CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 207155 SDN 20
Type/Category	Standard
Brand Name	EVOMELA™ (Captisol®-enabled Melphalan HCl) for Injection
Generic Name	Melphalan
Receipt Date	November 7, 2015
PDUFA Date	May 6, 2016
Proposed Indication	Captisol®-enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan) is an alkylating agent indicated for: use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell trans-plantation in patients with multiple myeloma. the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
Dosage Form	(b) (4) powder
Route of Administration	IV
Dosing Regimen and Strength	For **Conditioning Treatment**, the recommended dose of CE- Melphalan is 100 mg/m^2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0). For **Palliative Treatment**, the recommended dose of CE- Melphalan is 16 mg/m^2 administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week
Applicant	Spectrum Pharmaceuticals. Inc.
OND Division	Division of Hematology Products (DHP)
OCP Divisions	Division of Clinical Pharmacology V (DCPV)
OCP Reviewers	Christy S. John, Ph.D.
OCP Team Leaders	Gene Williams, Ph.D.

1.   EXECUTIVE SUMMARY

This 505 (b) (2) NDA was initially submitted on December 23, 2014. It was found approvable from a clinical pharmacology perspective (DARRTS date September 18, 2015). It was not approved because of CMC concerns. The applicant was sent a Complete Response letter on October 22, 2015. The current NDA resubmission (November 7, 2015) does not contain any new clinical pharmacology data or analyses. We continue to recommend approval.

1.1 RECOMMENDATIONS

The NDA 207155 is approvable from a clinical pharmacology perspective.

1.2 POST-MARKETING REQUIREMENTS AND COMMITMENTS

None

SIGNATURES

_____   _____

Christy S. John, Ph.D.   Gene Williams, Ph.D.
Reviewer   Team Leader
Division of Clinical Pharmacology V   Division of Clinical Pharmacology V

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

/s/

CHRISTY S JOHN
02/29/2016

GENE M WILLIAMS
02/29/2016
I concur with the recommendation

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 207155 SDN 1 and SDN12 \\CDSESUB1\evsprod\NDA207155\
Type/Category	Standard
Brand Name	EVOMELA™ (Captisol®-enabled Melphalan HCl) for Injection
Generic Name	Melphalan
Receipt Date	December 23, 2014 and September 2, 2015
PDUFA Date	October 11, 2015

Proposed Indication	Captisol®-enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan) is an alkylating agent indicated for:
	  1) use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell trans-plantation in patients with multiple myeloma.
	  2) the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Dosage Form	(b) (4) powder
Route of Administration	IV
Dosing Regimen and Strength	For **Conditioning Treatment**, the recommended dose of CE-Melphalan is 100 mg/m^2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0). For **Palliative Treatment**, the recommended dose of CE-Melphalan is 16 mg/m^2 administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.
Applicant	Spectrum Pharmaceuticals. Inc.
OND Division	Division of Hematology Products (DHP)
OCP Divisions	Division of Clinical Pharmacology V (DCPV)
OCP Reviewers/PM Reviewer	Christy S John, Ph.D./ Christy S John, Ph.D.
PM Secondary Reviewer	Justin Earp, Ph.D.
OCP Team Leaders	Gene Williams, Ph.D.

1

Table of Contents

1. EXECUTIVE SUMMARY

The applicant has submitted a 505(b)(2) application for the approval of Captisol® enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan). The proposed indications are 1) for use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma, and 2) for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. For conditioning treatment, the recommended dose of CE-Melphalan is 100 mg/m^2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day 3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0). For palliative treatment, the recommended dose is 16 mg/m^2 administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.

Study CDX-353-001 was a comparative bioavailability and bioequivalence, Phase 2a single-center, open-label, randomized, crossover study (N=24) of high-dose (100 mg/m^2) CE-Melphalan HCl and Melphalan HCl (Alkeran for Injection, FDA approved drug). The applicant demonstrated that the new formulation was equivalent (80 -125% for AUC and C_{MAX}) to Alkeran.

Study CDX-353-002 was a Phase IIb, Multicenter, Open-Label, Safety and Efficacy Study of High-Dose Melphalan HCl for Injection (Propylene Glycol-Free) for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation. The dose of CE-Melphalan HCl used in this trial was 100 mg/m^2 on Day -3 and -2 [Adjusted Ideal Body Weight (AIBW) for patients with > 130% ideal body weight]. CE-Melphalan produced clinically meaningful increases in overall multiple myeloma response rates: 95% versus 79% response rate at post-treatment versus pre-treatment, respectively. Myeloablation was achieved in all 24 patients on CE-Melphalan between Day 0 and 5. Mean myeloablation time was 2.9 days. Similarly, all 24 subjects met criteria for engraftment between Day 9 and Day 13. The mean time to engraftment was 11 days.

PK data was pooled from two studies to build population PK models. In the population PK models, fat-free mass was identified as a covariate on volume of distribution and clearance, and creatinine clearance was identified as a covariate on clearance. However, simulations based on the final model indicated that it is not necessary to adjust CE-Melphalan doses for patients with renal impairment. The median model-predicted AUC in the severe renal impairment group was approximately 20% higher than the median model-predicted AUC in the normal renal function group.

1.1 RECOMMENDATIONS

The NDA 207-155 is acceptable for approval from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding package insert language.

