Orphan Drug Designation for the treatment of multiple myeloma on 09/01/2011.

2.3.2.3 Gender (Sex)

The population PK analysis identified that female subjects had a 19% lower central volume of distribution compared to male subjects. However, sex did not have a remarkable effect on drug exposure.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

The population PK analysis identified that Asian (Japanese) subjects had a 13% lower central volume of distribution compared to non-Asian subjects. However, race did not have a remarkable effect on drug exposure.

2.3.2.5 Renal impairment

Based on the population PK analysis, renal impairment did not have a significant impact on elotuzumab exposure. In Study CA204007, the PK of elotuzumab administered with lenalidomide and dexamethasone were evaluated in patients with normal renal function, severe renal function (CrCL < 30 ml/min not requiring dialysis), and end-stage renal function(ESRD) (requiring dialysis). As shown in **Table 11**, there is no significant difference in exposure between patients with normal renal function and patients with severe renal impairment or ESRD.

Table 11: Comparison of the Elotuzumab PK Parameters in by Renal Function (Applicant Analysis)

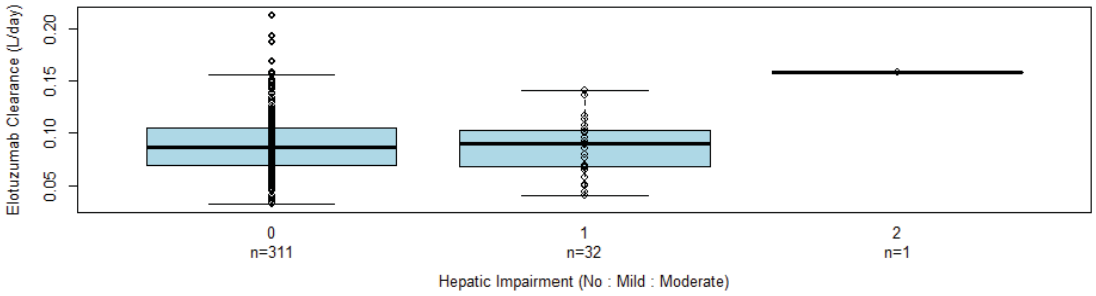
Renal Function Group and Comparison	**Adjusted Geometric Mean (90% CI)**		
	Cmax (µg/mL)	AUC(0-T) (µg•h/mL)	AUC(INF) (µg•h/mL)
NRF (n=8)	217 (192, 245)	39559 (32635, 47953)	46401 (36221, 59442)
SRI (n=7)	226 (198, 257)	50080 (40769, 61518)	60225 (46238, 78522)
ESRD (n=8)	218 (193, 246)	45937 (37896, 55684)	51227 (39310, 66756)
SRI vs NRF (%)	104 (87.0, 125) p=0.704	127 (95.5, 168) p=0.164	130 (90.4, 187) p=0.228
ESRD vs NRF (%)	100 (84.5, 119) p=0.965	116 (88.5, 152) p=0.355	110 (76.8, 159) p=0.642

Abbreviations: AUC(0-T) = Area under the serum concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF) = Area under the serum concentration-time curve from time zero extrapolated to infinite time; CI = confidence interval; Cmax = Maximum observed serum concentration; ESRD = end stage renal disease; NRF = normal renal function; SRI = severe renal impairment.

2.3.2.6 Hepatic impairment

Based on the population PK analysis, as shown in **Figure 9**, mild hepatic impairment had no significant impact on elotuzumab exposure. Patients with moderate to severe hepatic impairment were not included in the clinical trials.

Figure 9. Relationship between clearance and hepatic impairment



2.3.2.7 What pharmacogenetics information is there in the application and is it important or not

No pharmacogenetic information was included in the application.

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

The effect of elotuzumab in lactating and pregnant women has not been evaluated. Given that elotuzumab is intended to be administered with lenalidomide (b) (4) drugs believed to cause fetal harm, patients should avoid pregnancy while taking elotuzumab.

2.3.3 Immunogenitiсy. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA), including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule.

Patients were tested for anti-drug antibodies (ADAs) in all clinical trials. As shown in **Table 12**, 95 patients developed ADA during the studies. It is important to note that a majority of the ADA developed were transient and disappeared within a few months. A total of 30 subjects (19 in Study CA2040004) developed neutralizing anti-drug antibodies.

Table 12. Summary of Immunogenicity Results

ADA Status	Elotuzumab dose	
	10 mg/kg (N=390)[a]	5 to 20 mg/kg (N=521)[b]
Baseline ADA-positive	9 (2.3)	15 (2.88)
On-Study ADA-positive	72 (18.5)	95 (18.2)
Persistent Positive	2 (0.5)	8 (1.54)
Last Sample Positive	16 (4.1)	18 (3.45)
Other Positive	54 (13.9)	69 (13.2)
Nab-positive	19	30[c]

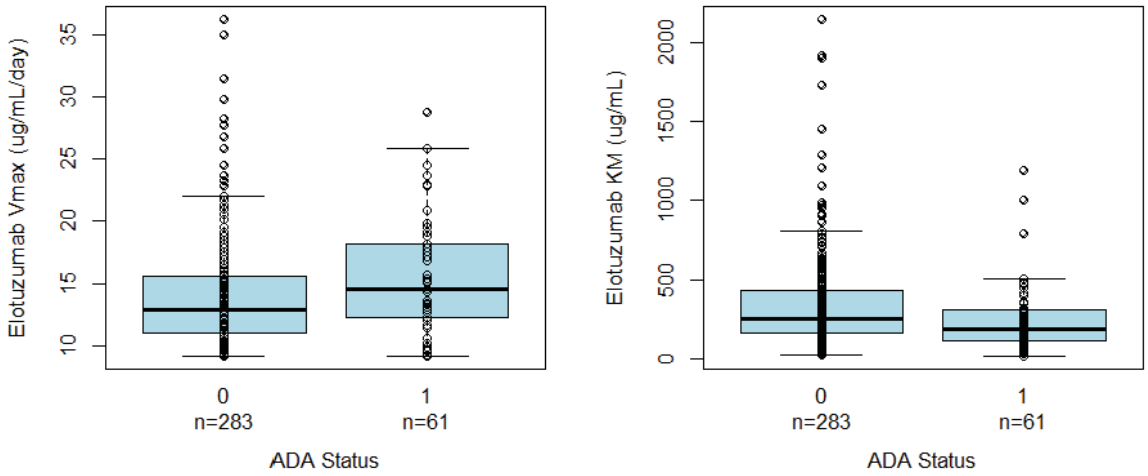
a. Elotuzumab with Len/Dex or Bort/Dex (Studies CA204004, CA204005, CA204007, CA204009)
b. Studies (CA204004, CA204005, CA204007, CA204009, CA204011, HuLuc63-1703)
c. Neutralizing antibody characterized in Study CA204004 (19) and HuLuc63-1703 (11). HuLuc63-1703 was assessed using a different precise assay

Please refer to the CMC immunogenicity review for more information regarding the immunogenicity assays.

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

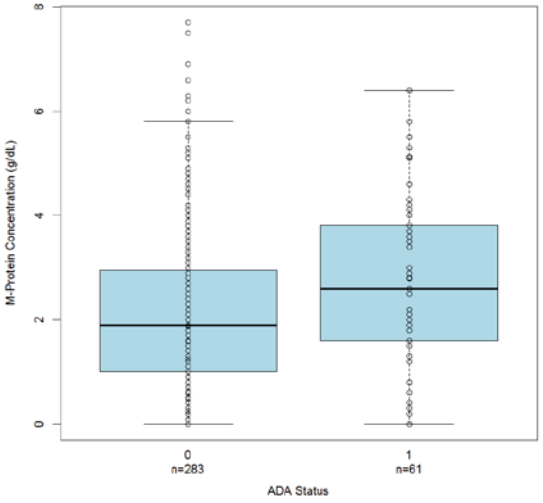
In the population PK model, the impact of ADA was assessed on drug exposure. As shown in **Figure 10**, post-hoc evaluation of the PK parameter estimates showed that subjects with positive ADA status had higher Vmax and lower Km than subjects with negative ADA status.

Figure 10. Relationship between ADA status and Elotuzumab Vmax and KM



The relationships between ADA status and Vmax and Km were confounded by the association of high baseline M-protein concentrations with positive ADA status (**Figure 11**) and also by the association of high baseline M-protein concentrations and low clearance. As a result of these confounding relationships, the impact of ADA on exposure could not be reliably assessed. However, given the transient nature of the ADA development, it is unlikely that it would have a remarkable impact on the PK of elotuzumab.

Figure 11. Relationship between M-protein Concentration and ADA Status



2.3.3.2 Do the anti-product antibodies have neutralizing activity?

See response to **Question 2.3.3**.

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

ADA did not have an effect on clinical efficacy.

2.3.3.4 What is the impact of anti-product antibodies on clinical safety?

ADA did not have an effect on clinical safety.

2.3.3.5 Other human factors that are important to understanding the drug's efficacy and safety

There are no other known human factors that are important to understanding of elotuzumab's safety and efficacy.

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 applicant did not submit results from specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet, smoking or alcohol use on the PK, safety, or efficacy of elotuzumab.

2.4.2 Drug-drug interactions

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

No. Elotuzumab is a monoclonal antibody. As such, it is not metabolized via the CYP enzymes and common metabolism pathways that are susceptible to drug-drug interactions.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No.

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

No.

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

No.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No experiments were conducted in metabolic or transporter systems.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Elotuzumab is intended to be administered with lenalidominde/dexamethasone (b) (4) As shown in **Table 10**, the population PK model showed that the administration of elotuzumab with lenalidomide/dexamethasone (b) (4) resulted in a 35% (b) (4) decrease in the nonspecific (linear) clearance of elotuzumab. This results in an increase in elotuzumab exposure when given with lenalidomide/dexamethasone (b) (4), compared to when given alone. This interaction is likely due to dexamethasone, an immunosuppressant that has been known to decrease the clearance of other antibodies. Given that elotuzumab is intended to be administered (b) (4) (b) (4) for efficacy and the exposure-response evaluation was conducted using data (b) (4) are not clinically relevant.

2.4.2.7 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?

See **Question 2.4.2.6**

2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

See **Question 2.4.2.6**

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no unresolved issues or significant omissions related to extrinsic factors.

2.5 General Biopharmaceutics

Elotuzumab is formulated for intravenous administration. As such, solubility, permeability, and dissolution issues will not influence the exposure to elotuzumab.

2.6 Analytical Section

PK samples to measure elotuzumab samples from studies HuLuc63-1701, HuLuc63-1702, and HuLuc63-1703 were analyzed using a ligand binding assay (LBA) using an ELISA platform validated by PDL BioPharma, Inc (SOP-30-0592_00). This assay was optimized and used to analyze serum samples for elotuzumab concentrations from studies CA204004, CA204005, CA204007, CA204009, and CA204011 (TLIAM-0180). Details of the assays are provided in **Table 13**. While each assay alone was acceptable, with greater variability in the SOP 30-0592_00 assay, the cross-validation criteria for the TLIAM-0180 assay to the SOP 30-0592_00 was not met with the SOP 30-0592_00 assay results being consistently higher than the TLIAM-0180 assay results for the QC samples and consistently lower for the pooled patient samples. As such, the PK results from Studies HuLuc63-1701, HuLuc63-1702, and HuLuc63-1703 need to interpreted with some caution when making comparisons to the PK results from studies CA204004, CA204005, CA204007, CA204009, and CA204011.

Table 13. Bioanalytical Methods for Elotuzumab concentrations

Validated Method	SOP 30-0592_00	TLIAM-0180
Detector	(b) (4)	
Regression Model Weighting		
Cross Validated to		
Standard Curve		
LLOQ (ng/mL)		
ULOQ (ng/mL)		
QC Precision Serum(%CV)		
Intra Assay		
Inter Assay		
QC Accuracy Serum (%Dev)		
QC Precision Plasma(%CV)		
Intra Assay		
Inter Assay		
QC Accuracy Plasma (% Dev)		
Stability (Serum)		
RT		
Refrigerated		
Freeze/Thaw		
-80C		
Stability (Plasma)		
RT		
Refrigerated		
Freeze/Thaw		
-80C		

Studies in which used	HuLuc63-1701, HuLuc63-1702, HuLuc63-1703	CA204004, CA204005, CA204007, CA204009, CA204011

Details of the assays used to measure anti-elotuzumab antibodies are provided in **Table 14**. Further details regarding the assay can be found in the CMC immunogenicity review.

Table 14. Bioanalytical Methods for Anti-Elotuzumab Antibodies

Validated Method	SOP 30-0621_00	TLIAM-0183	SOP 30-0692_00	MTHD15936.2
Species and Matrix	(b) (4)			
Analyte				
Testing				
Positive Control				
Sensitivity(ng/mL)				
Drug Tolerance				
Studies in which Method was Used	"HuLuc63-1701 HuLuc63-1702 HuLuc63-1703"	CA204004, CA204005, CA204007, CA204009, CA204011	HuLuc63-1701, HuLuc63-1702, HuLuc63-1703	CA204004

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested clinical pharmacology changes to the proposed labeling are shown in underline text and removal of content is shown by ~~strikethroughs~~. Labeling negotiations are currently ongoing and a final label has not been agreed upon by the Applicant and the Agency as of the date of this review.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to EMPLICITI.

Of 390 patients across four clinical studies who were treated with EMPLICITI and evaluable for the presence of anti-product antibodies, 72 patients (18.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 19 of 299 patients in Study 1. In the majority of patients, immunogenicity occurred early in treatment and was transient, resolving by 2 to 4 months.

(b) (4)

7 DRUG INTERACTIONS

(b) (4)

Laboratory Test Interference

Comment [A1]: To Applicant: No changes are noted. The items are not actionable , therefore, these were deleted.

(b) (4)

Comment [A2]: To Applicant: No changes are noted. The items are not actionable , therefore, these were deleted.

12.2 Pharmacodynamics

Cardiac Electrophysiology

EMPLICITI does not prolong the QT interval to any clinically relevant extent

(b) (4)

Comment [A3]: To Applicant: This was revised because this level of detail is unnecessary for this section when the QT studies are negative.

12.3 Pharmacokinetics

(b) (4)

–Elotuzumab exhibits nonlinear pharmacokinetics (b) (4)

target-mediated clearance,– (b) (4)

he administration of the recommended 10 mg/kg EMPLICITI treatment regimen in combination with lenalidomide/dexamethasone is predicted to resulted in geometric mean (CV%) steady-state trough concentrations of 194 (b) (4) 52%) (b) (4)

Elimination: The clearance of elotuzumab decreased from a mean (CV%) of 17. (b) (4) %) to 5. (b) (4) 31%) mL/day/kg with an increase in dose from 0.5 (i.e., 0.05 times the recommended dosage) to 20 mg/kg (i.e., 2 times the recommended dosage) (b) (4)

Based on a (b) (4) population PK model, when given in combination with lenalidomide and dexamethasone, (b) (4)

approximately 97% of the maximum steady state concentrations is predicted to be eliminated in a mean (CV%) of 82.4 (b) (4) 48%) days (b) (4)

Specific Populations

Clinically significant differences were not observed in the pharmacokinetics of elotuzumab based on age (37-88 years), gender, race, baseline LDH, albumin concentration, renal impairment ranging from mild to severe (creatinine clearance (CLcr) 15 to 89 mL/min) renal impairment, end-stage-renal disease (CLcr less than 15 mL/min) with or without hemodialysis, and mild (NCI-CTEP) hepatic impairment. The pharmacokinetics of elotuzumab in patients with moderate to severe hepatic impairment is unknown.

Body weight:- (b) (4) The clearance of elotuzumab increased with increasing body weight supporting a weight-based dose.

(b) (4)

(b) (4)

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 Proposed labeling (Original and Annotated)

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4.2 Pharmacometric Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

1.1.1 Is there value in optimizing the dose for improved efficacy in patients with lower exposure with the proposed dosing regimen?

Yes.

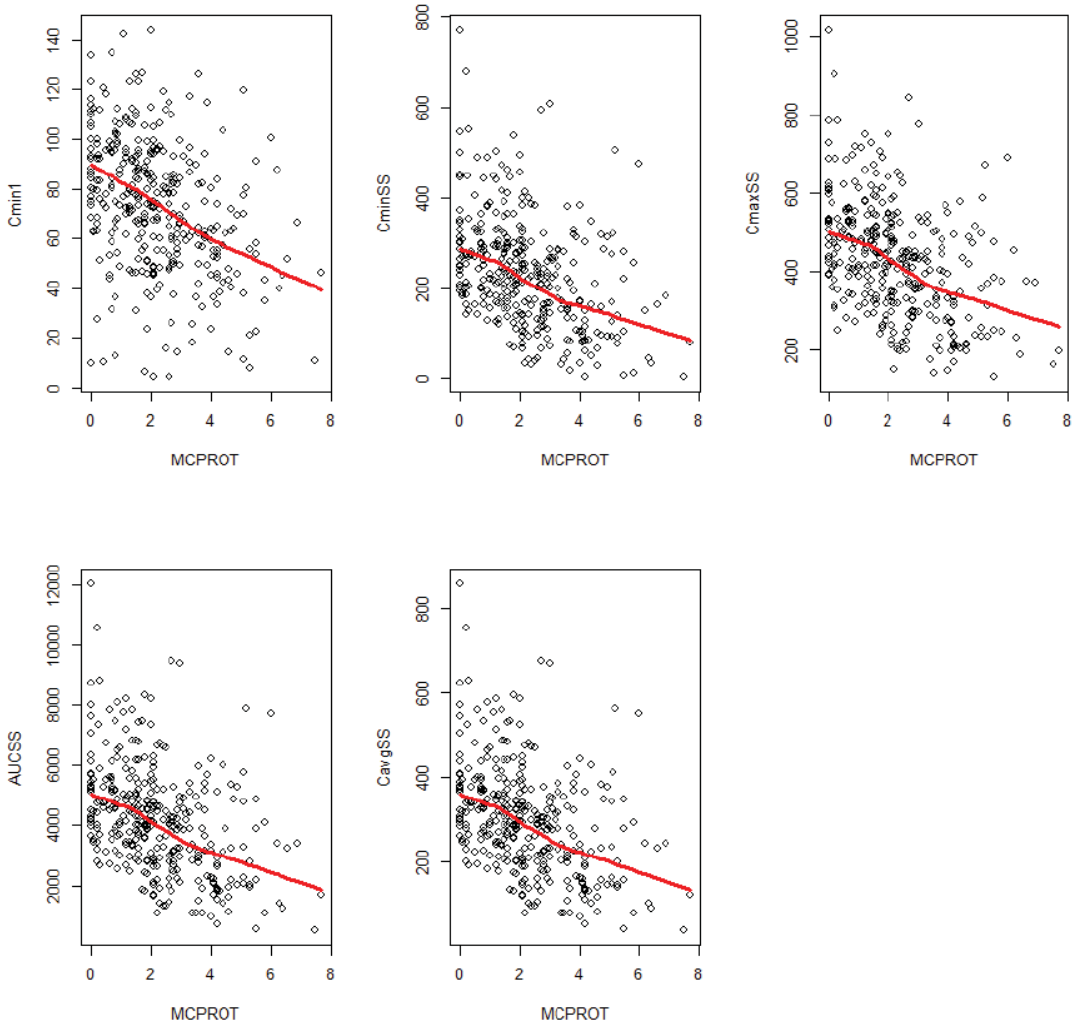
- The target-mediated clearance mechanism for elotuzumab suggests that patients with higher tumor burden may clear the drug faster
- There is a clear relationship between PFS and elotuzumab exposure, even after accounting for potential confounding factors such as β2-microglobulin, M-protein, lactate dehydrogenase, ECOG score, prior treatment duration, prior immuno-modulatory therapy, and prior stem cell transplantation. Additionally, Multiple Myeloma (MM) patients in Trial CA204004 with low exposure appeared show no improvement compared to the active control arm (lenolidamide/dexamethasone), whereas patients with high exposure show about a 5 month benefit in the median Progression-Free Survival (PFS) duration compared to the active control.

The analyses consistently suggest benefit in PFS with higher exposure after controlling for baseline risk factors. It is worth noting that even though the lack of benefit in patients with lower exposures (Cavgss < 209 μg/mL) was based on comparison of two treatments (25% patients with lower exposures in the Elotuzumab arm and matched patients from the LenDex arm) with similar baseline risk factors, the relationship between exposure and response could still be influenced by the specific distribution of risk factors across the four subgroups. For such an exposure-response relationship to be valid (higher exposure leading to better PFS), one has to make the assumption that this relationship is the same under any combination of those risk factors because of the unbalanced distributions of the risk factors across these four subgroups. Therefore, it is not possible to conclude with the current data, that patients with lower exposures who are also sicker patients, can have additional benefit with an increase in dose.

Patients with higher m-protein exhibit higher clearance of elotuzumab.