1.2 POST-MARKETING REQUIREMENTS AND COMMITMENTS

None

SIGNATURES

_____   _____

Christy S John, Ph.D.   Justin Earp, Ph.D
Reviewer   Secondary Reviewer
Division of Clinical Pharmacology V   Division of Pharmacometrics

_____

Gene Williams, Ph.D.
Team Leader
Division of Clinical Pharmacology V

4

1.3   SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Study CDX-353-001 was a comparative bioavailability and bioequivalence, Phase 2a single-center, open-label, randomized, crossover study (N=24) of high-dose (100 mg/m^2) CE-Melphalan HCl and Melphalan HCl (Alkeran for Injection, FDA approved drug). The applicant demonstrated that the new formulation was equivalent (80 - 125% for AUC and C_{MAX}) to Alkeran.

Study CDX-353-002 was a Phase IIb, Multicenter, Open-Label, Safety and Efficacy Study of High-Dose CE-Melphalan HCl for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation. The dose of CE-Melphalan HCl used in this trial was 100 mg/m^2 on Day -3 and -2. CE-Melphalan produced clinically meaningful increases in overall multiple myeloma response rates: 95% versus 79% response rate at post-treatment versus pre-treatment, respectively. Myeloablation was achieved in all 24 patients on CE-Melphalan between Day 0 and 5. Mean myeloablation time was 2.9 days. Similarly, all 24 subjects met criteria for engraftment between Day 9 and Day 13. The mean time to engraftment was 11 days.

Drug plasma concentrations declined in a biexponential manner with distribution-phase and terminal-elimination-phase half-lives of 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250-325 mL/min/m^2) were observed. The volume of distribution was 35.5 to 185.7 L/m^2. Melphalan is inactivated in plasma by non-enzymatic hydrolysis to monohydroxymelphalan and dihydroxymelphalan; these two melphalan hydrolysis metabolites are inactive. The excretion of unchanged drug into urine was 21.3% ± 17.1 of dose.

A population PK analysis of plasma concentrations of melphalan (from the proposed formulation [CE Melphalan HCl]) in MM patients undergoing ASCT was conducted from pooled data from two Phase 2 studies (CDX-353-001 and CDX-353-002). As part of the analysis, recommendations for dosage adjustment in patients with renal impairment were investigated by performing simulations using the final PK model. Fat-free mass and creatinine clearance were identified as covariates. The median model-predicted AUC in the severe renal impairment group was only approximately 20% higher than the median model-predicted AUC in the normal renal function group (**Figure 1.**). Due to the small magnitude of changes, it is not necessary to adjust melphalan doses for patients with renal impairment.

5
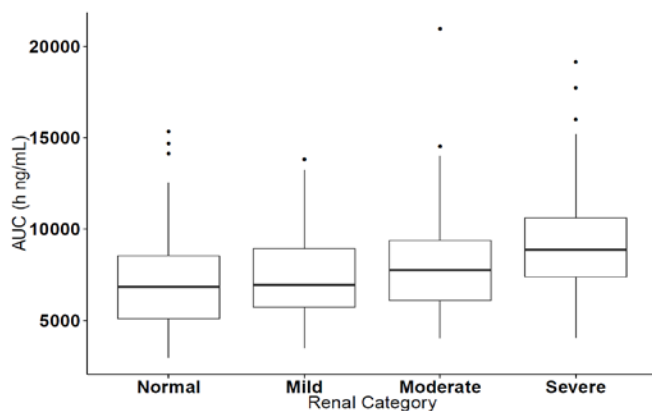
Figure 1. Model predicted AUC with varying CrCL and fat free mass

As part of the population PK analysis from pooled data from the two Phase 2 studies (CDX-353-001 and CDX-353-002), exploratory PK/PD analysis was performed on several PD endpoints of interest. For continuous PD endpoints, possible linear exposure-response relationships were investigated between the PK metrics (AUC, Cmax, and Cmin) and the change from baseline (or percent change from baseline) in white blood cell (WBC) count and platelet count. There were no significant exposure-response relationships between any of the PK metrics and the WBC or the platelet counts. Similarly, exploratory analyses of exposure metrics with AEs of interest (mucositis, diarrhea, nausea, and fatigue) also revealed that there were no exposure-response trends.

In study CDX-353-002, patient electrocardiogram (ECG) assessments were reviewed and analyzed by an independent core laboratory. Electrocardiogram data showed a significant increase in HR, with a peak increase in HR of nearly 20 bpm at Day 7, and HR increases of 10 to 15 bpm through Day 30. It is likely that the increase in HR was related to the stress of myeloablation and autologous transplantation rather than a direct effect of CE-Melphalan HCl on sinus node function. Pharmacokinetic-pharmacodynamic analysis suggested that CE-Melphalan had a small effect on cardiac repolarization, as measured by the positive slope for melphalan in the pharmacokinetic-pharmacodynamic model. The pharmacokinetic pharmacodynamics model predicted an 8.0 ms change from baseline for QTcF at a mean Cmax of 4701 ng/ml, with a one-sided upper 95% confidence interval of 11.4 ms. This small effect is acceptable given the history of the use of Alkeran.

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?

Melphalan is a phenylalanine derivative ⬛⬛⬛ (b) (4) of nitrogen mustard ⬛⬛⬛ (b) (4). CE-Melphalan HCl is a new injectable formulation of melphalan that incorporates the Captisol brand of β-cyclodextrin sulfobutyl ether sodium salts ⬛⬛⬛ (b) (4)

6

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

Melphalan's cytotoxic effects are cell cycle non-specific and are directly related to the concentration and the duration of cell exposure to melphalan. Melphalan adds alkyl groups ^{(b) (4)} to DNA bases and, in turn, interferes with DNA synthesis, RNA transcription, and protein synthesis, leading to mutations and cell death. The cytotoxicity of melphalan appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N7 position of guanine. Like other bifunctional alkylating agents, melphalan is active against both resting and rapidly dividing tumor cells.