Based on the applicant's population PK analysis patients with higher M-protein concentrations clear the drug faster and therefore have lower exposure. Figure 1 demonstrates the correlation between the applicant's metrics of elotuzumab exposure and the patient's baseline M-protein concentrations. This correlation is consistent with the mechanism of action of the drug, whereas elotuzumab binds the multiple myeloma cells and attracts the natural killer cell to destroy the cell, clearing the drug along with it. Therefore with a higher tumor burden and higher M-protein it might be expected that clearance of the drug is greater.

Figure 1. Elotuzumab exposure versus baseline serum M-protein (g/dL) following 10 mg/kg elotuzumab administered QW for two 28-day cycles followed by Q2W for subsequent cycles.



(Source: Applicant's Population PK Study Report, CA204004, Figure 5.1.5.4-3)

M-protein levels for each group are shown in Table 1 indicating that M-protein potentially confounds the analysis for PFS. As expected, M-protein is higher in the lowest exposure quartile, but that also leads to the observation that other PFS risk factors are higher in the lowest exposure quartile. M-protein accounts for roughly 50% of the exposure difference between Q1 and Q2. This is also consistent with the modest correlation between exposure and M-protein such

that such that M-protein alone cannot be used to select patients with lower exposures. Additionally after the case control analysis that matches for m-protein, the exposure benefit appears to remain. Therefore, evaluating a higher dose based on low exposure rather than M-protein may appear to be appropriate.

Table 1. Patient characteristics related to PFS risk and elotuzumab clearance for the active control group and each elotuzumab exposure quartile.

	N	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG Score ≥ 2	Prior Trt Duration	Prior Stem Cell
Lenolidamide/Dex Control	316	2.52	4.01	0.85	10%	50%	56%
Elotuzumab Q1	78	3.48	5.65	0.77	12%	45%	44%
Elotuzumab Q2	78	2.28	3.97	0.76	6%	47%	55%
Elotuzumab Q3	79	1.91	3.88	0.82	9%	65%	65%
Elotuzumab Q4	78	1.65	3.41	0.83	3%	46%	47%

Patients with lower exposure and higher risk factors appear to exhibit shorter PFS times.

Figure 2 shows Kaplan Meier (KM) curves for PFS a univariate exposure-response analysis. Based on this plot patients in the lowest exposure quartile had about an 8 month shorter PFS duration that patients with higher elotuzumab exposure. However, as indicated below, this difference is not only due to exposures but also due to imbalance in baseline risk factors among the four groups of exposure-quartile such that patients in the lowest quartile (Q1) are also sicker patients compared to the patients in Q2-Q4 (Table 1).

Figure 2. Patients with the lowest exposure (<209 µg/mL) had ~8 months shorter PFS than patients with higher elotuzumab exposure (Trial CA204004, ITT population).

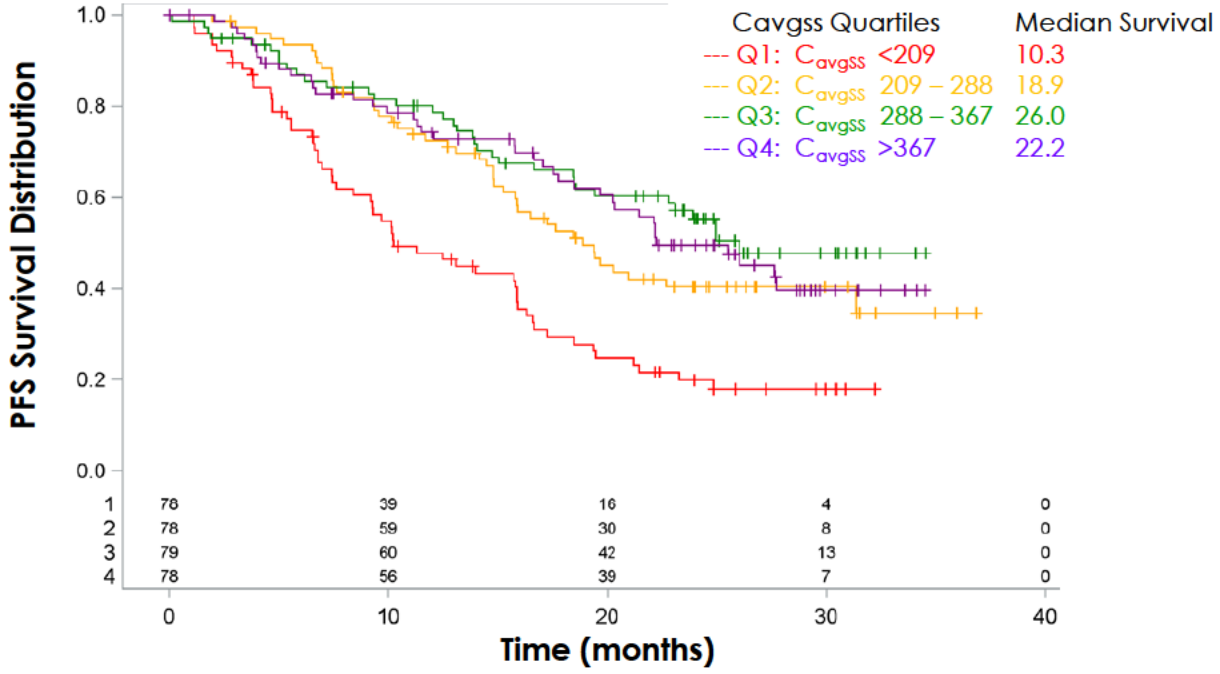
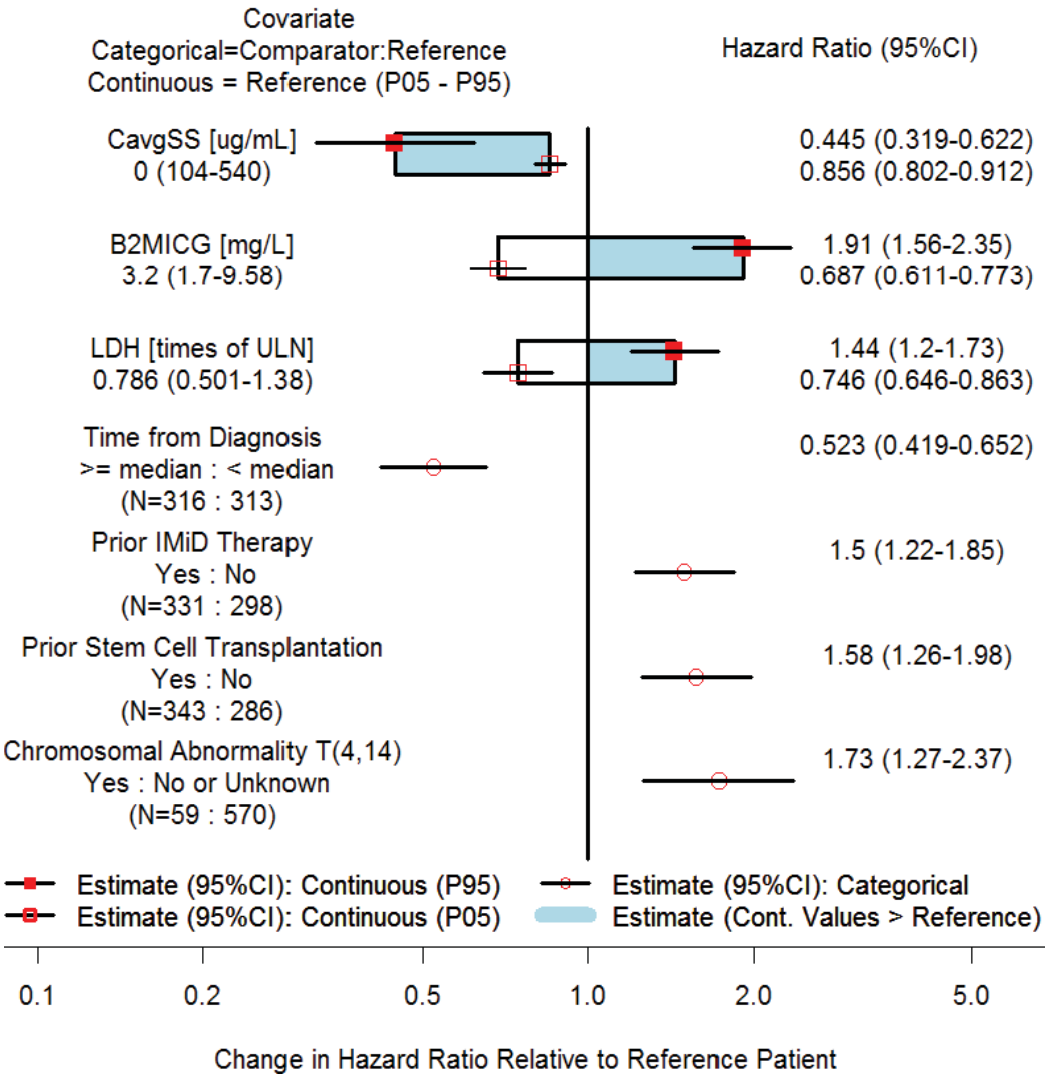


Figure 3 shows the final covariates and their impact on the PFS hazard ratio for the applicant's Cox proportional hazards model for PFS. Their multivariate analysis identified six factors in addition to elotuzumab exposure (b2-microglobulin, lactate dehydrogenase, prior treatment

duration, prior immunomodulatory therapy, stem cell transplantation, and chromosomal abnormality) that need to be considered when evaluating the exposure response for PFS. For the continuous covariates a box was used to connect the point estimates for the hazard ratios based on the 5th and 95th percentiles of the particular covariate. The shading in the box simply indicates a change from better to worse when compared to the reference.

Figure 3. Covariates identified by the applicant from their final exposure-PFS model that impact the hazard ratio for PFS.



(Source: Applicant's Population PK Report 204004, Figure 5.2.1.3-1)

Figure 4 depicts the KM curves for the active control group and the lowest exposure quartile. Without matching the patient demographics, the PFS curve for the elotuzumab treated arm appears to do worse than for the active control. However, this is explained by the imbalance in the PFS risk factors identified in the applicants multivariate model. Because of these imbalances two case control analyses were performed to 1) subset the active control arm to match the demographics of the lowest exposure quartile and 2) to match the demographic characteristics of the highest three quartiles of exposure. Table 2 and Table 3 show the demographics before and after the match for both comparisons.

Figure 4. Without matching patient demographics, patients with low exposure appear to have a shorter PFS time than the active control arm.

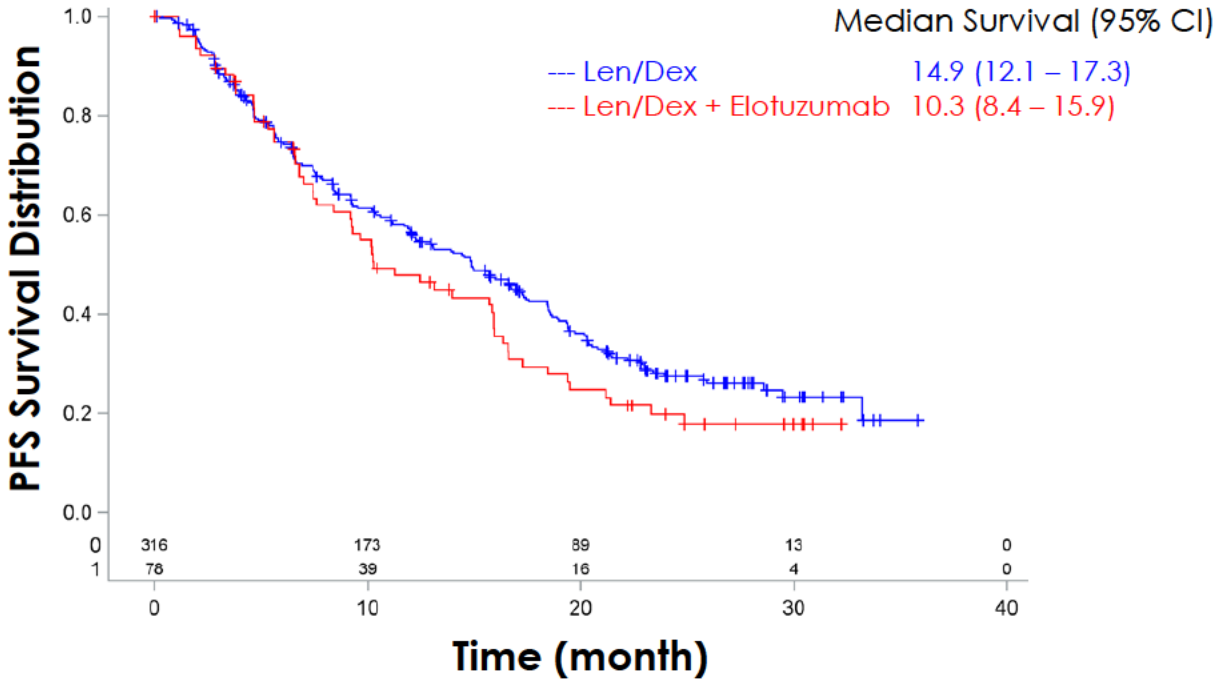


Table 2. Case control analysis Matched additional risk factors beyond elotuzumab exposure (Active control matched to Q1).

Before Matching: Len/Dex Control (n=316) to Q1 (n=78)

Demographic	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG Score ≥ 2	Prior Trt Duration	Prior IMiD Therapy	Prior Stem Cell
Len/Dex	2.52	4.01	0.85	10%	50%	54%	56%
Q1	3.48	5.65	0.77	12%	45%	54%	44%

After Matching: Len/Dex Control (n=78) to Q1 (n=78)

Demographic	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG Score ≥ 2	Prior Trt Duration	Prior IMiD Therapy	Prior Stem Cell
Len/Dex	3.34	5.35	0.77	10%	44%	54%	42%
Q1	3.48	5.65	0.77	12%	45%	54%	44%

Table 3. Case control analysis Matched additional risk factors beyond elotuzumab exposure (Active control matched to Q2-Q4 pooled).

Before Matching: Len/Dex Control (n=316) to Q2-Q4 Combined (n=235)

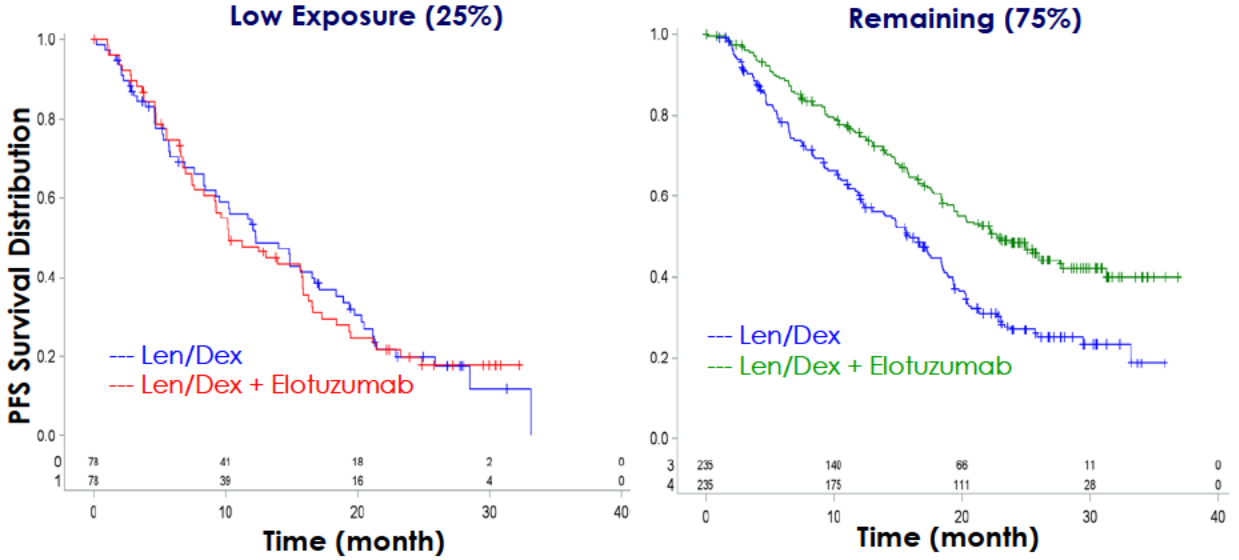
Demographic	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG Score ≥ 2	Prior Trt Duration	Prior IMiD Therapy	Prior Stem Cell
Len/Dex	2.52	4.01	0.85	10%	50%	54%	56%
Q2-Q4	1.95	3.75	0.80	6%	53%	51%	56%

After Matching: Len/Dex Control (n=235) to Q2-Q4 Combined (n=235)

Demographic	M-Protein (g/dL)	β2-microglobulin (mg/L)	LDH/ULN	ECOG Score ≥ 2	Prior Trt Duration	Prior IMiD Therapy	Prior Stem Cell
Len/Dex	2.16	3.68	0.81	7%	53%	52%	58%
Q2-Q4	1.95	3.75	0.80	6%	53%	51%	56%

After matching, the Kaplan Meier curves for the active control group are shown against the elotuzumab treated groups for the low exposure (Figure 5, left panel) and higher exposure (Figure 5, right panel) groups. At a sufficiently low exposure, it appears there is no treatment benefit. However in the highest three exposure groups there is about a 5 month difference between the two PFS curves.

Figure 5. Exposure-response is evident despite adjusting for other PFS risk factors.



As there is an inherent correlation between low exposure and high tumor burden/PFS risk factors, it is not possible to ascertain whether patients will benefit from a higher dose, from these data alone.

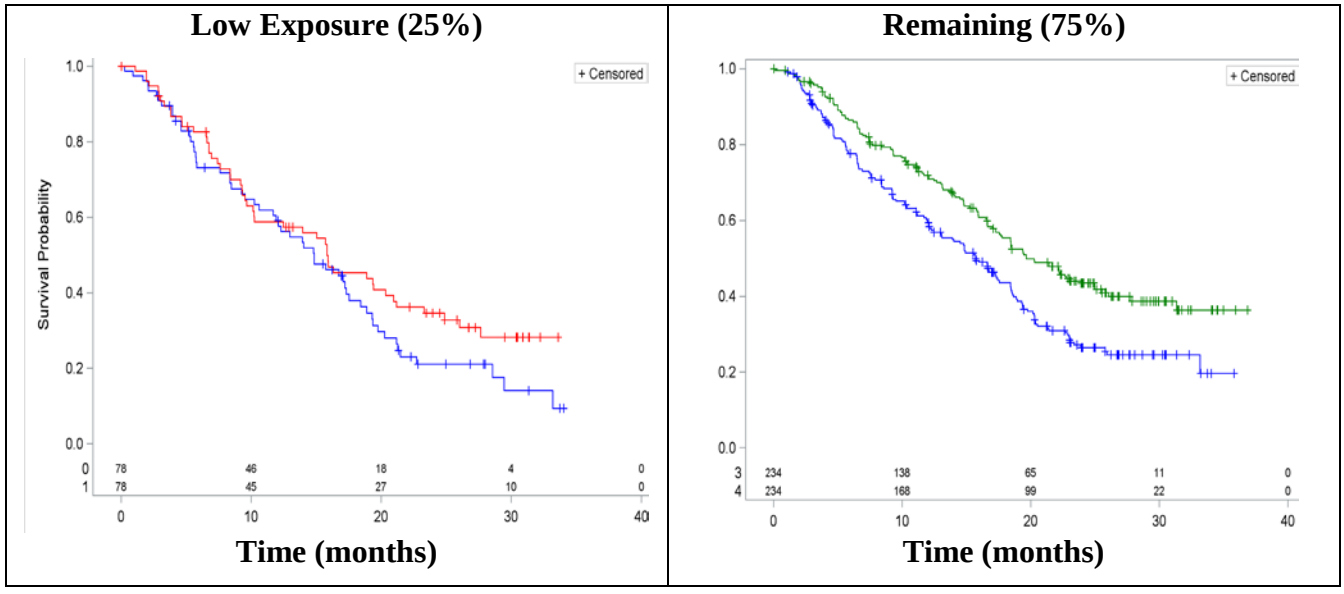
The applicant was informed about this analysis and they suggested use of the phase 2 study to gain additional evidence from the 20 mg dose evaluated in the same patient population with lenolidamide/dexamethasone background therapy as in trial 204004. The applicant's case control analysis and conclusions surrounding the phase 2 data are discussed further in Section 3.2.2.

Presently, the applicant has completed enrollment for another trial (CA204006) in treatment naive multiple myeloma patients. Based on the above analysis we are recommending as a PMC that this analysis be conducted for trial CA204006. If this trend holds true for different population, then we will engage applicant to do future trial(s) for dose optimization. One practical complication that arises with conducting such a trial is that we cannot identify these patients without measuring elotuzumab exposure. Gaining additional analysis from trial CA204006 may provide additional insight into identifying these patients, prior to designing a dose-optimization trial. As part of this review, an additional sensitivity analysis with a different exposure-metric was also evaluated but the results are unchanged. This is described further in Section 1.1.2.