The proposed indications are:
- For use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.
- For the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

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

For **Conditioning Treatment**, the recommended dose of CE-Melphalan is 100 mg/m^2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0).

For **Palliative Treatment**, the recommended dose of CE-Melphalan is 16 mg/m^2 administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.

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?

A Phase 2a, randomized, PK, crossover study of CE-Melphalan HCl and Melphalan HCl (Alkeran for Injection) for myeloablative conditioning in MM patients undergoing ASCT (Study CDX-353-001) was performed. The primary new efficacy and safety information for the new formulation is from Study CDX-353-002, "A Phase 2b, Multicenter, Open-Label, Safety and Efficacy Study of High Dose Captisol-enabled Melphalan HCl for Injection (Propylene Glycol-Free) for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation." Study CDX-353-002 included pharmacokinetic sampling.

Other data in support of this CE-Melphalan 505(b)(2) NDA were obtained from published literature describing the kinetics of IV melphalan; published literature describing the use of high-dose melphalan injection in patients with multiple myeloma, and data from the approved

7

prescribing information for the previously approved Melphalan HCl (Alkeran for Injection). The details of studies are shown in **Table 1**.

Table 1. Clinical studies conducted in support of NDA

Study ID/ No. Sites	Country	Study Objective	Study Design	Melphalan Dosing Regimen	Primary Inclusion Criteria	No. Patients/ Exposure (Planned)	Duration of Treatment	Study Population Gender (M/F) Age (Range)	Primary Endpoints
CDX-353-002 5 Sites	US	Estimate Efficacy, Assess Safety	Phase 2b Open-label, single arm, multicenter	CE-Melphalan HCl (total dose-200 mg/m²) 100 mg/m² on Day -3/ 100 mg/m² on Day -2	MM Patients undergoing ASCT	61 2 doses of CE-Melphalan HCl	2 days	M 35/F 26 62.0 (32-73)	Treatment-related Mortality MM response
CDX-353-001 1 Site	US	Bioequivalence; Safety	Phase 2a Open label, randomized, single center	CE-Melphalan HCl and Melphalan HCl (Alkeran® for Injection) (total dose-200 mg/m²) 100 mg/m² on Day -3/ 100 mg/m² on Day -2	MM Patients undergoing ASCT	24 2 doses (1 dose of CE-Melphalan HCl and 1 dose of Melphalan HCl [Alkeran® for Injection])	2 days	M 13/F 11 58.0 (48-65)	PK of CE-Melphalan HCl vs Alekeran for Injection

ASCT=autologous stem cell transplant; CSR=clinical study report; F=female; M=male; MM=multiple myeloma; PK=pharmacokinetics.
(a) Study period is denoted as the date of first patient enrolled and date last patient completed the last study visit.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The efficacy endpoints for Study CDX-353-001 were myeloablation and engraftment. Myeloablation was defined as an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, absolute lymphocyte count (ALC) $<0.1 \times 10^9$/L, platelet count $<20 \times 10^9$/L, or bleeding requiring transfusion. The first of 2 consecutive days for which cell counts drop below these cutoff levels was to be recorded as the date of myeloablation. All 24 subjects met criteria for myeloablation between Day 0 to 5. Mean myeloablation time was 2.9 days from the time of treatment.

Engraftment was defined as neutrophil (ANC $>0.5 \times 10^9$/L $\times$ on the first of 3 consecutive daily assessments) and platelet (untransfused platelet measurement $>20 \times 10^9$/L on the first of 3 consecutive daily assessments) response. All 24 subjects met criteria for engraftment between Day 9 to 13. The median Time to Myeloablation was 5.0 days. Neutrophil Engraftment and Platelet Engraftment were achieved by all 61 (100%) patients in this study. The median time to Neutrophil Engraftment was 12.0 days and to Platelet Engraftment was 13.0 days. No patient died during the study and none discontinued drug due to adverse events.

8

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?

Only total parent was measured. Melphalan does not undergo metabolic activation and is inactivated in plasma by non-enzymatic hydrolysis to monohydroxymelphalan and dihydroxymelphalan; these two melphalan hydrolysis metabolites are inactive.

2.2.4 Exposure-response

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

As part of the population PK analysis from pooled data from the two Phase 2 studies (CDX-353-001 and CDX-353-002), exploratory PK/PD analysis was performed on several PD endpoints of interest. For continuous PD endpoints, possible linear exposure-response relationships were investigated between the PK metrics (AUC, Cmax, and Cmin) and the change from baseline (or percent change from baseline) in white blood cell (WBC) count and platelet count. There was no statistically significant exposure-response relationship between any of the PK metrics and the WBC or the platelet counts. Exposures of melphalan did not show any significant relationship with efficacy scores according to the International Myeloma Working Group Guidelines for Multiple Myeloma Response score. (refer to **Appendix 4.1: Pharmacometrics Review**).

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

The safety of CE-Melphalan was evaluated in 61 patients with multiple myeloma in a single arm clinical trial in which patients were administered CE-Melphalan at a dosage of 100 mg/m^2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplant (ASCT, Day 0). Exploratory analyses of CE-Melphalan exposure metrics with four AEs of interest (mucositis, diarrhea, nausea, and fatigue) revealed no apparent exposure-response trends. (refer to **Appendix 4.1: Pharmacometrics Review**).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Study CDX-353-002 was conducted to evaluate the safety and efficacy of high-dose CE Melphalan HCl in 61 patients with MM undergoing ASCT. Patient electrocardiogram (ECG) assessments were reviewed and analyzed by an independent core laboratory. Measurements of heart rate (HR) and RR, PR, QRS, and QT interval durations were performed, and corrected QT interval using Bazett's formula (QTcB) and Fridericia's formula (QTcF), and were derived. Electrocardiogram data showed a significant increase in HR, with a peak increase in HR of nearly 20 bpm at Day 7, and HR increases of 10 to 15 bpm through Day 30. It is likely that the increase in HR was related to the stress of myeloablation and autologous transplantation rather than a direct effect of CE-Melphalan HCl on sinus node function.

9

Results on QTcF versus time are shown in **Figure 2.**, there is no apparent change in QTcF. In contrast to the data in **Figure X.**, a positive slope in a PK/PD model (**Figure 2.**) was suggestive of a possible small effect of melphalan on cardiac repolarization (predicted mean increase in QTcF at mean Cmax=8.0 msec, with one-sided upper 95% CI of 11.4 msec). While a possible small effect of CE-Melphalan HCl on QTcF with a magnitude of less than 10 msec cannot be ruled out, the data suggest that the QTc liability is low. This small effect is acceptable given the history of the use of Alkeran.
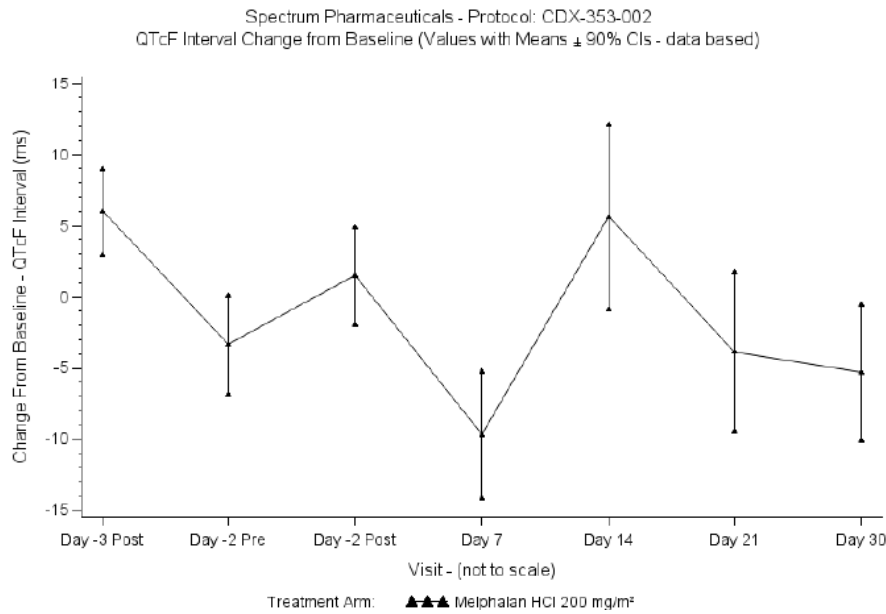
Figure 2. Mean Change from baseline QTcF for CE Melphalan
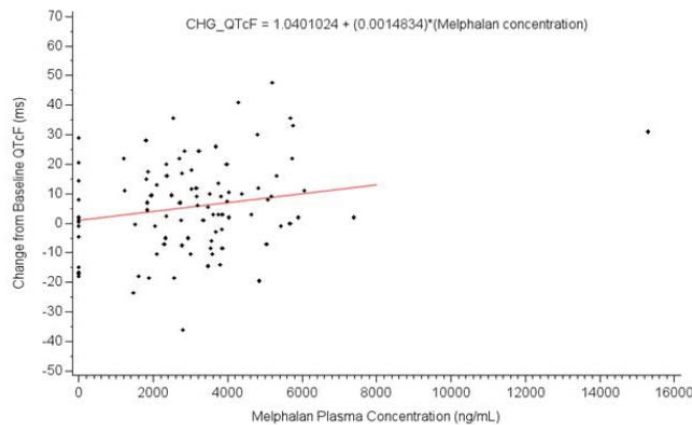
Figure 3. Change from Baseline QTcF versus Mean CE-Melphalan HCl Plasma Concentration Estimates from the Mixed Effects Model Regression (CDX- 353-002)

10

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

There are no unresolved issues for dosing or administration.

2.2.5 What are the PK characteristics of the drug?
2.2.5.1 What are the single dose and multiple dose PK parameters?
2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
2.2.5.3 What are the characteristics of drug absorption?
2.2.5.4 What are the characteristics of drug distribution?

Drug plasma concentrations declined in a biexponential manner with distribution-phase and terminal-elimination-phase half-lives of 10 and 75 minutes, respectively. Total body clearance was 250-325 mL/min/m^2. The volume of distribution was 35.5 to 185.7 L/m^2.

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

Mass balance data are not available.

2.2.5.6 What are the characteristics of drug metabolism?

Melphalan is eliminated from plasma by non-enzymatic hydrolysis to monohydroxymelphalan and dihydroxymelphalan; these two melphalan hydrolysis metabolites are inactive.

2.2.5.7 What are the characteristics of drug excretion?

When 220 mg/m^2 of melphalan was administered intravenously to patients with malignant tumors, the excretion of unchanged drug into urine 21.3% ± 17.1 of dose.

An Information Request (IR) was sent to the sponsor (indented) (Note: this current NDA converts the original melphalan HCL(Alkeran) labeling to PLR format).

> **Please perform literature searches to attempt to identify the origin of this information. If data allows, a value for the amount appearing in urine should be given.**

> **12.3 Pharmacokinetics: Excretion**
> > **…Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.**

> **Applicant's Response:**
> "This language was taken directly from the Alkeran for Injection (RLD) Prescribing Information.