1.1.2 Does the same relationship hold true if a PK exposure measure from Cycle 1 is used as the exposure metric?

Yes, changing the exposure metric from Cavg at steady-state to the exposure metric from cycle 1 using raw data instead of the population PK model gives a similar finding. A sensitivity analysis was performed to determine based on the raw observed concentrations whether correlations identified in the population PK model with other PFS risk factors might influence the evaluation of the exposure response. The same approach as in Section 1.1.1was taken. However the exposure metric for Cycle 1 is the average of the predose, 30 minute post dose, and 2 hr observed concentrations. The results of the case control analysis are shown in Figure 6 and suggest that patients in Q1 do not appear to show benefit compared to similarly matched control subjects while patients in the higher exposure groups (Q2-Q4) exhibit a treatment difference when compared with the control group. Further details of this analysis are described in Section 4.4.2.

Figure 6. Case-control matching analysis using Cycle 1 exposure metric. Blue lines depict the PFS for the subset of Lenolidamide/Dexamethasone control subjects that match the respective exposure groups. The red line indicates the PFS KM curve for subjects with the lowest quartile of exposure. The green line indicates the PFS KM curve for the remaining 75% of subjects treated with elotuzumab. PFS benefit appears to be nominally greater for lower exposures, and somewhat diminished for higher exposure quartiles.



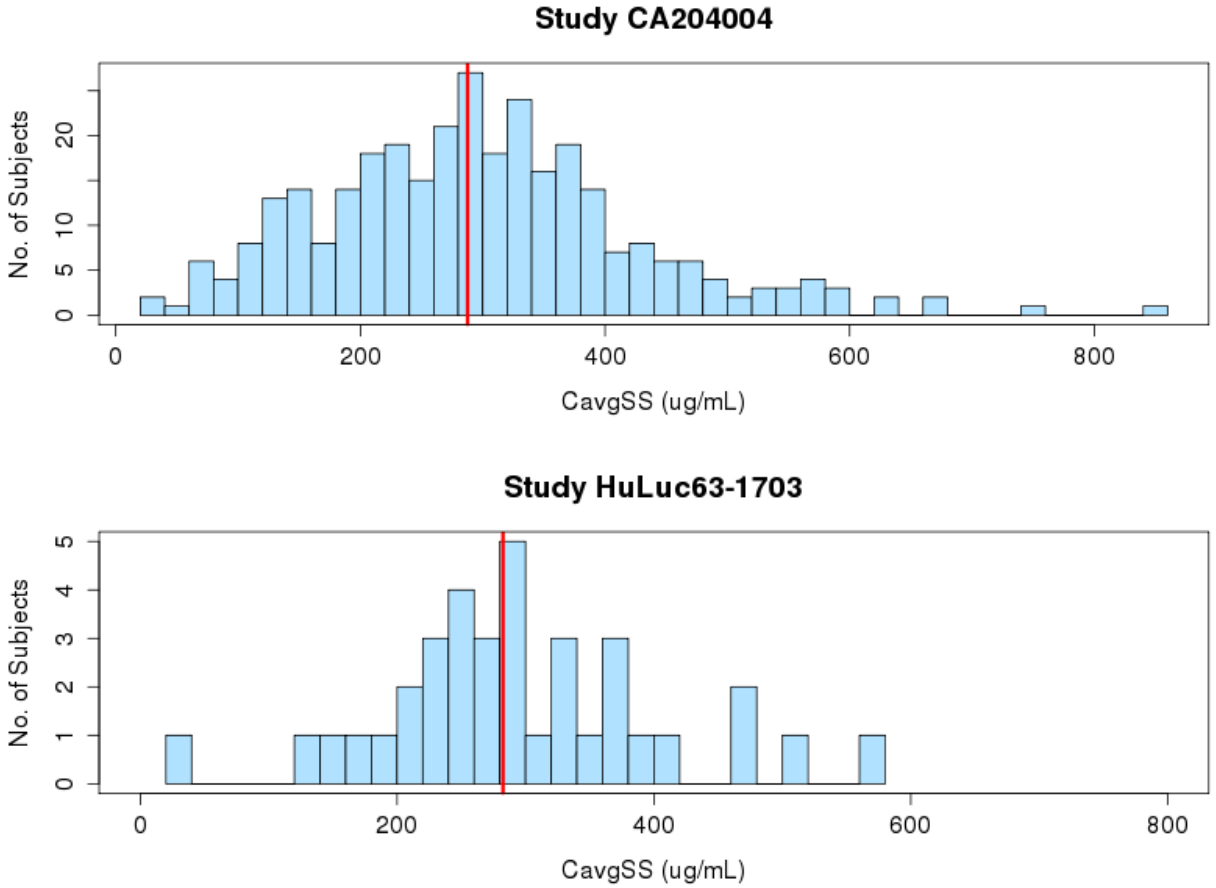
1.1.3 Can the phase 2 data from study huluc63-1073 be used to determine whether increasing elotuzumab dose in high-risk patients with low elotuzumab exposure is projected to increase PFS?

No, the demographics of the Phase 2 Study Huluc63-1073 were such that the baseline characteristics of these patients were different when compared to the Trial CA204004 (Table 4). The phase 2 data from Huluc63-1073 do not contain a sufficient number of high-risk subjects with low elotuzumab exposure (below 209 μg/mL, the upper limit of the low exposure/high-risk patient subset in Trial CA204004) to definitively characterize the PFS exposure-response relationship in the range of exposures relevant to the phase 3 population (Figure 7).

Table 4. Demographic characteristics that appear to differ between the Phase 2 data and the Phase 3 elotuzumab Q1 subset.

Demographic	N	M-Protein (g/dL)	β2-microglobulin (mg/L)	log(LDH)	ECOG Score ≥ 2	Prior Stem Cell
10 mg	36	2.15	3.86	-0.17	3%	89%
20 mg	37	1.96	3.86	-0.30	5%	76%
Elotuzumab Q1	78	3.48	5.65	-0.26	12%	44%

Figure 7. Comparison of CavgSS following 10 mg/kg Elotuzumab in Studies CA204004 (Top Panel) and HuLuc63-1703 (Bottom Panel).



(Source: Applicant's Response to FDA Information Request, Oct-9-2015, Figure 2)

NOTE: Number of subjects with Cavgss < 209 ug/ml combined in both dose groups= 5

1.1.4 Do simulations for alternate elotuzumab dosing regimens (higher dose or decreased frequency) suggest additional survival benefit in patients with high m-protein and/or lower exposure?

Yes, simulations using a Cox proportional hazards model suggest there could be an additional benefit by increasing elotuzumab Cavgss. However, because of the linear nature of the relationship between the hazard and elotuzumab Cavgss, the model appears to overestimate the PFS for patients in Q1 and underestimates the PFS for patients in Q4.

1.1.4.1 FDA Pharmacometric Reviewer's Results

Two simulation exercises were performed by the reviewer to evaluate how much the PFS duration increased by increasing Cavgss by up to four-fold in patients with differing exposure quartiles and with differing concentrations of M-protein. Using the data for the phase 3 Trial CA204004 and the applicants final Cox proportional hazards model for PFS a bootstrap was performed with 1000 replicates which included resampling the data, re-estimating the model, and simulating the results for the entire sampled population within each replicate. Median PFS durations were then reported for each exposure quartile for each dosing scenario (Table 5) or each M-protein group by dosing scenario (Table 6). While these tables show an increase in PFS with increasing exposure, it should be noted that the cox model overestimates the PFS in Q1 by at least 5 months. This is likely due to the linear nature of the cox model while the exposure-response relationship may lessen in slope at higher exposures.

Table 5. Increasing elotuzumab exposure may offer an additional 2-3 months of PFS benefit for patients in the lowest quartile of elotuzumab Cavgss. Median Progression Free Survival and 95% CI Simulations for a 4-fold range in elotuzumab Cavgss (Trial CA204004 with Bootstrap for 1000 replicates).

	10 mg/kg Q2w	2·Cavgss	3·Cavgss	4·Cavgss
Lenolidamide/Dex Control	14.8 (11.9, 17.3)	14.8 (11.9, 17.3)	14.8 (12, 17.3)	14.8 (12, 17.3)
Elotuzumab Q1	15.9 (13.9, 18.4)	17.3 (15.7, 19.4)	18.5 (16.6, 19.4)	18.6 (17.3, 20.3)
Elotuzumab Q2	18.4 (15.9, 20.5)	21.0 (18.6, 23.4)	23.1 (20.5, 27.2)	25.0 (22.4, 29.5)
Elotuzumab Q3	20.2 (18, 23)	24.9 (21.4, 25.2)	25.9 (25, 24.9)	25.5 (25.5, 28.6)
Elotuzumab Q4	20.6 (19.4, 23)	24.9 (22.7, 23.1)	23.0 (23.1, 29.5)	25.5 (22.8, NA)

Table 6. Increasing elotuzumab exposure may offer an additional 2 months of PFS benefit for patients with high M-protein. Median Progression Free Survival and 95% CI Simulations for a 4-fold range in elotuzumab Cavgss (Trial CA204004 with Bootstrap for 1000 replicates).

	10 mg/kg Q2w	2·Cavgss	3·Cavgss	4·Cavgss
Low M-Protein (<2.1 g/dL)	18.5 (16.6, 21.2)	21.4 (18.5, 22.7)	23 (20.3, 24.6)	23.3 (22.2, 25.5)
High M-Protein (≥ 2.1 g/dL)	15.9 (13.8, 19.6)	18.4 (16.1, 19.4)	17.8 (17, 18.6)	17 (17.3, 20.3)

1.1.4.2 Applicant's Simulation Results

The applicant conducted simulations for PFS as requested by the FDA Office of Clinical Pharmacology, for four dosing scenarios and reported the results in terms of patient elotuzumab Cavgss exposure and M-protein. The FDA's information is outlined as follows.

"Using your population PK model, for the patients in your exposure-response analysis, simulate the concentration-time profile and the Cssavg for the following dosing regimens:

1. ***10 mg/kg QW for cycle 1 and 2, followed by 10 mg /kg Q2W thereafter (regimen studied in CA204004)***
2. ***10 mg/kg QW for all cycles***
3. ***10 mg/kg QW for cycle 1 and 2, followed by 15 mg /kg Q2W thereafter***
4. ***10 mg/kg QW for cycle 1 and 2, followed by 20 mg /kg Q2W thereafter***

Using your final multivariate cox proportional hazard model, perform simulations to predict the PFS benefit (along with 95% CI) for the above dosing regimens in the following scenarios:

1. ***In the entire population***
2. ***In patients with high M-protein (i.e. greater than the median),***
3. ***In patients whose Cssavg that fall into the lower 25% quartile of your studied dose in Study CA204004.***

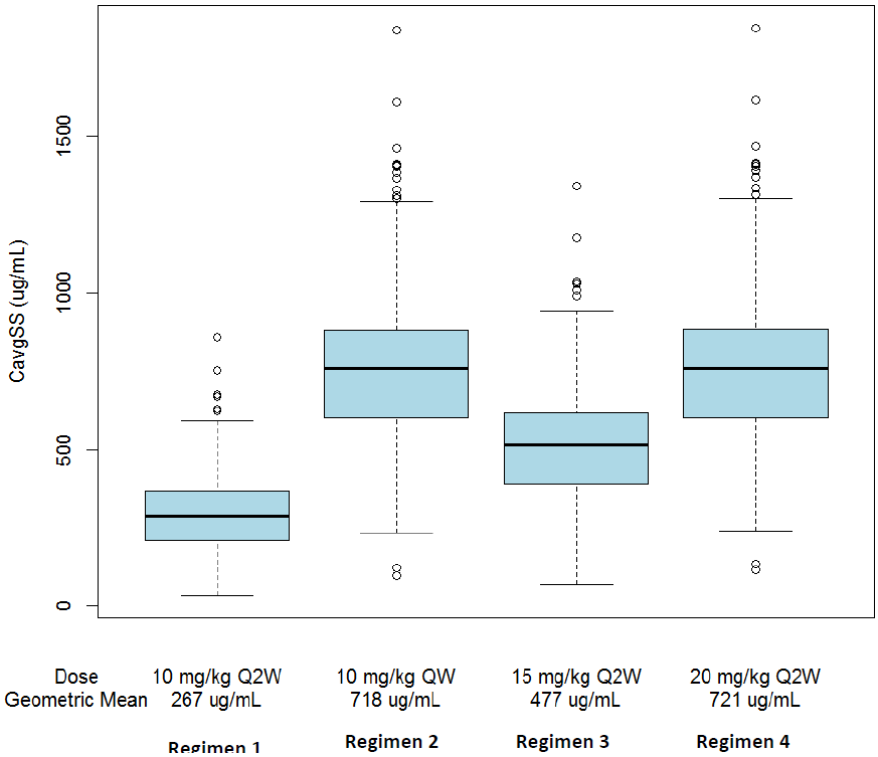
Also provide the following:

1. ***Discuss the predicted PFS benefit of the higher dosing regimens for each of the above population***
2. ***A table with the resultant Cssavg and predicted PFS for each patient for each dosing regimen. The table should also include each patients corresponding demographics, covariates included in the population PK and covariates included in the Cox proportional hazard model.***
3. ***The simulation dataset and model run script files used to generate the results."***

As part of this analysis the applicant chose to include the phase 2 data from Study Huluc63-1073 in their analysis. The agency requested that the results for the lowest quartile of exposures be also presented without the inclusion of the phase 2 data. The latter results are consistent with the reviewer's analysis in Section 1.1.4.1 and thus only the applicant's analysis for the pooled data are discussed in this section. The applicant's analysis for CA204004 alone and further details of this information request are discussed in Section 3.2.3.

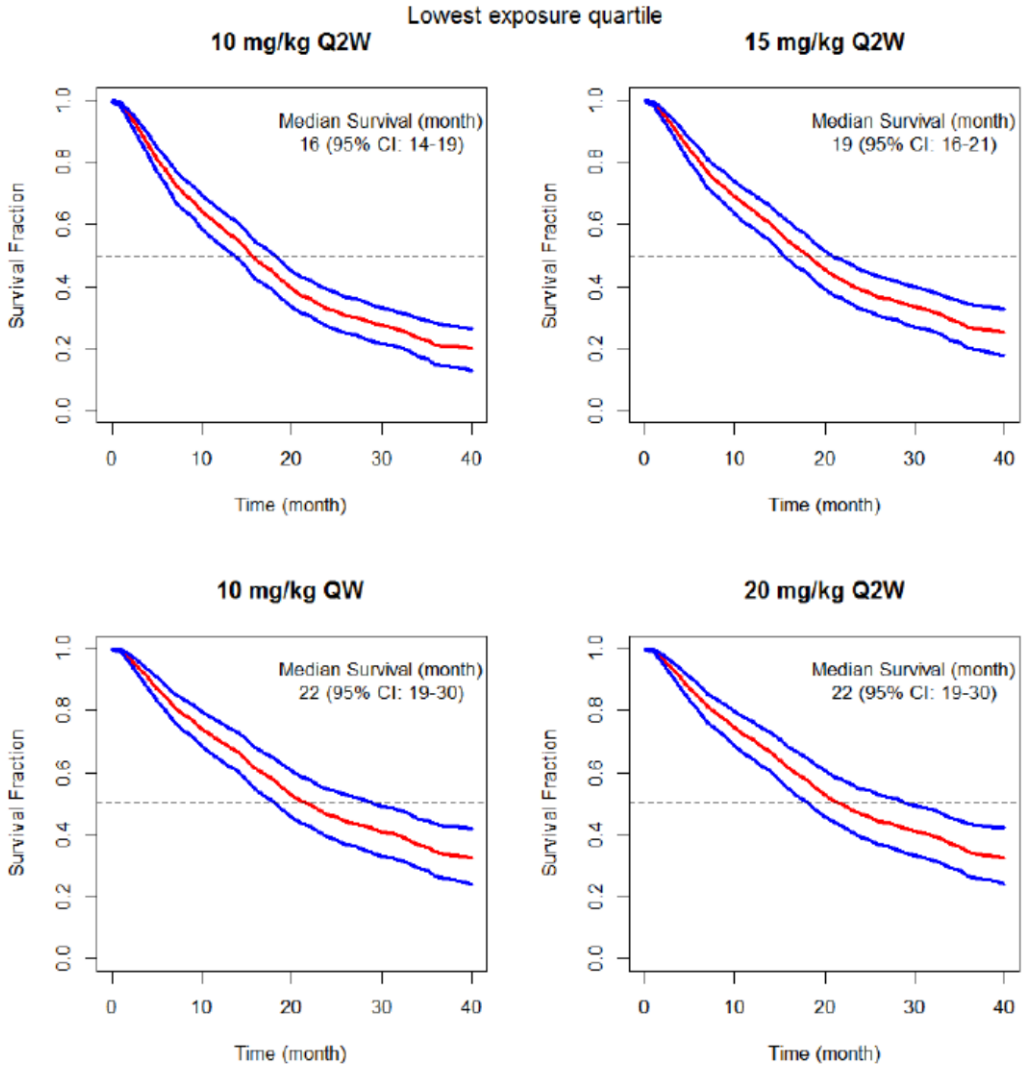
The exposure range for the dosing scenarios are shown in Figure 8. The applicant's simulations for the effect of dosing increases on PFS for patients with high M-protein are shown in Figure 9. The applicant's simulations for the effect of dosing increases on PFS for patients with lower elotuzumab exposure (first quartile of Cavgss) are shown in Figure 10. Both sets of simulations appear to be consistent in showing some benefit for increasing exposure. The values of median PFS are also similar to the reviewer's results discussed in Section 1.1.4.1 for up to a four-fold change in elotuzumab exposure.

Figure 8. Simulated elotuzumab Cavgss by dosing regimen



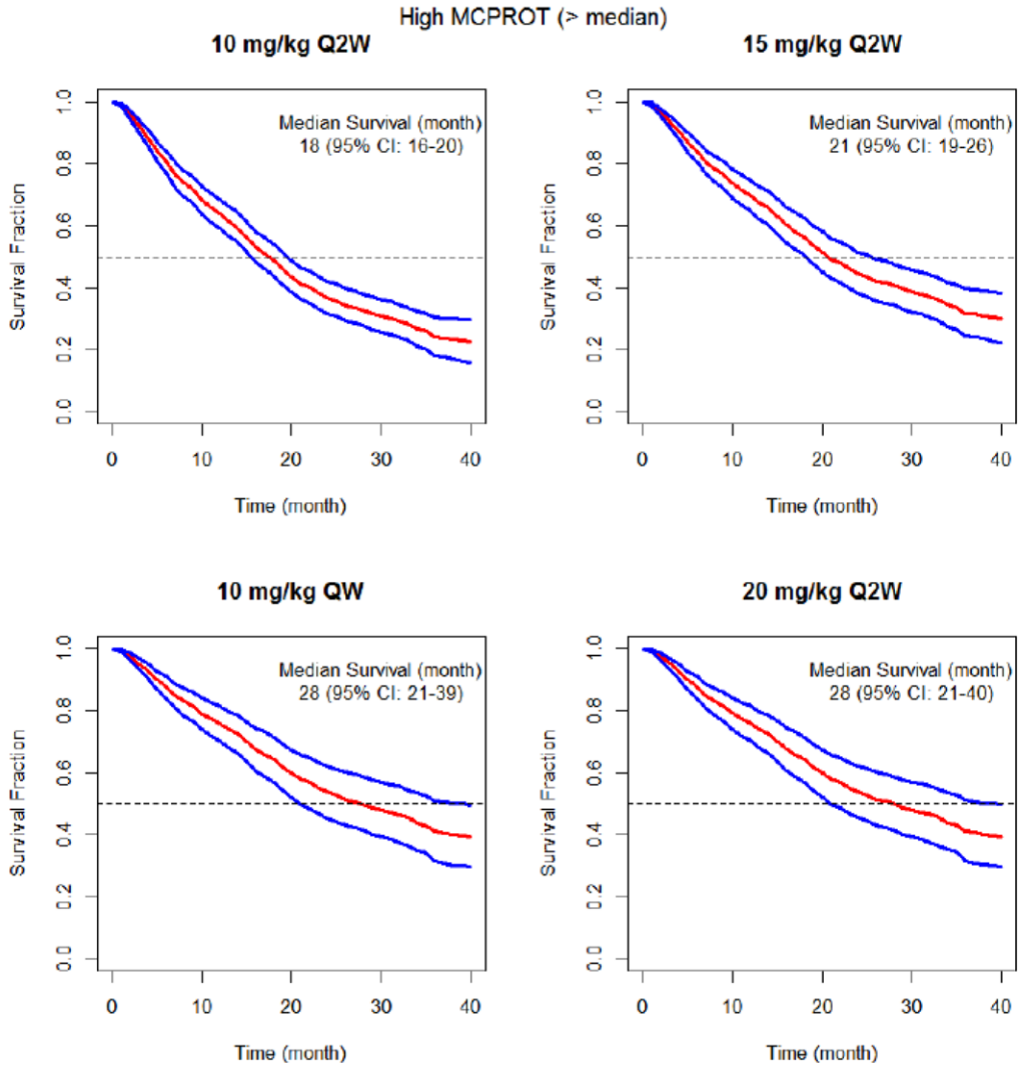
(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 2)

Figure 9. Predicted PFS for 4 different regimens in patients with Cavgss in the lower 25% quartile of Study CA204004 (Model developed from both Study HuluC1073 and Trial CA204004)



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 7)

Figure 10. Predicted PFS for 4 different regimens in patients with high M-protein (>median) (Model developed from both Study HuluC1073 and Trial CA204004)



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 6)

As part of this analysis the applicant chose to include the phase 2 data from Study Huluc63-1073 in their analysis. This was done in part because these patients received a 20 mg/kg dose, but it should be recognized that they were a different population and bias the analysis towards lower M-protein and β2-microglobulin. The concern from this analysis has been for patients that have higher risk factors for PFS and lower elotuzumab exposure.

The applicant noted that a linear effect may suggest benefit for patients with higher exposure, when effect may already be at plateau. The reviewer agrees with this. However, we are primarily concerned with patients that do not fall into this plateau and are at the lower end of exposure. One additional check that was performed was to evaluate exposure-response within Q1 to determine if the trend remained. In fact there still appeared to be a correlation with exposure within Q1 of the phase 3 data (see Figure 21 for further details).

While these analyses suggest some benefit in this population, the simulations do not accurately predict the PFS behavior at the low and high exposure extremes of the data. Additionally patients were not evaluated with dose increases and model covariates may be from mutually exclusive subsets of patients within the population. Thus, it cannot be concluded how much effect increasing the dose will have at this point without conducting a study to evaluate increasing the dose in patients with higher risk factors. Given that the observed data and the case control analysis appear to suggest that an even greater benefit may be possible for patients at higher risk, and this is consistent with one of the clearance mechanisms of elotuzumab, there is no reason why patients with lower exposure should be ignored. For this reason we are recommending a post marketing commitment for an analysis of data from the ongoing trial in multiple myeloma patients, trial CA204006 before requesting that a dose optimization study be initiated.

1.2 Recommendations

Based on the multiple analyses above from both the applicant and the reviewer we are recommending a post-marketing commitment to evaluate additional data from an ongoing trial with multiple myeloma patients (Trial CA204006).

PMC:

Conduct elotuzumab exposure-response analysis for efficacy and safety utilizing data from trial CA204006. The result of the exposure-response analysis from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10 mg/kg). Submit a final report of the exposure-response analysis based on CA204004 and CA204006.

2 PERTINENT REGULATORY BACKGROUND

Elotuzumab is a first-in-class, immunostimulatory, humanized immunoglobulin G1 monoclonal Antibody. The applicant is seeking approval of elotuzumab in combination with (b) (4) lenolidame/dexamethasone (b) (4) for the treatment of multiple myeloma in patients who are refractory to at least one prior therapy. The applicant submitted a phase 3 trial (CA204004) to support approval in combination with lenolidamide/dexamethasone (b) (4) (b) (4) (b) (4)

The phase 3 study CA204004 resulted in a median PFS of 19.4 months for the elotuzumab plus lenolidamide/dexamethasone arm compared to 14.9 months for the lenolidamide/dexamethasone control arm. Additionally, the odds ratio for ORR was 1.94 (99.5% CI: 1.17, 3.23; p-value= 0.0002) in favor of the elotuzumab plus lenolidamide/dexamethasone arm.

(b) (4)

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK

The applicant conducted two population PK analyses with phase 2 and phase 3 elotuzumab data.

The first analysis was done with the phase 3 data of elotuzumab in combination with lenolidamide/dexamethasone in multiple myeloma patients (trial CA204004). The second analysis was done as an extension of the first analysis and included the phase 2 data from the elotuzumab in combination bortezomib/dexamethasone trial (CA204009).

As the review of the pop PK model is centered on the use of the values for the exposure-response analyses and the focus has been primarily on its use with lenolidamide/dexamethasone, the first pop PK analysis is discussed as this analysis provided the CavgSS values for the exposure-response and exposure-safety analyses.

Elotuzumab PK was characterized by population pharmacokinetic (PPK) analysis with 6958 elotuzumab serum concentration values from 375 subjects with multiple myeloma, who were enrolled in the following 4 clinical studies: 2 Phase 1 studies (CA204005 and CA204007), 1 Phase 2 study (CA204011), and 1 Phase 3 study (CA204004).

Table 7 describes the clinical studies and data characteristics for the PK and exposure response analyses. Table 8 outlines the final population PK parameter estimates and model structure.

Table 7. Summary descriptions of clinical studies included in the population PK and exposure-response analyses.

Protocol #: Title *Study Population*	Treatment	Sample Size	Nominal PK/PD Sampling Schedule	Analyses
HuLuc63-1701: Phase 1, Multi-Center, Open-Label, Dose Escalation Study of Elotuzumab (Humanized Anti-CS1 Monoclonal IgG1 Antibody) in Subjects With Advanced Multiple Myeloma	Elotuzumab monotherapy in 1 of the following dose cohorts 0.5, 1, 2.5, 5, 10, and 20 mg/kg q14d	34 patients	PK: serial (1st dose: 8 samples; 4th dose: 10 samples with follow-up) and sparse samples mostly with 20 mg/kg	PPK sensitivity analysis
HuLuc63-1703: Phase 1b/2, Multi-Center, Open-Label, Dose Escalation Study of Elotuzumab (Humanized Anti-CS1 Monoclonal IgG1 antibody) in Subjects With Advanced Multiple Myeloma	Elotuzumab in combination with lenalidomide and dexamethasone Phase 1 part: 5 to 20 mg/kg; Phase 2 part: 10 or 20 mg/kg. Doses administered on Day 1, 8, 15 and 22 of first 2 cycles, then Day 1 and 15 (28 day cycles) of subsequent cycles.	Phase 1 part: 28 patients; Phase 2 part: 73 patients.	PK: Cycle 1: Days 1 and 22, predose; 0.5 and 2 hours after end of infusion. Day 8 predose; 2 hours after end of infusion. Day 15, predose; 0.5 hour after end of infusion. Cycle 2: Days 1 and 22, predose; 2 hours after end of infusion. Cycle 3+: Day 1 predose; 0.5 hour after end of infusion. ADA: Day 1 of each cycle; end of treatment; 30 and 60 days follow up	PPK sensitivity analysis
CA204004: ELOQUENT-2; A Phase 3, Randomized, Open Label Trial of Lenalidomide/ Dexamethasone With or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma	Elotuzumab in combination with lenalidomide/dexamethasone 10 mg/kg Day 1, 8, 15 and 22 of first 2 cycles, then Day 1 and 15 (28 day cycles) of subsequent cycles.	646 patients	PK: Cycles 1-4, 6, 9, 12, 15, and 18: Day 1 predose. Cycles 1-3: Day 1 0.5 and 2 hours after the end of infusion. PD: Safety and Efficacy endpoints	PPK and E-R (Safety and Efficacy)
CA204005: Phase 1 Multiple Ascending Dose Study of Elotuzumab (BMS-901608) in Combination with Lenalidomide/Lowdose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma in Japan	Elotuzumab in combination with lenalidomide and dexamethasone 10 or 20 mg/kg Day 1, 8, 15 and 22 for the first 2 cycles, then Day 1 and 15 (28 day cycles) of subsequent cycles.	6 patients	PK: Cycle 1: Day 1 and Day 22: predose, 0.5 and 2 hours after the end of infusion. Day 8: Predose and 2 hours after the end of infusion. Day 15: predose and 0.5 hour after the end of infusion. Cycle 2: Day 1 and Day 22 predose and 2 hours after the end of infusion.	PPK

Protocol #: Title *Study Population*	Treatment	Sample Size	Nominal PK/PD Sampling Schedule	Analyses
CA204007: A Phase 1b Study of Elotuzumab in Combination with Lenalidomide and Dexamethasone in Subjects with Multiple Myeloma and Normal Renal Function, Severe Renal Impairment, or End Stage Renal Disease Requiring Dialysis	Elotuzumab in combination with lenalidomide and dexamethasone Cycle 1: 10 mg/kg on Day 1; Cycles 2, 3: 10 mg/kg on Day 1, 8, 15, and 22; Cycles 4+: 10 mg/kg on Day 1 and 15.	24 patients (8 patients in each of the following groups: (i) severe renal impairment not requiring dialysis; (ii) end stage renal disease requiring hemodialysis; (iii) normal renal function	PK: Cycle 1: predose; 0, 0.5, 2, 4 after the end of infusion; 24 and 48 hours after the start of infusion; immediately prior and immediately after dialysis session on Day 2 or 3; at day 8, 11, 15, and 22. Cycle 2 and 3: predose on Day 1, 8, 15, and 22. Cycles 4, 6, 9, 12, 15, and 18: predose on Day 1; End of study/discontinuation; 30 and 60 days follow up. ADA: Day 1 of cycles 2, 3, 4, 6, 9, 12, 15, and 18; end of study/discontinuation; 30 and 60 days follow up.	PPK
CA204011: A Phase 2 Biomarker Study of Elotuzumab (Humanized Anti-SC1 Monoclonal IgG1 Antibody) Monotherapy to Assess the Association Between NK Cell Status and Efficacy in High Risk Smoldering Myeloma	Elotuzumab monotherapy Cohort 1: 20 mg/kg Day 1 of all 28 day cycles with an additional dose on Cycle 1 Day 8. Cohort 2: 10 mg/kg Day 1, 8, 15, and 22 of Cycles 1 and 2 (28-day cycles), then Day 1 and 15 of Cycles 3+.	Cohort 1: 15 patients; Cohort 2: 15 patients.	PK: All patients: Cycle 1: Day1: predose, 0.5, and 2 hours after the end of infusion; Day 8: predose and 2 hours after the end of infusion. Cycle 2: Day 1 pre-dose; Cycle 3: Day 1 predose, 0.5 and 2 hours after the end of infusion. Cycles 4, 6, 9, 12, 15, 18: predose. Cohort 2 only: Cycle 1, 2, 3: Day 15: predose	PPK

Abbreviations: ADA = anti-drug antibodies; E-R = exposure-response; NK = natural killer; PK = pharmacokinetics; PPK = population pharmacokinetics.

(Source: Applicant's Population PK Report 204004, Table 3.1-1)

The elotuzumab PPK model was developed in 3 steps, namely base, full and final model. The base model was a two compartment model with zero order IV infusion, parallel linear and Michaelis-Menten elimination from the central compartment, and additional target-mediated elimination from the peripheral compartment. The model was parameterized in terms of the following PK parameters: clearance (nonspecific linear clearance denoted as CL), volume of distribution of the central compartment (VC), intercompartmental clearance (Q), volume of distribution of the peripheral compartment (VP), the maximum rate of Michaelis-Menten elimination (VMAX), Michaelis-Menten constant (KM), initial target SLAMF7 concentration in the peripheral compartment (RMAX), and second-order elimination rate constant of the drug-target complex from the peripheral compartment (kint).

Second, a full model was developed to determine the magnitude of covariate effects on the base model PK parameters. The following parameter-covariate relationships were included in the full model:

- CL ~ body weight (BW), age, sex, estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), Eastern Oncology Group (ECOG) performance status, serum M-protein, serum β2-microglobulin (B2MICG), race, hepatic impairment, albumin, and concomitant lenalidomide/dexamethasone
- VC ~ BW, sex, B2MICG, race
- VMAX ~ serum M-protein;
- VC and Q ~ Body weight.

Lastly, the final model was developed by backward elimination of these based upon improvement in Bayesian Information Criterion (BIC).

The performance of the final model was assessed by standard diagnostic plots.

Table 8. Parameter Estimates of the Final Population PK Model.

Parameter		Value	%RSE	95% CI[a]	CV[b]	Shrinkage
Structural Parameters						
CL_{REF} (L/day)	$\exp(\theta_1)$	0.0895	3.22	0.0791 - 0.0962	NA	NA
$V_{C, REF}$ (L)	$\exp(\theta_2)$	4.04	1.89	3.87 - 4.2	NA	NA
Q_{REF} (L/day)	$\exp(\theta_3)$	0.676	9.11	0.548 - 0.806	NA	NA
$V_{P, REF}$ (L)	$\exp(\theta_4)$	2.22	4.41	1.99 - 2.48	NA	NA
R_{MAX} (µg/mL)	$\exp(\theta_5)$	790	8.23	678 - 938	NA	NA
k_{int} (10^{-3}/day/(µg/mL))	$\exp(\theta_6)$	0.191	11.4	0.144 - 0.25	NA	NA
$V_{MAX, REF}$ (µg/mL/day)	$\exp(\theta_7)$	9.21	0.85	9.17 - 9.23	NA	NA
K_M (µg/mL)	$\exp(\theta_8)$	253	7.43	205 - 297	NA	NA
Covariate Effects Parameters						
CL_{WT}	θ_9	1.16	12	0.886 - 1.49	NA	NA
CL_{LenDex}	$\exp(\theta_{20})$	0.666	7.82	0.546 - 0.802	NA	NA
$V_{C,WT}$	θ_{10}	0.332	17.3	0.237 - 0.472	NA	NA
$V_{C,female}$	$\exp(\theta_{17})$	0.796	2.57	0.76 - 0.844	NA	NA
$V_{C,ASIAN}$	$\exp(\theta_{18})$	0.861	3.87	0.801 - 0.931	NA	NA
$V_{C,B2MICG>3.5}$	$\exp(\theta_{19})$	1.13	2.33	1.08 - 1.18	NA	NA
Q_{WT}	θ_{11}	0.75		Fixed[c]	NA	NA
$V_{P,WT}$	θ_{12}	0.617	23.4	0.333 - 0.92	NA	NA
$V_{MAX,MCPROT}$ $(g/dL)^{-1}$	Θ_{21}	0.178	0.842	0.177 - 0.179	NA	NA
Inter-individual Variability (IIV) Parameters						
ω^2_{CL}	$\Omega(1;1)$	0.101	15.7	0.0616 - 0.134	31.8%	40.6%
ω^2_{VC}	$\Omega(2;2)$	0.0396	9.86	0.031 - 0.0473	19.9%	8.5%
ω^2_{Q}	$\Omega(3;3)$	0.495	18	0.321 - 0.6	70.4%	34.3%
ω^2_{VP}	$\Omega(4;4)$	0.123	20.4	0.0644 - 0.181	35.1%	32.8%
ω^2_{RMAX}	$\Omega(5;5)$	0.217	24.2	0.104 - 0.327	46.5%	40.3%
ω^2_{KINT}	$\Omega(6;6)$	1.66	14.1	1.18 - 2.3	128.9%	17.9%
ω^2_{VMAX}	$\Omega(7;7)$	0.0001	NA	Fixed[d]	1%	NA

Parameter		Value	%RSE	95% CI[a]	CV[b]	Shrinkage
ω^2_{KM}	Ω(8;8)	0.956	10.3	0.706 - 1.19	97.8%	17.1%
ω^2_{ε}	Ω(9;9)	0.192	9.42	0.156 - 0.227	43.8%	3.0%
Intra-individual Variability Model Parameters						
SD_L	θ_{13}	2.5	15.2	1.59 - 3.61	NA	NA
SD_H	θ_{14}	0.0994	6.55	0.0873 - 0.115	NA	NA
SD_{50} (µg/mL)	θ_{15}	6.76	19.8	4.13 - 11.9	NA	NA
$SD_{phase1,2}$	θ_{16}	0.67	6.14	0.597 - 0.756	NA	NA

Analysis-Directory: /global/pkms/data/CA/204/C01/prd/QuantPharm/sd
Program Source: Analysis-Directory/Elotuzumab/R/DiagnosticPlotsPK_No1703.R
Analysis-Directory/Elotuzumab/R/ BootsrapTable_221.R
Source: Analysis-Directory/Elotuzumab/Reports/ReportTables/221impmapParEst.csv
Analysis-Directory/Elotuzumab/Reports/ReportTables/CI221impmap.csv

[a] Bootstrap 95% confidence intervals.

[b] Coefficient of variation was computed as $100*\omega^2_P$ where ω_P is the square root of the corresponding variance parameter ω^2_P.

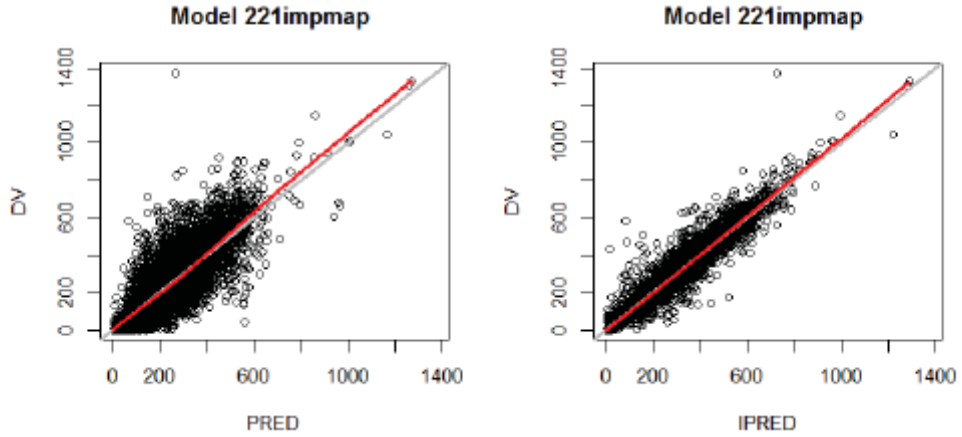
[c] Exponent for Q was fixed to allometric value 0.75 as this parameter estimate of the model with all estimated exponents was estimated imprecisely but close to 0.75. See Section 5.1.1.1.

[d] After the best model was selected, variance of the random effect on V_{MAX} with very small value and very high shrinkage was set to almost zero (1%) allowing to retain this effect, as required by the IMPMAP method, and obtain a stable model with negligible variability of this parameter.

Abbreviations: ω^2_{Par} = variance of the random effect on parameter Par (Par = CL, V_C, Q, V_P, Rmax, k_{int}, V_{MAX}, K_M); $\omega^2\varepsilon$: variance of the random effect on the magnitude of the residual error; CI = confidence interval; CL = clearance; CL_{LenDex} = effect of concomitant dexamethasone/lenalidomide administration on CL; CL_{WT} = power coefficient of CL dependence on body-weight; CL_{REF} = typical clearance at reference values of covariates (WT = 75 kg, GFR = 100 mL/min, LDH = 200 U/L, ALB = 3.5 g/dL, AGE = 65 years, Male, non-Asian, Normal Liver Function, with LenDex, ECOG = 0, B2MICG < 3.5 mg/L); CV = coefficient of variation; ECOG = Eastern Cooperative Oncology Group; k_{int} = elotuzumab target-mediated elimination rate from the peripheral compartment; K_M = Michaelis-Menten constant of the target-mediated elimination from the central compartment; R_{MAX} = baseline target concentration in the peripheral compartment; RSE = relative standard error; R_{MAX} = initial target concentration in the peripheral compartment; Q = inter-compartment clearance; Q_{REF} = typical inter-compartment clearance at reference values of covariates (WT = 75 kg); Q_{WT} = power coefficient of Q dependence on body-weight; SD_{50} = elotuzumab concentration when standard deviation of the exponential error model is equal to $(SD_L + SD_H)/2$; SD_H = standard deviation of the exponential residual error model at high concentrations; SD_L = standard deviation of the exponential residual error model at low concentrations; $SD_{phase1,2}$ = Phase 1-2 study effect on the magnitude of the residual error; V_C = volume of the central compartment; $V_{C,female}$ = female sex effect on V_C; $V_{C,ASIAN}$ = Asian race effect on V_C; $V_{C,REF}$ = typical volume of the central compartment at reference values of covariates (WT = 75 kg, Male, non-Asian, B2MICG < 3.5 mg/L); $V_{C,WT}$ = power coefficient of V_C dependence on body-weight; Vmax = maximum target-mediated elimination rate from the central compartment; $V_{MAX,MCPROT}$ = effect of serum M-protein on V_{MAX}; $V_{max,REF}$ = typical maximum target-mediated elimination rate from the central compartment at reference values of covariates (MCPROT = 0 g/dL); V_P: volume of the peripheral compartment; $V_{P,REF}$ = typical volume of the peripheral compartment at reference values of covariates (WT = 75 kg); $V_{P,WT}$ = power coefficient of V_P dependence on body-weight.