Per the Agency request, we conducted a literature search and found the following articles that provided the basis for this recommendation. We found three articles that describe the amount of melphalan excreted in urine. **Reece et al (1988)** reported a mean value of 21.3% ± 17.1% (range, 3.8% to 41.8%) excreted in patients treated with high dose melphalan (220 mg/m^2) [2]. **Alberts et al (1979)** reported a value of 13.0% ± 5.4% (range, 1.5% to 21.6%) in patients treated with a melphalan dose of 30 to 50 mg/m^2 [3]. Finally, **Ninane et al (1985)** reported urinary excretion of melphalan of 5.8% ± 2.2% (range, 1.7% to 12.8%) in patients treated with 150 to 180 mg/m^2 melphalan [4]."

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

Several articles from literature support that clearance, elimination half-life and volume of distribution are linear with doses up to 140 mg/m^2.

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

Data post-Cycle 1 are not available. The conditioning regimen is two administrations given over two days, the palliative regimen is an administration every two weeks.

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

Inter subject variability in PK parameters (CL) arises due to fat free mass (ideal body weight) and renal function. See section 2.3.2, below.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

A more complete analysis of the effect of renal impairment and size on pharmacokinetics appears in **Appendix 4.1: Pharmacometrics Review**.

A population PK analysis of plasma concentrations of melphalan (from the proposed formulation [CE Melphalan HCl]) in MM patients undergoing ASCT was conducted from pooled data from two Phase 2 studies (CDX-353-001 and CDX-353-002). As part of the analysis, recommendations for dosage adjustment in patients with renal impairment were investigated by performing simulations using the final PK model. The dose for all simulations was fixed at 185 mg with an infusion duration of 32 minutes consistent with the median dose and infusion duration across studies CDX-353-001 and CDX-353-002. The fat-free mass was either fixed at its mean value of 56 kg or was allowed to vary between 30 kg and 84 kg, the observed range in

studies CDX-353-001 and CDX-353-002. For estimated creatinine clearance (Cockcroft-Gault), the following renal function categories were used based on the FDA draft guidance on renal studies (March 2010):

> Normal: at least 90 mL/min
> Mild: between 60 mL/min and 89 nL/min
> Moderate: between 30 mL/min and 59 mL/min
> Severe: between 15 mL/min and 29 mL/min

For each renal function classification, 100 virtual patients were uniformly, randomly created with a fixed fat-free mass of 56 kg or any value between 30 kg and 84 kg. The final model was then used to estimate the exposure metrics, such as AUC and C_{MAX}. Fat-free mass and creatinine clearance were identified as influential covariates. The median model-predicted AUC in the severe renal impairment group was only approximately 20% higher than the median model-predicted AUC in the normal renal function group (**Figure 1.**). Due to the small magnitude of changes, it is not necessary to adjust melphalan HCl doses for patients with renal impairment.
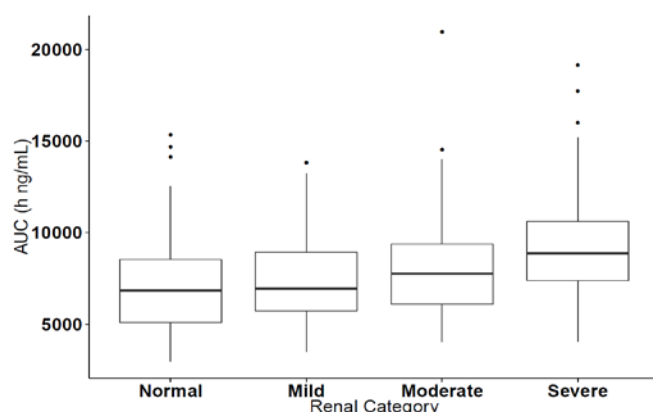
Figure 1. Model predicted AUC with varying CrCL and fat free mass

2.4 EXTRINSIC FACTORS

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

Extrinsic factors are not used to adjust Alkeran doses. No extrinsic factors studies have been performed by the applicant for this submission.

2.4.2 Drug-drug interactions?

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*
2.4.2.2 *Is the drug a substrate of CYP enzymes?*
2.4.2.3 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*
2.4.2.4 *Is the drug an inhibitor and/or an inducer of transporters?*
2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

13

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

2.4.2.7 What other co-medications are likely to be administered to the target population?

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

No in vitro metabolism or drug interaction studies have been performed by the applicant.

Melphalan does not undergo metabolic activation and is inactivated in plasma by non-enzymatic hydrolysis to monohydroxymelphalan and dihydroxymelphalan; these two melphalan hydrolysis metabolites are inactive.

The following drug-drug interaction information (indented) is _____ (b) (4) _____ information is the current package insert for Alkeran.

> "The development of severe renal failure has been reported in patients treated with a single dose of IV melphalan followed by standard oral doses of cyclosporine.
>
> Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan may also reduce the threshold for BCNU lung toxicity.
>
> When nalidixic acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in pediatric patients.

(b) (4)

An IR was sent to the applicant requesting justification for the inclusion of these drug interactions in PLR format labeling. The applicant's responses are reproduced, below. Our review judgment appears at the end of each of the applicant's responses.

Applicant's Response:

(b) (4)

14

3. *IV melphalan may also reduce the threshold for BCNU lung toxicity.*
Drug interaction between IV melphalan and BCNU lung toxicity was described in the following articles:
- Zulian GB, Selby P, Milan S, Nandi A, Gore M, Forgeson G, et al. High Dose Melphalan, BCNU and Etoposide with Autologous Bone Marrow Transplantation for Hodgkin's Disease. Br J Cancer. 1989;59 (4):631-5 [8].
- Alkeran for Injection US Prescribing Information [5].