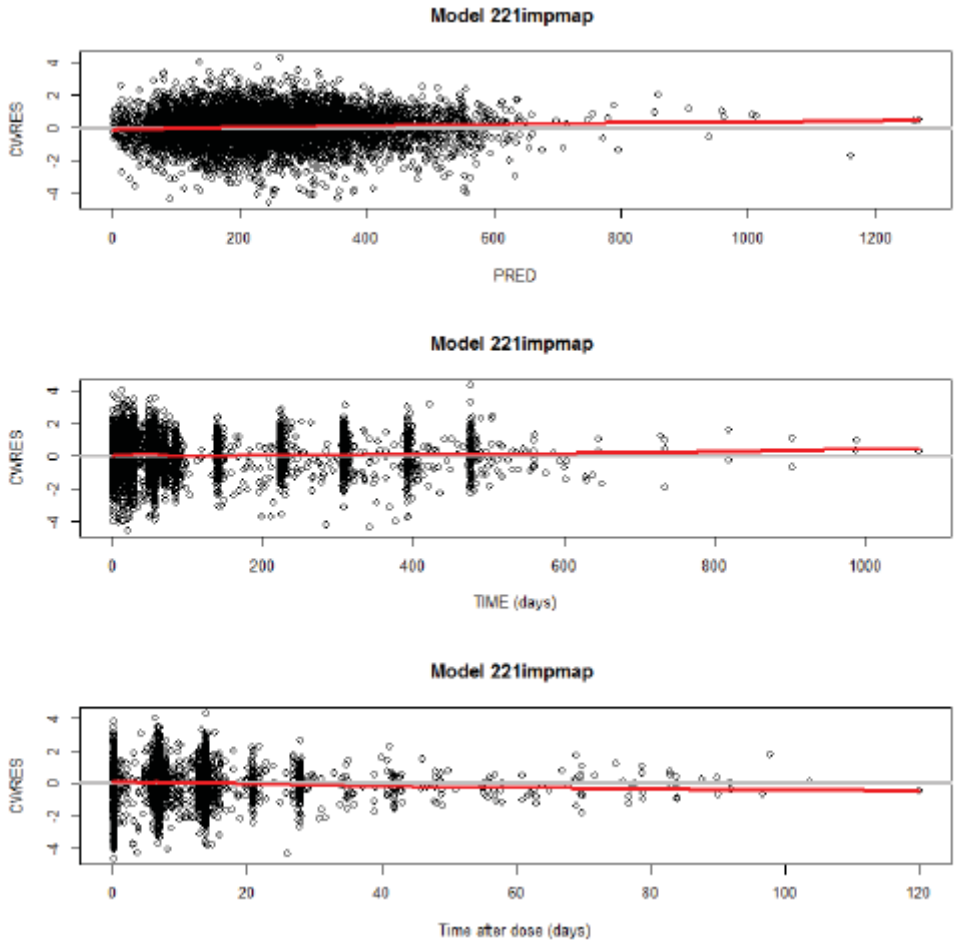
(Source: Applicant's Population PK Report 204004, Table 5.1.1.3-1)

Figure 11. Basic Goodness-of-Fit Plots for Final Model: Observed Values versus Population and Individual Predictions.



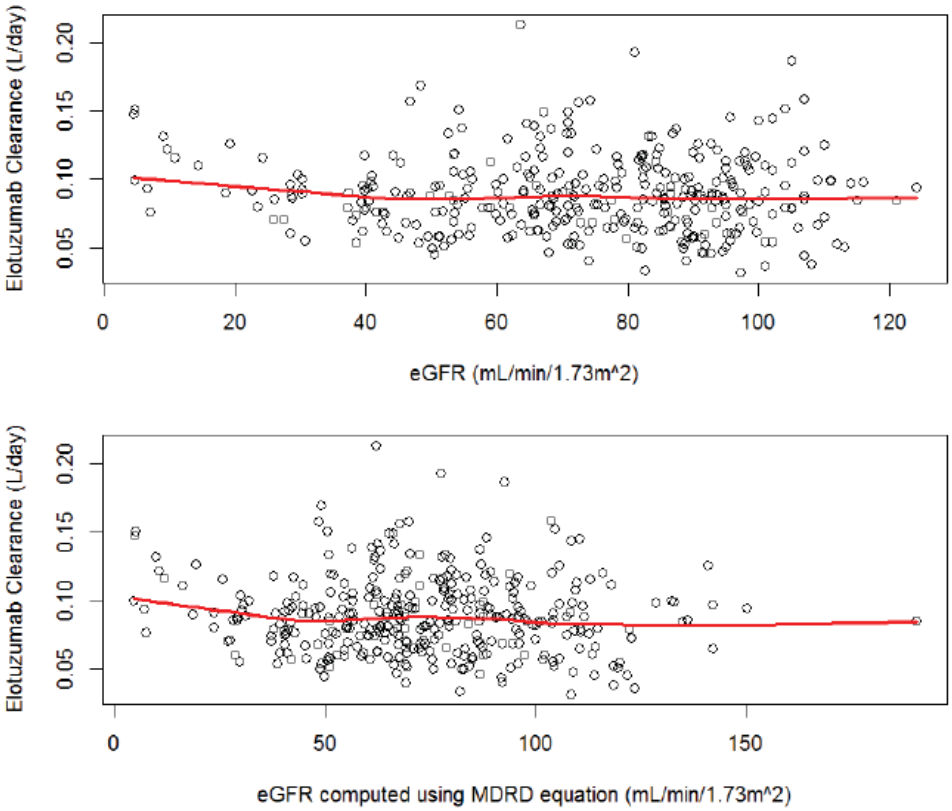
(Source: Applicant's Population PK Report 204004, Figure 5.1.2-1)

Figure 12. Basic Goodness-of-Fit Plots for Final Model: Conditional Weighted Residuals versus Population Predictions, Time, and Time after Dose.



(Source: Applicant's Population PK Report 204004, Figure 5.1.2-2)

Figure 13. Individual Estimates of Elotuzumab Nonspecific (Linear) Clearance versus Baseline Estimated Glomerular Filtration Rate and Modified Diet in Renal Disease.



(Source: Applicant's Population PK Report 204004, Figure 5.1.5.9-3)

Reviewer's Comments:

The applicant's population PK model was reviewed for two purposes:

1) labeling statements regarding the specific populations whereby no clinically relevant effect was claimed for gender, race, albumin, renal, and hepatic impairment.

The data appeared to be sufficient to evaluate the effect of renal impairment on elotuzumab PK (105 subjects with normal function, 169 with mild impairment, 79 with moderate impairment, 13 with severe impairment, and 9 with ESRD). Additionally, the covariate selection by elimination ruled out CRCL as a covariate and this is consistent with the expected mechanism of clearance of large protein therapeutics. The lack of correlation with eGFR was noted in Figure 13.

The range of the degree of hepatic impairment in patients in the PPK analysis was insufficient to make any labeling claims regarding moderate or severe hepatic impairment (33 subjects with mild impairment and 1 with moderate impairment). However, the lack of effect for mild hepatic impairment based on the population PK analysis is reasonable and consistent with the elimination mechanism of elotuzumab.

2) To assess the validity of the PK values used for the exposure-response analysis that were determined from the population PK model. Based on the applicant's plots and the reviewer's plots (See Section 4) the population PK model is reasonable to support the exposure response analyses. As some oncology products have time-varying clearance of the drug, the diagnostic

plots in Figure 12 suggest that the time-independent clearance nature of the model is reasonable to capture the steady-state PK of elotuzuamb.

3.2 Exposure-Response

The exposure-response (E-R) analysis of PFS and time to first occurrence of Grade 3+ AEs and time to AEs leading to discontinuation or death was conducted using data from multiple myeloma patients from study CA204004 who received lenalidomide/dexamethasone with or without elotuzumab and for whom estimates of elotuzumab exposure were available from the PPK analysis (N = 629). The elotuzumab exposure in patients in the control arm (lenalidomide/dexamethasone with placebo) of CA204004 was assumed to be zero.

3.2.1 Multivariate Exposure Response for Progression-Free Survival

After stepwise backward elimination, the covariates retained in the final E-R PFS model were CavgSS, LDH and B2MICG at baseline, prior IMiD therapy (Yes:No), prior stem cell transplantation (Yes:No), chromosome abnormality T(4,14) (Yes:No or Unknown), and time from diagnosis (≥ median [3.5 years]: < median [3.5 years]). The final CPH model parameter estimates and the corresponding hazard ratios and 95% CIs are summarized in Table Table 9 and Figure 3.

As observed in the full model, higher CavgSS appears to be associated with an increase in PFS. However, based on PPK analysis, VMAX is dependent on baseline serum M-Protein, resulting in elotuzumab exposure being lower in patients with high baseline serum M-Protein. Since the observation of an apparent E-R relationship between elotuzumab exposure and the risk of disease progression is confounded by baseline serum Mprotein levels (and possibly other factors associated with disease state), no causal relationship can be established between low elotuzumab exposure and higher risk for disease progression. Higher LDH and B2MICG at baseline, prior IMiD therapy, prior stem cell transplantation, and chromosome abnormality T(4,14) increase the hazard, while longer time from diagnosis decreases it.

Table 9. Parameter Estimates for Final Cox Proportional-Hazards Model: Progression-free Survival.

Predictor (Comparator:Reference)[a]	Coefficient	SE	RSE (%)	Hazard Ratio	Hazard Ratio 95% CI
C_{avgSS}[b] [µg/mL]	-0.001497	0.0003151	21.05	0.9985	0.9979-0.9991
LDH[b,c] [time of LDH_{ULN}]	0.6491	0.1639	25.25	1.914	1.388-2.639
B2MICG[b,d] [mg/L]	0.5925	0.09455	15.96	1.809	1.503-2.177
Time from disease diagnosis (≥ median: < median)	-0.6479	0.1127	17.4	0.5232	0.4195-0.6525
Prior IMiD Therapy (Yes: No)	0.4069	0.1058	26.01	1.502	1.221-1.848
Prior stem cell transplantation (Yes: No)	0.4581	0.1153	25.16	1.581	1.261-1.982
Chromosomal Abnormality T(4,14) (Yes: No or Unknown)	0.5505	0.1595	28.97	1.734	1.269-2.37

Analysis-Directory: /global/pkms/data/CA/204/C01/prd/QuantPharm/sd
Program Source: Analysis-Directory/Elotuzumab/R/E_R_PFS_204004.R,
Source: Analysis-Directory/Elotuzumab/Reports/ReportTablesPFS/finalModelTablePFS.csv

[a] Applicable to categorical covariates.

[b] Hazard ratio coefficient represents the hazard ratio for one unit of change in the predictor variable.

[c] LDH/LDH_{ULN} ratio has been log transformed; log transformed ratio increases by one unit for approximately 2.7 fold increase in LDH.

[d] B2MICG has been log transformed, log transformed value increases by one unit for approximately 2.7-fold increase in B2MICG.

(Source: Applicant's Population PK Report 204004, Table 5.2.1.3-1)

Reviewer's Comments:

The Cox PH hazards models in this presented in this documents have been useful at identifying factors that play a role in the prediction of patient PFS. However, because of the linear nature of the relationships, the model appears to be misspecified at the extremes of exposure as seen when comparing the simulations in Table 5 *compared to the observed median PFS in* Figure 2. *The linear relationship does not permit a plateau of response to be characterized at higher exposures and thus the model will over-estimate the benefit of increasing exposure for Q3 and Q4. Whereas, it will likely overestimate the PFS for the lower exposures and thus under-estimate the benefit on increasing the exposure for patients in Q1.*

3.2.2 Response to FDA Information Request Dated Sept 24, 2015: Case Control Analyses

On September 24, 2015 the FDA submitted the following information request to the applicant based on the case-control analysis discussed in Section 1.1.1

> ***"We would like to bring to your attention our finding regarding the apparent lack of drug effect of elotuzumab in patients with relatively low elotuzumab concentrations at the proposed dosing regimen of 10 mg/kg QW for Cycles 1 and 2 followed by 10 mg/kg Q2WKS thereafter. Your exposure-response analysis for efficacy identified Cssavg as correlated with PFS after***

controlling for other baseline risk factors. We conducted an independent exposure-response evaluation for PFS using case control analysis to control for all the factors in your final exposure-response model (B2-microglobulin, LDH levels, prior treatment duration, prior iMiD therapy, prior stem cell transplant) as well as M-protein and ECOG score. The active control group was matched to the patients in the lowest quartile of elotuzumab exposure (Cssavg) with respect to these risk factors. The active control group was also matched to the patients in the highest three quartiles of exposure. The case control analysis shows the following:

1. ***There was no difference in median PFS between patients with Cssavg in the lowest quartile of elotuzumab exposure (Cssavg < 209 mg/L) and patients on active control (Patients in the Len/Dex arm) after controlling for all the risk factors as described above. It is worth noting that patients who have lower exposures inherently also have higher risk factors such as high M-protein, higher B2-microglobulin, and higher LDH levels.***
2. ***Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors as described above.***

"Given that approximately a quarter of the patients administered elotuzumab do not appear to have benefit at the currently proposed dosing regimen, it is possible that these patients may benefit from higher exposures. We are informing you about this issue in order to provide you the opportunity to share your thoughts on this with us, provide us with any analysis that you may have conducted or would now like to conduct to evaluate this issue, and explore strategies that will ensure that patients that can derive some benefit from elotuzumab have an opportunity to do so."

The applicant's response regarding the results of the Case-Control Analyses, Their Phase 2 data, and their overall conclusions are outline below.

Case-Control Analyses

The applicant conducted two additional case-control analyses as follows:

"Two additional case-control analyses were conducted using the exposure-response analysis dataset for progression free survival (PFS) for study CA204004. BMS conducted these casecontrol analyses adjusting for risk factors using two methods: (1) nearest neighbor matching based on Mahalanobis distance and (2) matching within a propensity score distance.

"The BMS-conducted Mahalanobis based matching analysis accounted for risk factors that were significant in a CPH regression model, namely: chromosomal abnormalities [del 17p, 1Q21 gain and T(4,14)], prior IMiD therapy, time from disease diagnosis, prior stem cell transplantation, baseline lactate dehydrogenase and beta-2 microglobulin. ECOG performance status and baseline serum M-Protein were not included in the Mahalanobis based matching as they were not significant in the full model."

The applicant's conclusions regarding their case-control analyses are:

"Subsequent to matching for risk factors and other covariates, the PFS hazard ratios for each Cavgss quartile relative to matched controls in CA204004 were estimated by Cox proportional hazards models for both the Mahalanobis and propensity score based methods. As shown in Table 1 below, the point estimate of hazard ratio (HR) for Q1 of 1.38 (95% CI 0.93 to 2.04) obtained with the Mahalanobis based method suggests that the elotuzumab treated patients with Cavgss in the Q1 quartile have worse prognosis than those of the matched control patients. Adding elotuzumab to backbone therapy is not expected to result in a HR >1, suggesting that

there is likely a bias in patient selection with the BMS-conducted Mahalanobis case-control exercise.

The HR of elotuzumab patients in the Q1 quartile of Cavgss was 1.08 (95% CI: 0.73 to 1.60), indicating that the bias is less pronounced with the propensity score method which included baseline serum M-protein and ECOG score. Indeed, the results of the BMS propensity score analysis appear to be consistent with the results of the FDA-conducted Mahalanobis analysis (as described in Question 1). Nonetheless, even though the HR of patients in the Q1 quartile of Cavgss is close to 1, it is possible that this is due to risk factors not included in the analysis, such that the benefit of elotuzumab is counterbalanced by the higher risk of patients in the elotuzumab Q1 cohort.

Table 10. Hazard ratios for progression-free survival with 95% confidence intervals from Cox regression by exposure quartiles matched using Mahalonbis distance and propensity score methods.

Cavgss	Mahalanobis Distance	Propensity Score
Q1	1.38 (0.93, 2.04)	1.08 (0.73, 1.60)
Q2	0.82 (0.54, 1.24)	0.74 (0.49, 1.12)
Q3	0.49 (0.32, 0.77)	0.55 (0.35, 0.86)
Q4	0.56 (0.37, 0.84)	0.60 (0.39, 0.92)

(Source: Applicant's Response to FDA Information Request, Dated 10-1-2015, Table 1)

The applicant additionally proposed using the phase 2 data from HuLuc63-1703 to determine whether there is benefit from a dose higher than 10 mg/kg.

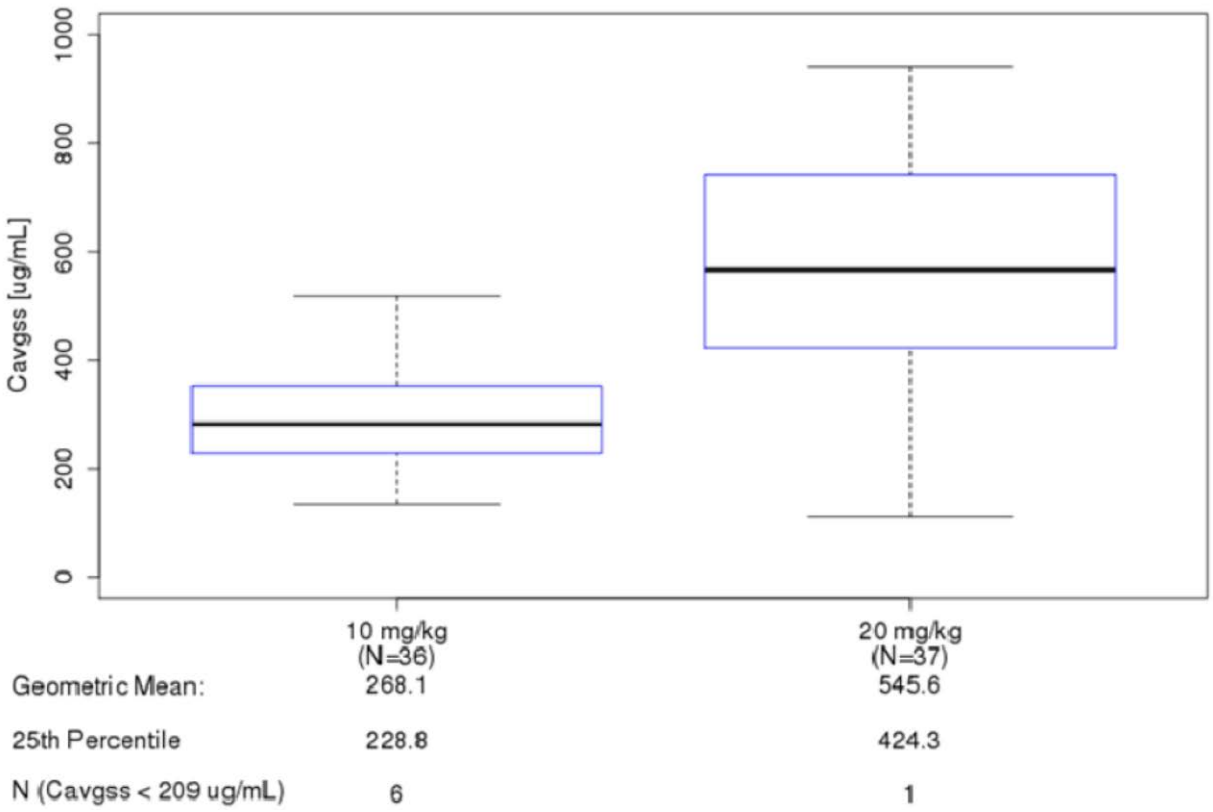
Comparison of efficacy achieved with 10 and 20 mg/kg elotuzumab in Study HuLuc63-1703

"Study HuLuc63-1703 (A Phase 1b/2, Multi-Center, Open-Label, Dose Escalation Study of Elotuzumab [Humanized Anti-CS1 Monoclonal IgG1 antibody] in Subjects With Advanced Multiple Myeloma) was designed to identify the maximum tolerated dose in patients with relapsed multiple myeloma. The study was expanded to include a randomized Phase 2 dose ranging portion aimed at further evaluating the safety and clinical activity of 10 and 20 mg/kg elotuzumab Q2W. The Phase 2 portion of the trial included 73 patients who were randomized to receive elotuzumab 10 mg/kg (N = 36) or 20 mg/kg (N = 37) in combination with lenalidomide/dexamethasone. A comparison of predicted Cavgss between the 10 and 20 mg/kg dose groups is provided in Figure 14. Patients in the 20 mg/kg group attained exposures (geometric mean Cavgss) that were approximately twice that of patients in the 10 mg/kg group. Notably, the Cavgss values of patients in the 20 mg/kg dose group were markedly higher than the Cavgss Q1 quartile from Study CA204004 (209 µg/mL). Moreover, the Cavgss Q1 values were 228.8 and 424.3 µg/mL in the 10 and 20 mg/kg groups, respectively, indicating that Q1 patients in 20 mg/kg group had much higher exposures than corresponding patients in the 10 mg/kg dose group (Figure 14).

"Efficacy endpoints were investigator-assessed ORR based on IMWG criteria (primary endpoint), further characterized by best confirmed response, DOR, TTR, and PFS. Efficacy results from these patients are presented in Table 11 and the Kaplan-Meier for progression free survival is presented in Figure 15. In this randomized study, none of the efficacy measures in the 20 mg/kg dose group were better than the corresponding measures in the 10 mg/kg dose group.

In spite of substantially higher exposures seen with the 20 mg/kg dose (with all but one patient attaining exposures greater than 209 µg/mL, the Cavgss Q1 quartile from Study CA204004), patients in this higher dose group did not show a better efficacy outcome in this randomized dose-ranging trial. The results of this study provide strong evidence that no additional benefit in efficacy would be achieved with elotuzumab doses higher than 10 mg/kg."

Figure 14. Elotuzumab Model-Predicted CavgSS by dose level from Phase 2 portion of Study HuLuc63-1703.



(Source: Applicant's Response to FDA Information Request, Dated 10-1-2015, Figure 5)

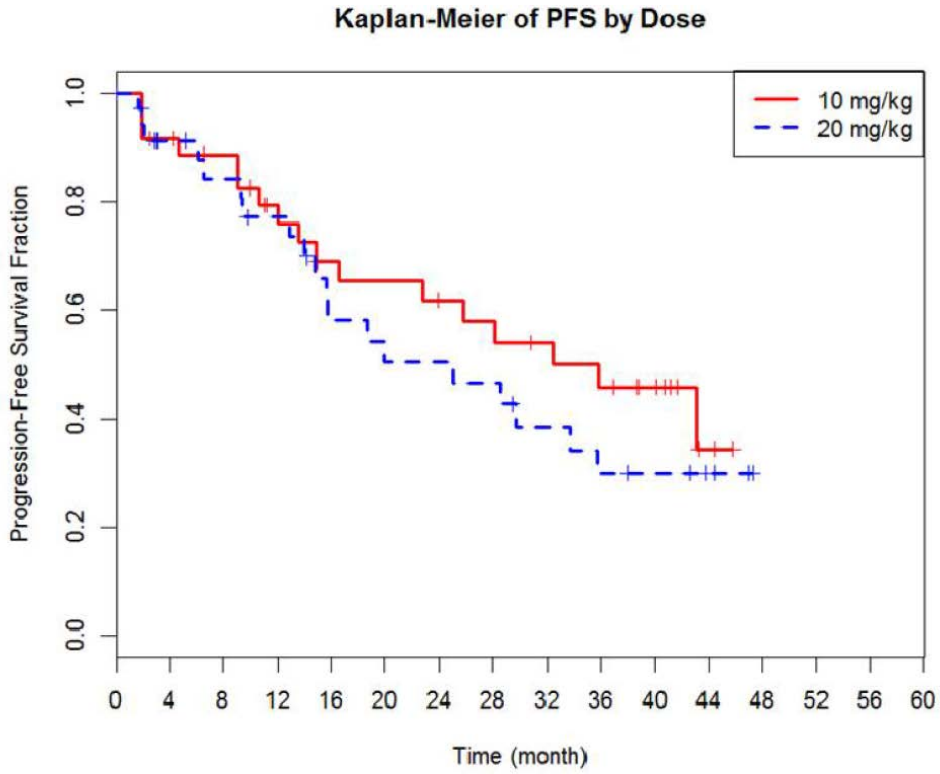
Table 11. Median PFS and ORR in the Phase 2 Portion of Study HuLu63-1703.

Efficacy Parameter	10 mg/kg (N = 36)	20 mg/kg (N = 37)	Total (N = 73)
ORR, N (%)	33 (92)	28 (76)	61 (84)
Median TTR (months)	1.0	1.7	1.0
Median DOR (months)	34.8	29.0	29.2
Median PFS (months)	32.5	25.0	28.6

Source: Table 31, Table 32, and Table 33 in HuLuc63-1703 Final CSR[4]

Abbreviations: ORR = objective response rate; TTR = time to response; DOR = duration of response; PFS = progression free survival

Figure 15. Progression Free Survival for Phase 2 portion (ITT Population) of HuLuc63-1703.



(Source: Applicant's Response to FDA Information Request, Dated 10-1-2015, Figure 6)

Applicant's Conclusions:

Overall, the results of our analyses show that it is not possible to conclude, on the basis of case-control analyses, that patients with Cavgss in the lowest quartile of Cavgss achieved by 10 mg/kg Q2W do not derive benefit from elotuzumab. Furthermore, the results of the HuLuc63-1703 randomized Phase 2 study demonstrate that it is unlikely that an elotuzumab dose higher than 10 mg/kg will lead to improvements in efficacy.

- We have demonstrated that neither of the two matching methods for case-control analyses (Mahalanobis and propensity score) applied to a selected subset of the treatment group adequately match for unobserved factors when the selection of patients is associated with that factor. Specifically, the methods are not adequate to match for CL (unobserved in control patients) when treatment group patients are selected on the basis of Cavgss (which is inversely related to CL). Sub-selecting patients based on Cavgss quartiles from the elotuzumab treated arm will inherently introduce a bias in patient selection, despite matching for known risk factors and covariates.
- It is difficult to fully deconvolute the confounding effects of disease state and PK on the efficacy of elotuzumab. It might appear that lower Cavgss is associated with greater risk for disease progression but this apparent relationship is confounded by baseline serum M-protein levels (and possibly other factors associated with disease state).
- Results from the randomized Phase 2 study Huluc63-1703 provides strong evidence that no additional efficacy benefit is achieved with a dose of 20 mg/kg compared to 10 mg/kg

Reviewer's Comments:

The applicant states: "Overall, these findings do not permit the conclusion that there is a causal relationship between low elotuzumab exposure and higher risk for disease progression." However, while these data are limited they consistently show the possibility that with increased exposure there may be increased benefit and as a counter to the above statement they do not rule out the possibility that increasing exposure may offer benefit to these patients with lower exposure.

The applicant also concludes: "Overall, the results of our analyses show that it is not possible to conclude, on the basis of case-control analyses, that patients with Cavgss in the lowest quartile of Cavgss achieved by 10 mg/kg Q2W do not derive benefit from elotuzumab." This reviewer is in agreement that the data are not structured in a way as to answer this question. However, this is an important question for patient health which needs to be addressed.

This reviewer is in disagreement with the applicant's conclusion that "the results of the HuLuc63-1703 randomized Phase 2 study demonstrate that it is unlikely that an elotuzumab dose higher than 10 mg/kg will lead to improvements in efficacy." The main reason for this is that the patients enrolled in the phase 2 were different than those enrolled in the phase 3 trial and their baseline risk factors for PFS (β2-microglobulin, lactate dehydrogenase, prior stem cell transplantation, etc) suggest that they would perform better. It is not unexpected that the 20 mg dose perform no better than the 10 mg dose if 1) the exposures were in the plateau of maximal effect for the exposure-response relationship and 2) if the PFS risk factors identified in the final cox PH model suggest that the 10 mg dose will do better.

3.2.3 Response to FDA Clinical Pharmacology Information Request Dated Oct-15-2015

The FDA submitted an information request to the applicant on Oct-15-2015. This request is outlined in Section 1.1.4.2. The sponsor simulated elotuzumab exposures for 4 dosing scenarios (Section 3.2.3.1) and then used these regimens to simulate PFS for varying degrees of elotuzumab exposure and M-protein concentrations using pooled data from CA204004 and HuLuc63-1703 (Section 3.2.3.2) and from Trial CA204004 only (Section 3.2.3.3)

3.2.3.1 Predicted Concentration-Time Profiles and Cavgss

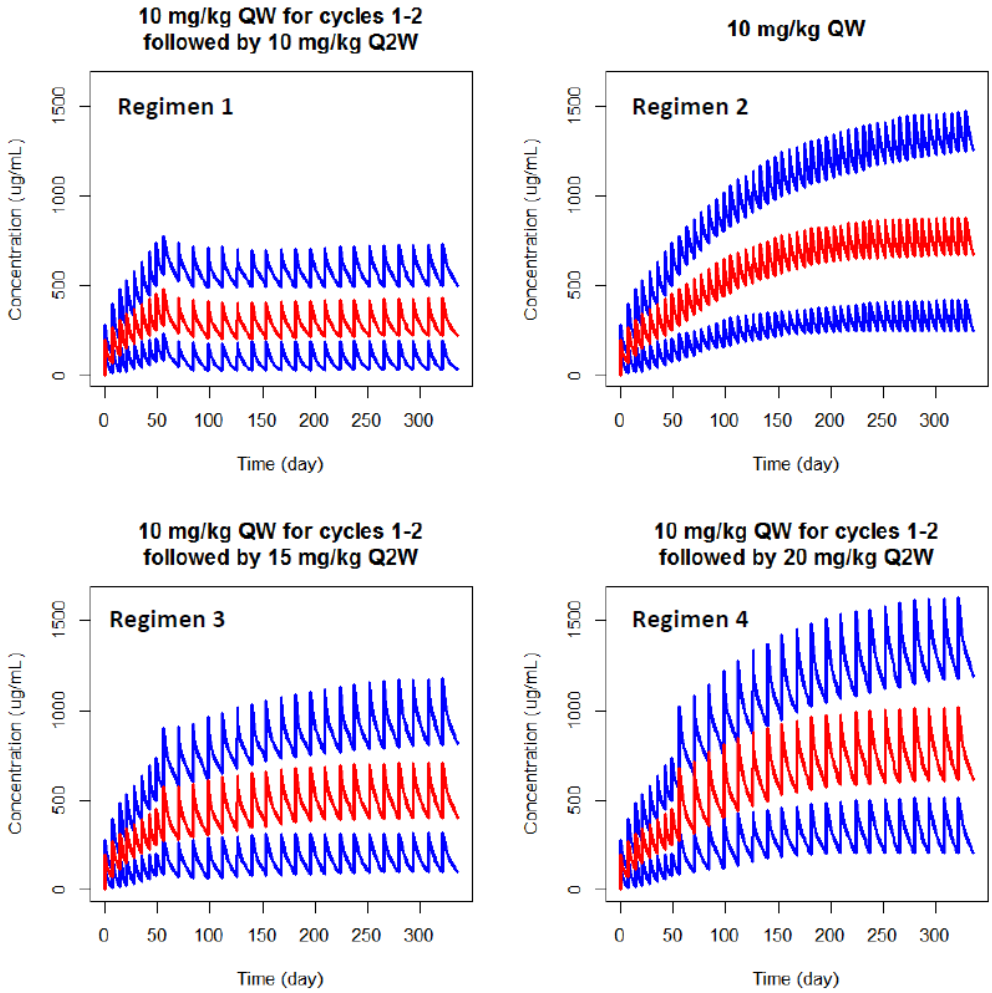
"The final population PPK model, submitted in support of elotuzumab in combination with lenalidomide and dexamethasone in multiple myeloma (MM) patients, was used to simulate the concentration-time profiles and the time-averaged steady state concentration (Cavgss) for the following 4 dosing regimens:

- Regimen 1: 10 mg/kg QW for cycle 1 and 2, followed by 10 mg /kg Q2W thereafter (regimen studied in CA204004)
- Regimen 2: 10 mg/kg QW for all cycles
- Regimen 3: 10 mg/kg QW for cycle 1 and 2, followed by 15 mg /kg Q2W thereafter
- Regimen 4: 10 mg/kg QW for cycle 1 and 2, followed by 20 mg /kg Q2W thereafter

"The simulated concentration-time profiles and Cavgss are provided in Figure 16 and Figure 8, respectively. As can be seen from Figure 16, elotuzumab serum concentrations continue to increase beyond Cycle 2 (Day 56) for Regimens 2, 3, and 4; compared to Regimen 1 (the

regimen used in CA204004). Compared to Regimen 1, the median simulated Cavgss was approximately 2-fold higher in Regimen 3 and approximately 3-fold higher in Regimens 2 and 4 (Figure 8)."

Figure 16. Simulated elotuzmab concentration-time profile, by dosing regimen.



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 1)

3.2.3.2 Pooled Model and Simlations for HuLuc63-1703 and CA204004 combined.

The parameters in the PFS model (developed with data from only CA204004)1 were re-estimated with a pooled data set (CA204004 and HuLuc63-1703), to minimize the extent to which PFS model predictions would have to be extrapolated beyond the range of the data used to develop the model. HuLuc63-1703 was a randomized Phase 2 study in which relapsed MM patients were treated with either 10 or 20 mg/kg elotuzumab, and the Cavgss exposures of the patients who received 20 mg/kg elotuzumab were similar to the exposures in Regimens 2 and 4. Inclusion of the data from HuLuc63-1703 minimized the extent to which Cavgss model predictions were extrapolated.

The parameters of the re-estimated PFS model are presented in Table 12 and the covariate effect plot for this model is presented in Figure 17. Covariate Effects on the PFS Hazard

Ratio for Final Cox Proportional-Hazards Model – Progression-free Survival with pooled data from CA204004 and HuLuc63-1703.

Table 12. Parameter Estimates for Final Cox Proportional-Hazards Model, Progression-free Survival for Pooled Model (HuLuc63-1703 and CA204004).

Predictor (Comparator:Reference)[a]	Coefficient	SE	RSE (%)	Hazard Ratio	Hazard Ratio 95% CI
C_{avgSS}[b] [µg/mL]	-0.00137	0.000271	19.82	0.9986	0.9981-0.9992
LDH[b,c] [time of LDH_{ULN}]	0.6776	0.1564	23.09	1.969	1.449-2.676
B2MICG[b,d] [mg/L]	0.5794	0.09226	15.92	1.785	1.49-2.139
Time from disease diagnosis (≥ median: < median)	-0.7143	0.1087	15.22	0.4896	0.3956-0.6058
Prior IMiD Therapy (Yes: No)	0.3994	0.1016	25.44	1.491	1.222-1.82
Prior stem cell transplantation (Yes: No)	0.4193	0.1108	26.42	1.521	1.224-1.89
Chromosomal Abnormality T(4,14) (Yes: No or Unknown)	0.5603	0.1543	27.54	1.751	1.294-2.369

Analysis-Directory: global/pkms/data/CA/204/C01/prd/ppk-pfs-sim/sd/For_FDA_10_22_2015
Source: Analysis-Directory/PFS_simulations_tables/finalCombinedModelTablePFS.csv

[a] Applicable to categorical covariates.

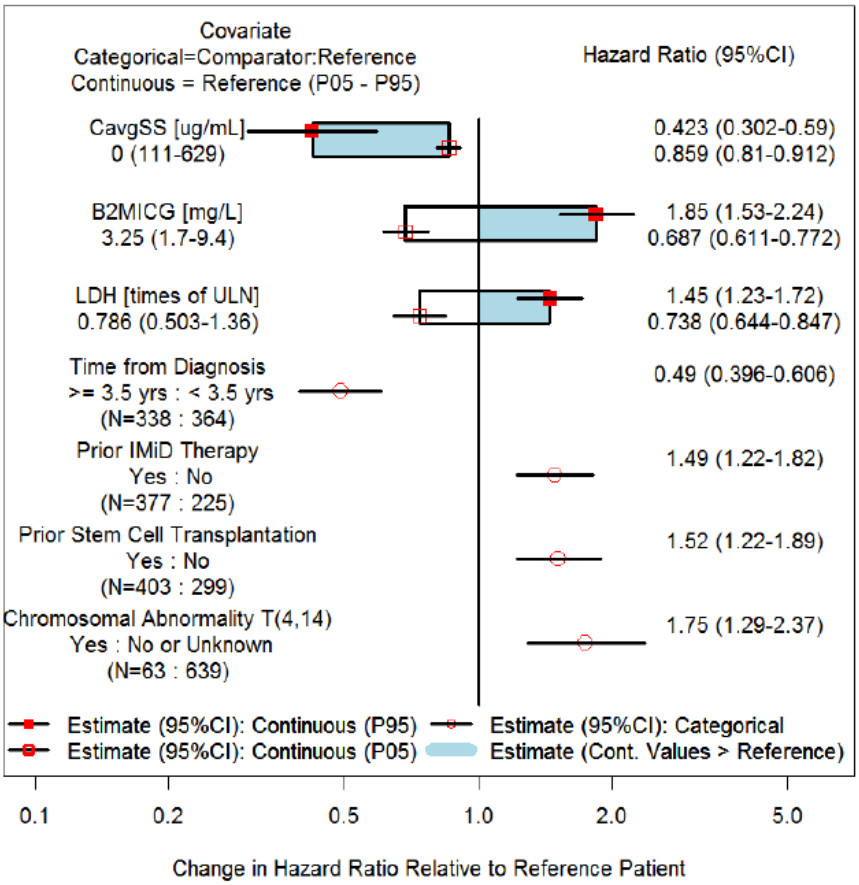
[b] Hazard ratio coefficient represents the hazard ratio for one unit of change in the predictor variable.

[c] LDH/LDH_{ULN} ratio has been log transformed; log transformed ratio increases by one unit for approximately 2.7 fold increase in LDH.

[d] B2MICG has been log transformed, log transformed value increases by one unit for approximately 2.7-fold increase in B2MICG.

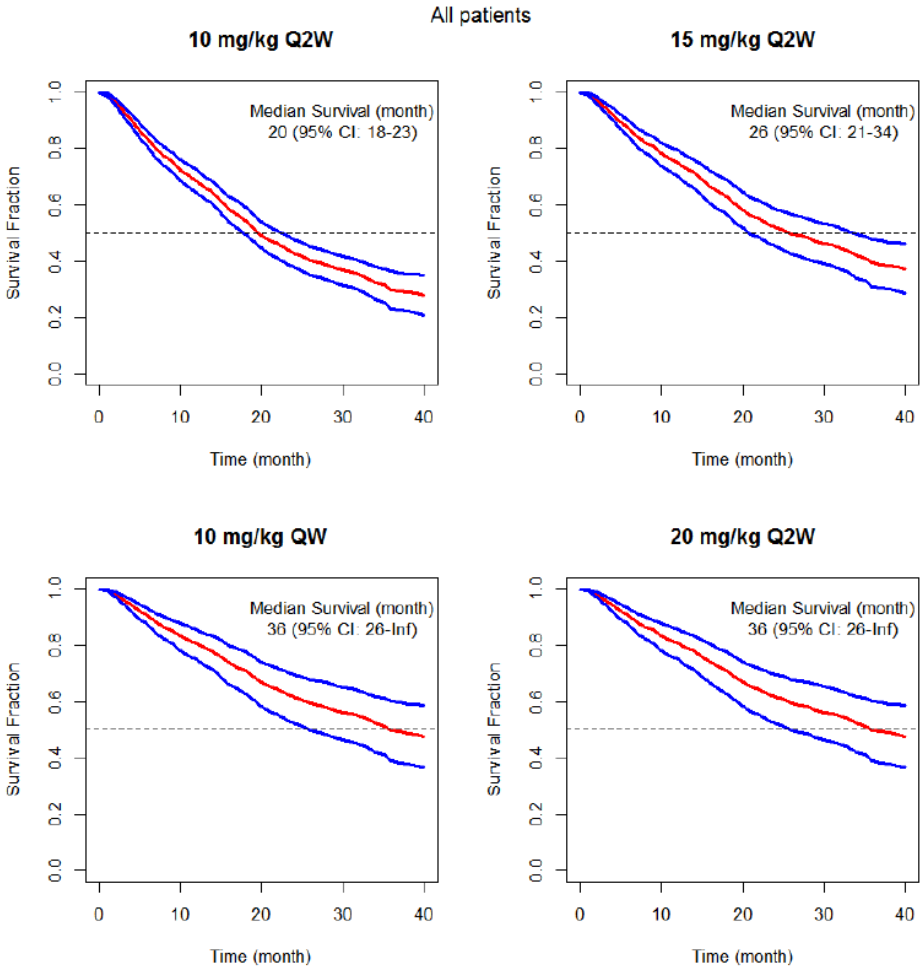
(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Table 1)

Figure 17. Covariate Effects on the PFS Hazard Ratio for Final Cox Proportional-Hazards Model – Progression-free Survival with pooled data from CA204004 and HuLuc63-1703



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 3)

Figure 18. Predicted PFS using 4 different elotuzumab dosing regimens in the combined population.



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 5)

The applicant's conclusions regarding the simulations are noted as follows:

"Predicted PFS in patients with high M-protein (> median)

The Kaplan-Meier plots for the predicted PFS for the 4 different regimens in a subgroup of patients with high M-protein (> median) are shown in Figure 10. In patients with high M-protein, an increase in median PFS predicted for the regimens that produce higher Cavgss values (see exposure estimates in Figure 8). An increase in Cavgss by approximately 2-fold (Regimen 3, see Figure 8) results in an increase in median PFS by 4 months, and an increase in exposures by 3-fold (Regimens 2 and 4, Figure 8) results in an increase in median PFS by 10 months, relative to Regimen 1. However, the increase in predicted median PFS with increasing Cavgss in patients with high M-protein is much lower in magnitude as compared to the entire elotuzumab-treated population (Figure 10 vs Figure 18).

It is important to note that although M-protein is not a significant covariate retained in the final CPH model, the predicted PFS for patients with high M-protein is lower than the predicted PFS in the entire population. This suggests that M-protein is correlated with other disease state factors

that might be related to efficacy, suggesting that the effect of M-protein is accounted for by these covariates."

"Predicted PFS in patients with Cavgss in the lower 25% quartile of study CA204004

The Kaplan-Meier plots for the predicted PFS for the 4 different regimens in patients with Cavgss in the lower 25% quartile (Quartile 1) of study CA204004 is shown in Figure 9. As can be seen from the figure, an increase in median PFS is predicted for the regimens that produce higher Cavgss values (see exposure estimates in Figure 8). Increasing Cavgss by 2-fold (as shown in Figure 8 for Regimen 3) results in an increase in median PFS by 3 months, and increasing the Cavgss by 3-fold (as shown in Figure 8 for Regimens 2 and 4) results in an increase in median PFS by 6 months, relative to Regimen 1. However, the increase in median PFS with increasing Cavgss in the Quartile 1 from CA204004 is much lower in magnitude compared to the entire population."