Reviewer's assessment: The literature data justifies the inclusion of this information in the package insert.

4. *When nalidixic acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in pediatric patients.*
Drug interaction between nalidixic acid and IV melphalan was described in the following sources:
- Voute PA, van der Noordaa J, Dobbelaar CDM, Kindertumoren W, Kinderziekenhuis E, Institute NC. Simultaneous Administration of Nalidixic Acid (NA) and High-Dose Melphalan (HDM in Children, Causing Death Due to Severe Side Effects on the Intestinal Tract. European Journal of Cancer. 1982:1047, Abstract #51 [9].
- Nalidixic Acid US Prescribing Information [10]."

Reviewer's assessment: The literature data and nalidixic acid package insert justify the inclusion of this information in the package insert.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?
2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

15

None

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

None

2.5   GENERAL BIOPHARMACEUTICS

2.5.1   Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
2.5.2   What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

The applicant conducted a clinical study to establish the equivalence of the proposed new formulation (CE-Melphalan) to that of previously marketed product (Alkeran). Study CDX 353-001/ was titled, "A Phase IIa, Open-Label, Randomized, Pharmacokinetic Comparative, Cross-Over Study of Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation." The doses of CE-Melphalan HCl and Alkeran were 100 mg/m^2. Melphalan formulations were administered by IV infusion over 30 minutes ± 3 minutes. All 24 enrolled patients received both formulations, and no patients discontinued prematurely in this study. Pharmacokinetic results are summarized in **Figure 4., Table 2.** and **Table 3. (Table 3.** shows equivalence analysis results).
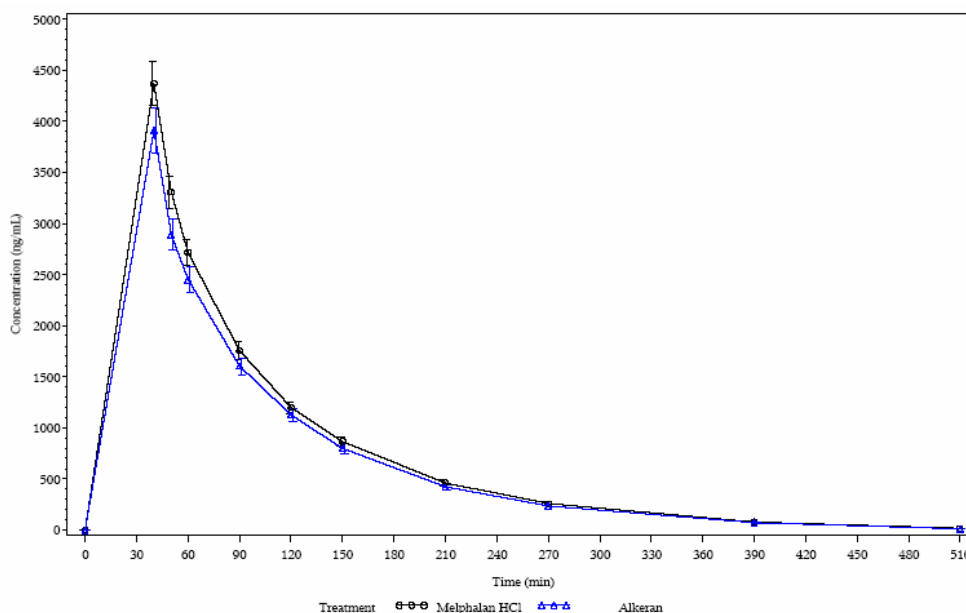
Figure 4. Mean (±SEM) Melphalan Plasma Concentration Following Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection.

16

Table 2. Summary of Mean $\pm$ SD Melphalan Pharmacokinetic Parameters Following Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection

Parameter	Melphalan HCl (PG-Free) N=24	Alkeran N=24
C_{max} (ng/mL)	5839$\pm$1485	5406$\pm$2001
AUC_{0-inf} (min-ng/mL)	450,997$\pm$109,230	416,118$\pm$116,779
$T_{1/2}$ (min)	68.7$\pm$6.60	72.3$\pm$16.8
Kel (min)	0.0012$\pm$0.0010	0.0012$\pm$0.0010

Table 3. Statistical Comparison of Model-Estimated Pharmacokinetic Parameters for Melphalan HCl for Injection (Propylene Glycol- Free) and Alkeran for Injection

Parameter	Geometric Mean Ratio (%)		
	Estimate	90% Confidence Interval	
C_{max}	111.42	101.36	122.48
AUC_{0-inf}	109.40	103.50	115.62
AUC_{0-t}	110.90	105.13	116.98

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

CE-Melphalan is administered via IV injection. The effect of food on bioavailability is not applicable.

2.5.4 When would a fed BE study be appropriate and was one conducted?
2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?
2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?
2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?
2.5.8   If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

There are no unresolved issues with the new formulation or bioequivalence. See Section 2.5.2.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?
2.6.2 Which metabolites have been selected for analysis and why?
2.6.3 For all moieties measured is free, bound or total measured?
2.6.4 What bioanalytical methods are used to assess concentrations?

The concentration of "total" melphalan in samples were analyzed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method validated over the concentration range of 25.0 to 11,200 ng/mL. (Davies ID, Allanson JP, Causon RC. Rapid determination of the anti-cancer drug Melphalan (Alkeran) in Human Serum and Plasma by Automated Solid-Phase Extraction and Liquid Chromatography-Tandem Mass Spectrometry. *Chromatographia,* 2000;52 Suppl:S92–S97). The applicant's validation report demonstrates that the method is linear over the range of 25.0 – 11200 ng/mL.