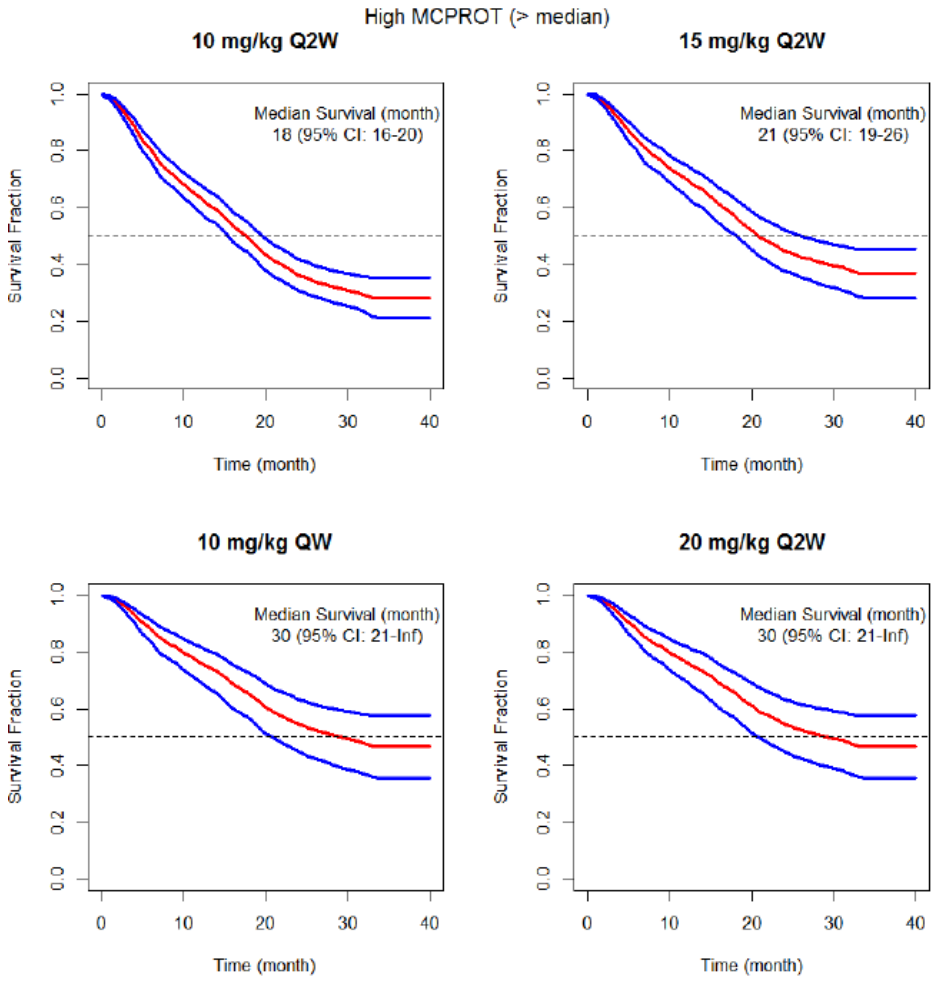
3.2.3.3 Simulations using the final Cox proportional hazards model for PFS from the Applicant's original submission for CA204004 only.

The applicant's conclusions regarding the simulations are noted as follows:

"Predicted PFS in patients with high M-protein (>median)

Figure 19 provides the Kaplan-Meier plots for predicted PFS in patients with high M-protein (> median). As can be seen from the figure, an increase in median PFS is predicted for the regimens that produce higher Cavgss values (see exposure estimates in Figure 8). Increasing Cavgss by 2-fold (as shown in Figure 8 for Regimen 3) results in an increase of median PFS by 3 months, and increasing the Cavgss by 3-fold (as shown in Figure 8 for Regimens 2 and 4) results in an increase of median PFS by 12 months in patients with high M-protein.**"**

Figure 19. Predicted PFS for 4 different regimens in patients with high M-protein (>median).

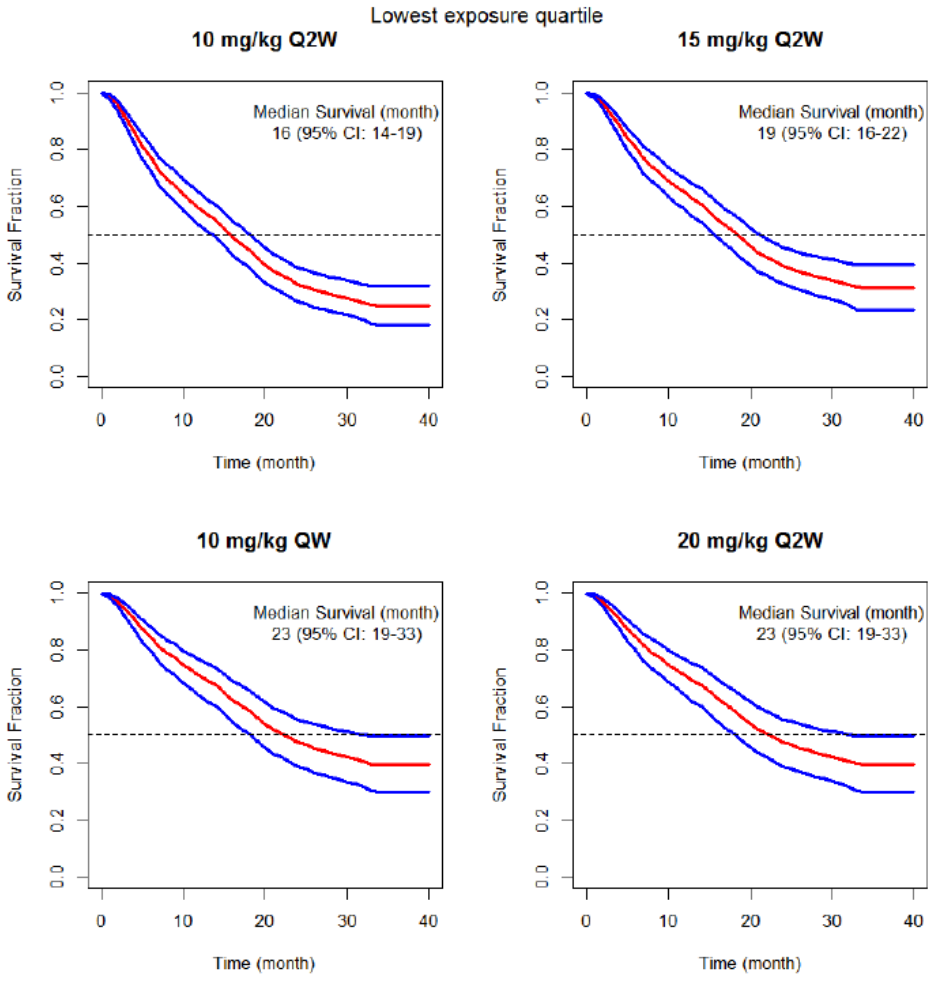


(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 8)

"Predicted PFS in patients with Cavgss in the lower 25% quartile of study CA204004

Figure 20 provides the Kaplan-Meier plots for predicted PFS in patients with Cssavg in the lower 25% quartile of Study CA204004. As can be seen from the figure, an increase in median PFS is predicted for the regimens that produce higher Cavgss values (see exposure estimates in Figure 8). Increasing Cavgss by 2-fold (as shown in Figure 2 for Regimen 3) results in an increase in median PFS by 3 months and increasing the Cavgss by 3-fold (as shown in Figure 2 for Regimens 2 and 4) results in an increase in median PFS by 7 months.**"**

Figure 20. Predicted PFS for 4 different regimens in patients with Cavgss in the lower 25% quartile of Study CA204004



(Source: Applicant's Response to FDA Information Request, Oct-22-2015, Figure 9)

Applicant's Conclusions:

- "Compared to Regimen 1 (10 mg/kg QW for cycle 1 and 2, followed by 10 mg /kg Q2W thereafter), the median simulated Cavgss was approximately 2-fold higher in dosing Regimen 3 (10 mg/kg QW for cycle 1 and 2, followed by 15 mg /kg Q2W thereafter) and approximately 3-fold higher in Regimens 2 (10 mg/kg QW for all cycles) and 4 (10 mg/kg QW for cycle 1 and 2, followed by 20 mg /kg Q2W thereafter).
- Simulations to predict PFS based on the pooled model (CA204004 and HuLuc63-1703 study) as well as CA204004-only model demonstrated an increase in median PFS with increasing Cavgss for Regimens 2, 3 and 4, relative to Regimen 1 in all the simulated scenarios
- The increase in median PFS was lower in magnitude in patients with high M-protein or in patients in the lower 25% quartile of Cavgss in study CA204004, relative to the entire population.

- Modeling Cavgss as a linear functional form has the limitation of inherently demonstrating a trend of increasing PFS with increasing Cavgss, even though the underlying relationship might reach an asymptote with increasing Cavgss. This was illustrated by performing an ER analysis for PFS performed using quartiles of Cavgss instead of using Cavgss as a continuous covariate. Based on this analysis, the hazard ratio for Q2-Q4 was very similar (0.47-0.63) and the HR for Q1 was close to 1 indicating that the benefit from increasing elotuzumab Cavgss is likely to reach an asymptote beyond a certain elotuzumab concentration.
- CL, but not Cavgss, was a significant predictor in the ER analysis for PFS in study HuLuc63-1703 indicating that disease state factors, not fully accounted for in the model, may contribute to PFS.

"Although this analysis suggests that Q1 Cavgss patients could theoretically benefit from increased CavgSS using from Regimens 2, 3 and 4, the confounding effect of disease state on the overall patient population, and specifically Q1 patients, makes it difficult to draw any definitive conclusions. In addition, there was no additional PFS benefit of increased elotuzumab exposure observed with the 20 mg/kg dosing regimen investigated in Study HuLuc63-1703 (which had Cavgss exposures similar to those simulated for Regimens 2 and 4)."

Reviewer's Comments:

As part of this analysis the applicant chose to include the phase 2 data from Study Huluc63-1073 in their analysis. This was done in part because these patients received a 20 mg dose, but it should be recognized that they were a different population and bias the analysis towards for patients with lower M-protein and β2-microglobulin. The concern from this analysis has been for patients that have higher risk factors for PFS and lower elotuzumab exposure.

The applicant noted that a linear effect may suggest benefit for patients with higher exposure, when effect may already be at plateau. The reviewer agrees with this. However, we are primarily concerned with patients that do not fall into this plateau and are at the lower end of exposure. It appears that this model overestimates the PFS duration even before increasing the Cavgss to assess the effect of increasing the dose. This might suggest that the benefit of increasing the dose may be underestimated, particularly if these exposures are not in the plateau of response. One additional check that was performed was to evaluate exposure-response within Q1 to determine if the trend remained. In fact there still appeared to be a correlation with exposure within Q1 of the phase 3 data (see Figure 21 for further details).

While these analyses suggest some benefit in this population, the simulations do not accurately predict the PFS behavior at the low and high exposure extremes of the data. Additionally patients were not evaluated with dose increases and model covariates may be from mutually exclusive subsets of patients within the population. Thus, it cannot be concluded how much effect increasing the dose will have at this point without conducting a study to evaluate increasing the dose in patients with higher risk factors. Given that the observed data and the case control analysis appear to suggest that an even greater benefit may be possible for patients at higher risk, and this is consistent with one of the clearance mechanisms of elotuzumab, there is no reason why patients with lower exposure should be ignored. For this reason we are recommending a post marketing commitment for analysis of data from the ongoing trial in multiple myeloma patients, trial CA204006.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The applicant identified M-protein as a major covariate of elotuzumab clearance. As M-protein is correlated with elotuzumab exposure and also progression free survival, the question was raised as to whether patients with higher M-protein could benefit (in PFS) from a higher dose. Additionally this question was taken one step further to evaluate other potential covariates of response (B2-microglobulin and lactate dehydrogenase) that also correlate with exposure and give a demographic where the sicker patients are those that had the lowest exposure and these patients have the shortest PFS. In essence, there is a correlation between two factors (tumor burden and exposure) that influence the response (PFS). It is the aim of this review to identify whether exposure is one of these factors and if so could increasing the dose increase PFS for patients with lower exposure.

4.2 Objectives

Analysis objectives are:

1. Evaluate the impact of M-protein on elotuzumab clearance
2. Determine the exposure-response relationship for PFS
3. Ascertain whether the exposure response relationship for PFS still exists after a case control analysis for all other significant covariates in the applicant's model and also M-protein.
4. Ascertain whether phase 2 data with a higher dose can support the determination for additional benefit at higher exposures.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 13.

Table 13. Analysis Data Sets

Study Number	Name	Link to EDR
CA204004 Population PK	*.xpt	\\CDSESUB1\evsprod\BLA761035\0001\m5\datasets
CA204009 Population PK	*.xpt	\\CDSESUB1\evsprod\BLA761035\0001\m5\datasets
Huluc63-1703	*.xpt	\\CDSESUB1\evsprod\BLA761035\0001\m5\datasets
CA204009	*.xpt	\\CDSESUB1\evsprod\BLA761035\0001\m5\datasets

4.3.2 Software

The statistical software R (version 2.15, http://www.r-project.org/) was utilized for all cox-propotional hazards models and figures. The statistical software SAS (version 9.3, Cary, NC) was utilized for the case control analyses. NONMEM (Version 7.3) was used for running the applicant's population PK models.

4.3.3 Models

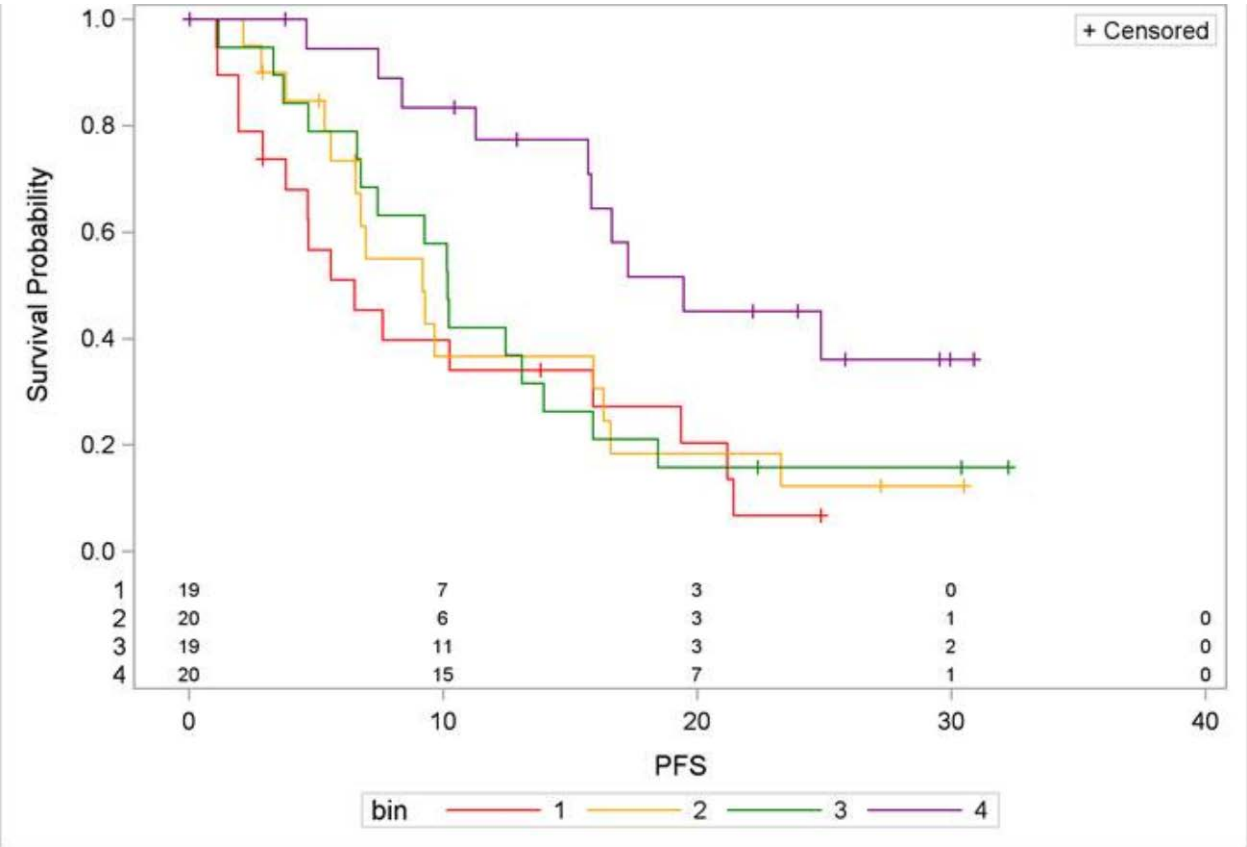
No original population PK or cox-proportional hazards modeling was performed.

4.4 Results

4.4.1 Does the exposure response-PFS trend hold for data within the first quartile of elotuzumab exposure?

As an additional check to evaluate whether there is truly and exposure benefit within the first quartile of elotuzumab exposure, another exposure response analysis was conducted for only the Q1 data. The first quartile of exposure was broken into four quartiles based on exposure and the KM curves are shown in Figure 7. It appears this relationship hold in that patients with lower exposure exhibit shorter PFS duration.

Figure 21. Exposure-response for PFS appears to hold within patients in the first 25% of elotuzumab exposure in trial 204004.



4.4.2 Do the results of the exposure-response change with different PK metrics of exposure over time?

Yes, the exposure-response appears to change with different metrics of exposure based on different times of PK assessment. The exposure-response relationship becomes somewhat dampened with the use of PK metrics characterizing the exposure earlier in time. But, there appears to be internal consistency for exposure-response analysis results with various exposure-

metrics indicating that patients in the lowest elotuzumab exposure quartile may not derive additional benefit with addition of elotuzumab over lenalidomide/dexamethasone.

As baseline M-protein is a covariate of exposure in the population PK model, the time course of M-protein was plotted for a number of subjects to evaluate whether a time-varying analysis would be necessary. Figure 6 shows that M-protein appears to decline in concentration within the first few cycles of elotuzumab administration and remains suppressed for the majority of the trial.

Figure 22. An example subset of M-protein time courses illustrates that M-protein concentrations decrease after administration of elotuzumab. Y-axis is M-protein concentration (g/dL)

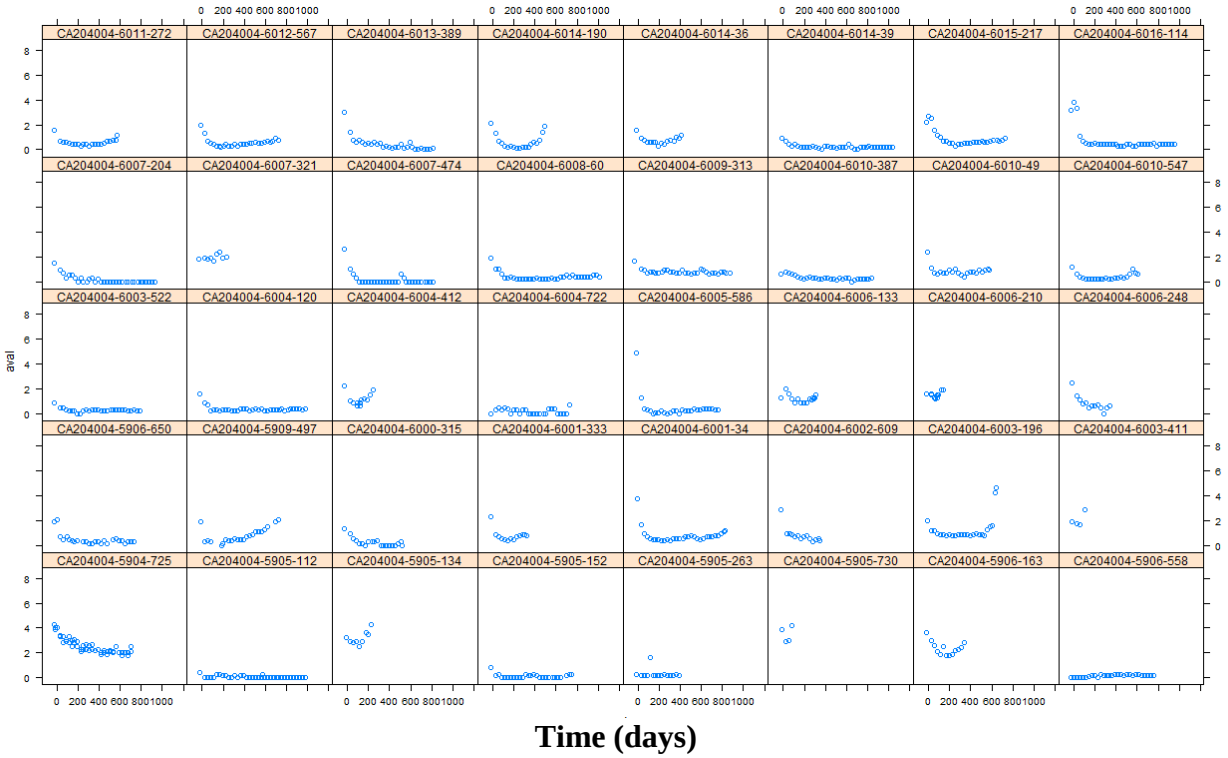


Figure 7 shows an example time course of concentrations available for a number of subjects in trial CA204004. Four metrics of elotuzumab exposure were defined in addition to the CavgSS defined by the sponsor for the exposure response analysis. The average of elotuzumab concentrations for predose, 30 minutes post dose, and 2 hrs post dose were taken for cycle 1 to define the exposure metric for that cycle. The average of the observed concentrations of each of the first 3 cycles were the first three metrics of exposure. The fourth was the average of the predose concentrations for each cycle after cycle 2, a steady-state trough concentration.

Figure 23. Example PK Time Courses. Y-axis is the elotuzumab concentration (ug/mL)

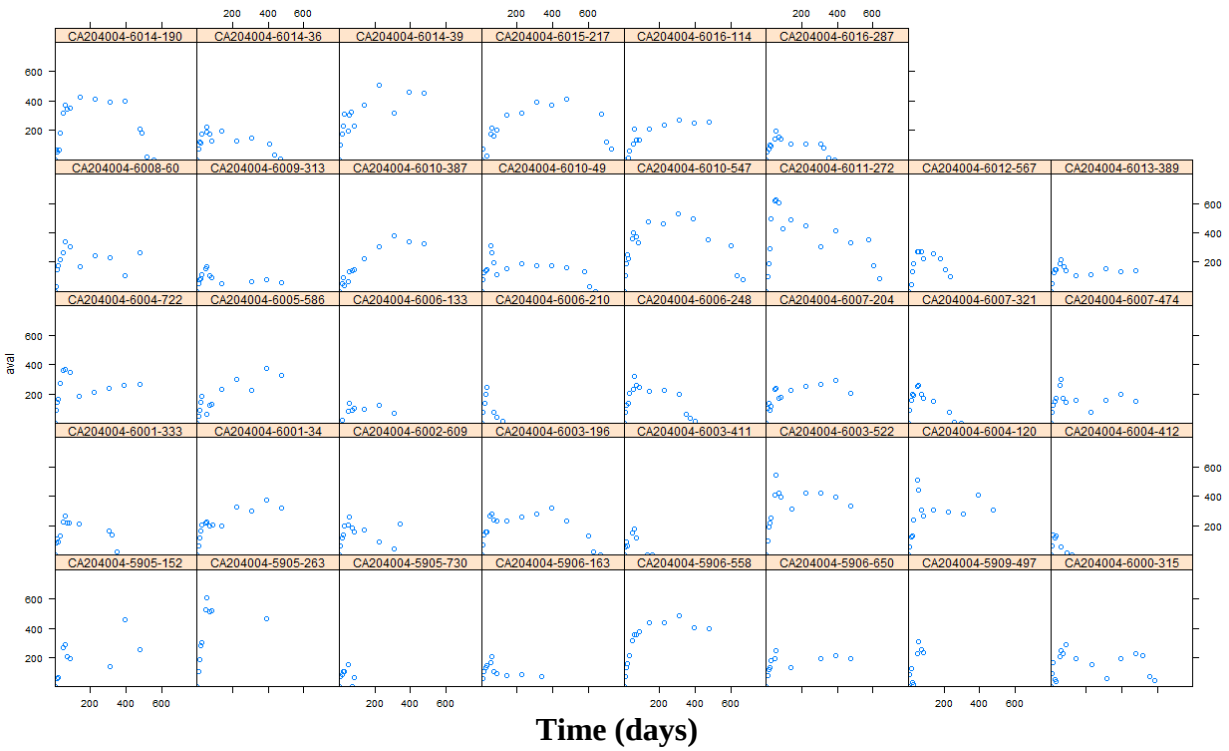


Figure 2 through Figure 5 shows the KM curves for each elotuzumab exposure quartile and the lenolidamide/dexamethasone control for the Cycle 1, Cycle 2, Cycle 3 exposure metrics, and the average Cmin after cycle 3. These KM curves are based on a univariate assessment of exposure for each exposure metric and do not reflect and equal distribution of other potential confounding factors. It is apparent from these plots that the KM curve and demographic of patients in Q1, Q2, Q3, and Q4 shift depending on the time of the exposure metric used and that the plot for Cmin at steady-state (Figure 5) is very similar to that for the steady-state Cavg computed by the applicant using their population PK model (Figure 2). However, there still appears to be an apparent exposure-response relationship after accounting for this change in metric using Cycle 1 Cavg (Figure 6).

Figure 24. Univariate exposure-response for PFS using the Cycle 1 exposure metric (average of predose, 30 minute, and 2 hrs).

Black = Len/Dex Control, Blue = Add-on Elotuzumab Q1, Light Blue = Add on Elotuzumab Q2, Green = Add on Elotuzumab Q3, Red = Q4

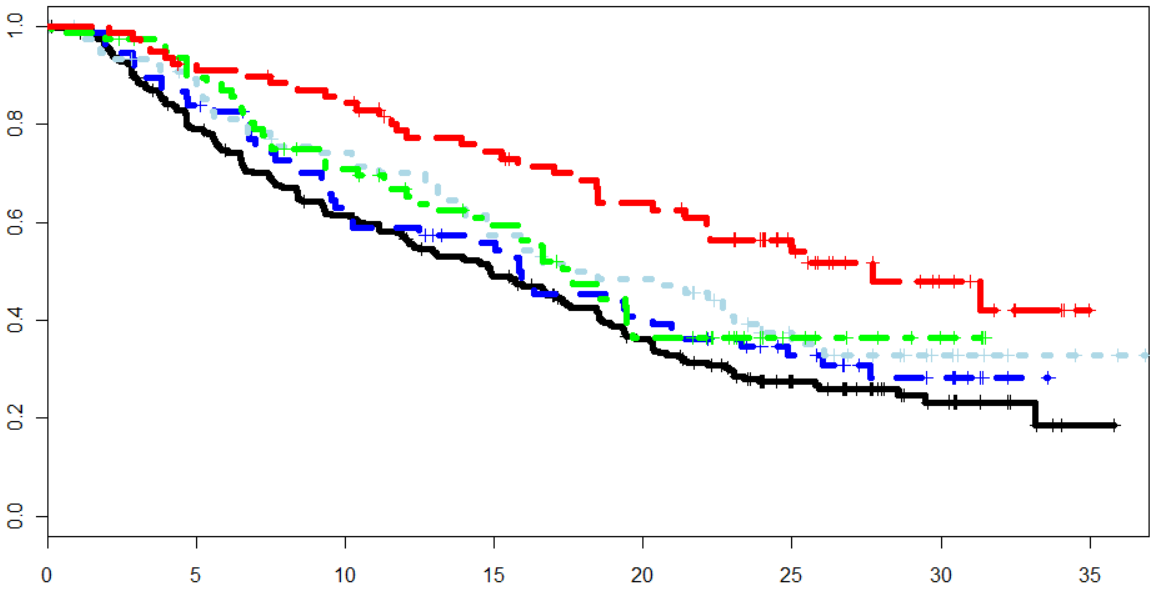


Figure 25. Univariate exposure-response for PFS using Cycle 2 exposure metric (average of predose, 30 minute, and 2 hrs).

Black = Len/Dex Control, Blue = Add-on Elotuzumab Q1, Light Blue = Add on Elotuzumab Q2, Green = Add on Elotuzumab Q3, Red = Q4

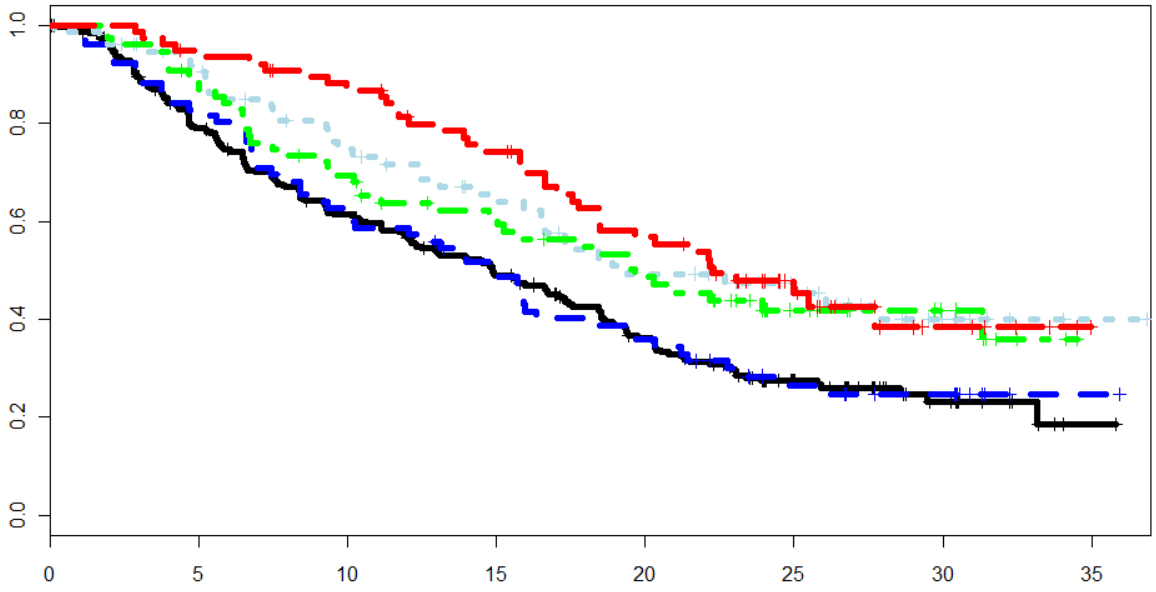


Figure 26. Univariate exposure-response for PFS using Cycle 3 exposure metric (average of predose, 30 minute, and 2 hrs).

Black = Len/Dex Control, Blue = Add-on Elotuzumab Q1, Light Blue = Add on Elotuzumab Q2, Green = Add on Elotuzumab Q3, Red = Q4

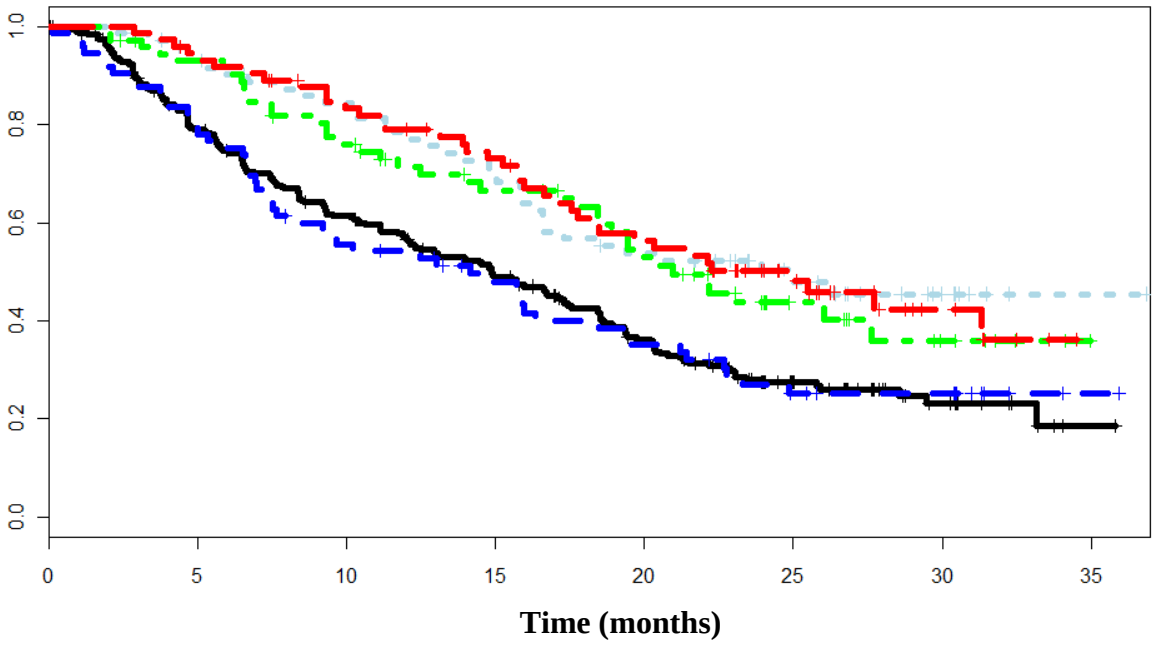
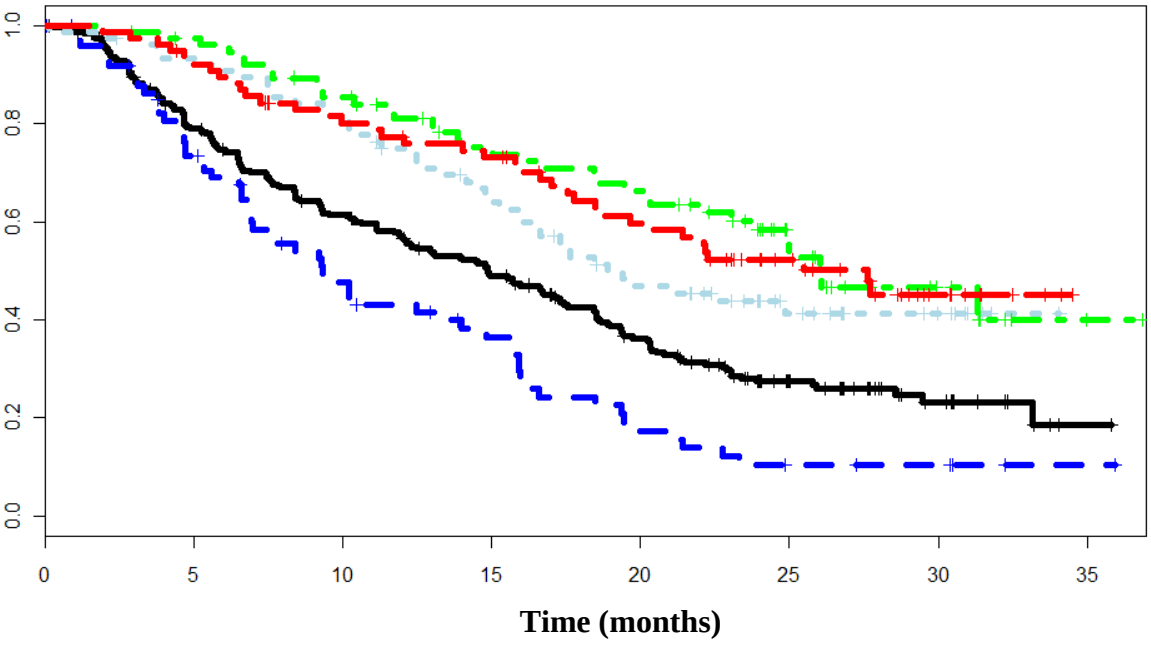


Figure 27. Univariate exposure response for PFS using the average steady-state Cmin after Cycle 3.

Black = Len/Dex Control, Blue = Add-on Elotuzumab Q1, Light Blue = Add on Elotuzumab Q2, Green = Add on Elotuzumab Q3, Red = Q4



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
CoxPH_PFS.R	Cox proportional hazards analysis evaluation	..\PM Review Archive\2015\Elotuzumab_BLA761035_JCE\ER Analyses
ER_CaseControl_2.sas	Final Case Control analysis file and file used to evaluate phase 2 study data.	..\PM Review Archive\2015\Elotuzumab_BLA761035_JCE\ER Analyses
Run*.mod	Population PK model variations used to evaluate applicant's PK model	..\PM Review Archive\2015\Elotuzumab_BLA761035_JCE\PPK Analyses\NONMEM_Elotuzumab

4.3 Cover sheet and OCPB Filing/Review Form

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

Elotuzumab is a SLAMF7-directed immunostimulatory antibody indicated for the treatment of patients with MM who have received ≥ 1 prior therapies in combination with lenalidomide and dexamethasone (Len/Dex) [redacted] (b) (4) The applicant proposes the following doses:
With Len/Dex: 10 mg/kg IV QWK for the first two cycles and Q2WKS thereafter until disease progression or unacceptable toxicity.
[redacted] (b) (4) The applicant has submitted the results of 1 pivotal trial in which Elotuzumab was administered in combination with lenalidomide and dexamethasone and a Phase 2 clinical trial in which Elotuzumab was administered with bortuzemib and dexamethasone.
For this submission, the clinical pharmacology sections include the results of a population PK and exposure-response analysis for efficacy, the results of a renal study as well as the results of a study evaluating the ECG effects of Elotuzumab. The immunogenic potential of Elotuzumab interacting with its PK was also evaluated.

	Information		Information
NDA/BLA Number	**BLA 761035**	**Brand Name**	**EMPLICITI**
OCP Division (I, II, III, IV, V)	**DCPV**	**Generic Name**	**elotuzumab**
Medical Division	**DHP**	**Drug Class**	**SLAMF7-directed immunostimulatory antibody**
OCP Reviewer	**Olanrewaju Okusanya, PharmD, MS**	**Indication(s)**	**the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone** [redacted] (b) (4)
OCP Team Leader	**Gene Williams, Ph.D.**	**Dosage Form**	**lyophilized powder for injection**
Pharmacometrics Reviewer		**Dosing Regimen**	**10 mg/kg IV every week (qwk) for the first two cycles (28 day) and q2wk thereafter when administered with lenalidomide and low-dose dexamethasone.** [redacted] (b) (4)
Date of Submission	**June 29, 2015**	**Route of Administration**	**intravenous**
Estimated Due Date of OCP Review		**Sponsor**	**Bristol-Meyer Squibb**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**December 29, 2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**14**		**Validation for PK, PD, ADA, NADA. Reports for HuLuc63-1701, and HuLuc63-1702**
I. Clinical Pharmacology				
Mass balance:	**NA**			**not applicable for Mab**
Isozyme characterization:	**NA**			
Blood/plasma ratio:	**NA**			
Plasma protein binding:	**NA**			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**NA**			
multiple dose:	**NA**			
Patients-				
single dose:	**NA**			
multiple dose:	**X**	**8**		**HuLuc63-1701, HuLuc63-1702, CA204005, HuLuc63-1703, CA204007, CA204009, CA204011, CA204004**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		**HuLuc63-1701**
fasting / non-fasting multiple dose:	**X**			**HuLuc63-1701, HuLuc63-1702**
Drug-drug interaction studies -				
In-vivo effects **on** primary drug:	**X**	**1**		**HuLuc63-1702**
In-vivo effects **of** primary drug:	**NA**			
In-vitro:	**NA**			
Subpopulation studies -				
ethnicity:	**NA**			
gender:	**NA**			
pediatrics:	**NA**			
geriatrics:	**NA**			
renal impairment:	**X**	**1**		**CA204007**
hepatic impairment:	**NA**			**Assessed in POP PK eval. CA204004**
PD -				
Phase 2:	**X**	**7**		
Phase 3:	**X**	**1**		**CA204004**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**			**CA204004**
Population Analyses -				
Data rich:				
Data sparse:	**X**	**2**		**CA204004, CA204009**
II. Biopharmaceutics	**NA**			
Absolute bioavailability	**NA**			
Relative bioavailability -	**NA**			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**NA**			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**NA**			
Bio-waiver request based on BCS	**NA**			
BCS class	**NA**			
Dissolution study to evaluate alcohol induced dose-dumping	**NA**			
III. Other CPB Studies				
Genotype/phenotype studies	**1**			**CA204011**
Chronopharmacokinetics	**NA**			
Pediatric development plan	**NA**			
Literature References	**X**	**184**		
Total Number of Studies		**8**		

On **initial** review of the NDA/BLA application for filing:

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			Mab, so no metabolism data. Some DDI data was provided
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable. A key question evaluating if patients with higher M-protein values at baseline have the option to receive a higher dose of Elotuzumab will be considered in this application.

PLEASE IDENTIFY AND LIST ANY POTENTIAL REVIEW ISSUES TO BE FORWARDED TO THE APPLICANT FOR THE 74-DAY LETTER.
None.

Olanrewaju Okusanya, Pharm.D, MS	08/17/2015
Reviewing Clinical Pharmacologist	Date
Gene Williams, Ph.D	08/17/2015
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OLANREWAJU OKUSANYA
11/02/2015

JUSTIN C EARP
11/02/2015

GENE M WILLIAMS
11/02/2015
I concur with the recommendations

NITIN MEHROTRA
11/02/2015

VIKRAM P SINHA
11/02/2015

NAM ATIQUR RAHMAN
11/02/2015
I concur with the recommendation.