Calibration and Quality Control Samples: Standards and QC samples in human plasma were prepared from stock solution previously verified for accuracy. Each batch of study samples was processed with a set of 8 calibration standards and a minimum of 3 QC samples, processed in duplicate. In addition, 3 matrix blanks (one with internal standard and two without internal standard) as well as one reconstitution solvent blank, were processed with each batch.

In order for the calibration curve to be accepted, at least 12 of the 16 non-zero starting calibration standards (i.e. at least 75%) were required to interpolate within ± 15.0% of nominal, except at the LLOQ, where up to ± 20.0% was allowed. All analytical runs met the required acceptance criteria.

3 DETAILED LABELING RECOMMENDATIONS:

The sponsor proposed labeling and the Agency's recommendations are shown in the **Table 4.**, below

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

18

APPENDICES

4.1   PHARMACOMETRICS REVIEW

4.2   OCP FILING FORM
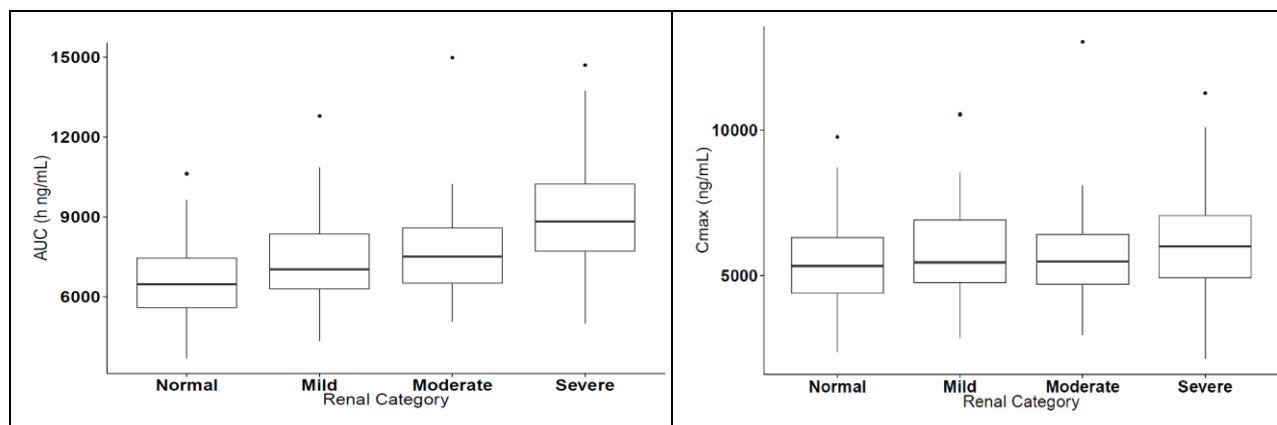
APPENDIX 4.1   PHARMACOMETRICS REVIEW

1 SUMMARY OF FINDINGS
## 1.1 Key Review Questions

The purpose of this review is to address the following key question:

Should the recommended high dose of CE-melphalan (100 mg/m^2/day for two consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0) for conditioning treatment be adjusted based upon renal function (creatinine clearance)?

A population PK analysis of plasma concentrations of melphalan (from the proposed formulation [CE Melphalan HCl]) in MM patients undergoing ASCT was conducted from pooled data from two Phase 2 studies (CDX-353-001 and CDX-353-002). As part of the analysis, recommendations for dosage adjustment in patients with renal impairment were investigated by performing simulations using the final PK model. Based on population PK results, estimated creatinine clearance and fat free mass were identified as influential covariates for plasma elimination clearance (CL). It was estimated that a decrease in estimated creatinine clearance from 100 mL/min to 30 mL/min resulted in an 18.4% reduction in CL for a typical person with a fat-free mass of 58.3 kg. A decrease in fat-free mass from 90 kg to 60 kg and 30 kg resulted in a 26.1% and 55.8% decrease of melphalan CL, respectively. In addition, based on the simulations of 400 patients, the median model predicted exposure (AUC or Cmax) did not differ greatly between patients with severe renal impairment and patients with normal renal function (**Figure 1** and **Figure 2**). **No dose adjustment is considered necessary for patients with different stages of renal impairment.**

Figure 1. The Model Predicted AUC (left panel) and Cmax (right panel) with Varying Creatinine Clearances and Fixed Fat Free Mass
(Source: Applicant's POP PK Report, Figures 12 and 13)
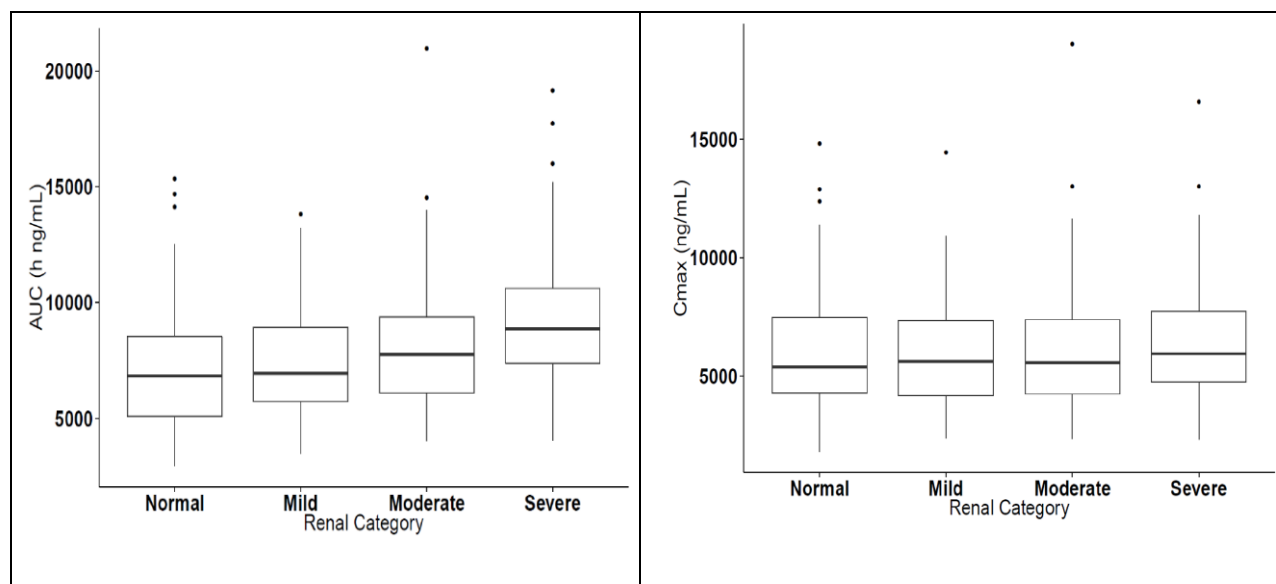
Figure 2. Model predicted AUC (Left Panel) and Cmax (right panel) with varying CrCl and fat free mass
(Source: Applicant's POP PK Report, Figures 14 and 15)

Therefore, due to the small magnitude of changes, it is not necessary to adjust melphalan HCl doses for patients with renal impairment.

1.2   Recommendations
The NDA 207-155 is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language.

1.2.1   Label Statements
Please see the labeling recommendations in QBR Section 3.0

2   PERTINENT REGULATORY BACKGROUND
The applicant has submitted a 505(B)(2) application for the approval of Captisol®-enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan). CE-Melphalan is an alkylating agent indicated for 1) use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma; 2) for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The applicant is seeking the following indications: "Captisol®-enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan) is an alkylating agent indicated for:

1)   use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell trans-plantation in patients with multiple myeloma.

2)   the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The second indication is being carried forth from Alkeran PI.

3 SPONSOR'S ANALYSIS

An analysis was performed by sponsor to characterize the population pharmacokinetics of Melphalan HCl for Injection (Propylene Glycol-free) in multiple myeloma patients undergoing autologous stem cell transplantation. As part of this analysis, potential demographic and clinical factors affecting the pharmacokinetics of melphalan (e.g., metrics of body size, organ function) were assessed.

3.1 Population PK Analysis
3.1.1 Data

A total of 604 plasma melphalan concentrations from 85 (24+61) subjects with MM were included in the final population PK analysis. Data from two studies were pooled for the population pharmacokinetic analysis:
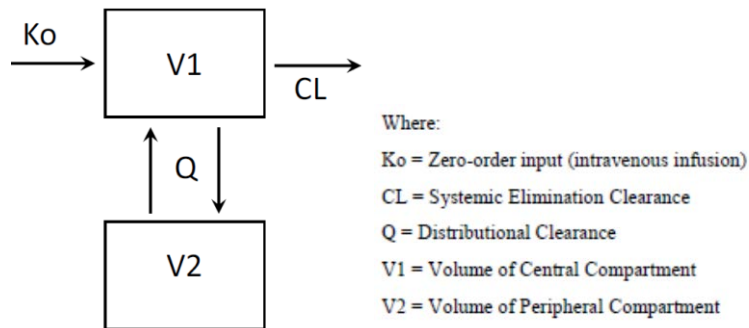
• **Study CDX-353-001**: A Phase IIa, Open-Label, Randomized, Pharmacokinetic Comparative, Cross-Over Study of Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran® for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation (N=24).

• **Study CDX-353-002**: A Phase IIb, Multicenter, Open-Label, Safety and Efficacy Study of High Dose Melphalan HCl for Injection (Propylene Glycol-Free) for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation. In Study CDX-353-002, high-dose (range: 139 mg – 232 mg or 80 – 102 mg/m2)

The dose of CE-Melphalan HCl used in this trial was 100 mg/m2 Day -3 and -2 [Adjusted Ideal Body Weight (AIBW) for patients with > 130% ideal body weight]. The primary goal of this study was to determine the overall safety and toxicity profile in MM patients receiving 200 mg/m2 of CEMelphalan HCl (100 mg/m2×2) as myeloablative therapy prior to ASCT. The secondary goals were to 1) evaluate the efficacy of CE-Melphalan HCl in this patient population as measured by MM response rate (according to International Myeloma Working Group [IMWG] uniform response criteria), myeloablation, and engraftment rates and 2) to determine covariates that affect CE-Melphalan HCl PK parameters using a population PK approach.

3.1.2 Structural Model

A two compartment model with inter-individual variance on clearance (CL), V1, Q, and V2 (Figure 1) was selected as the base structure model. Full block inter-individual covariance structures were used for the central clearance-central volume of distribution (CL-V1) and for the distributional clearance-peripheral volume of distribution (Q-V2).

The population PK analysis was conducted via nonlinear mixed-effects modeling with the software package NONMEM®, version 7.2 (ICON plc, 7250 Parkway Drive, Suite 430, Hanover, MD, 21076, USA) with its library subroutines (ADVAN and its appropriate TRANS). The structural model is shown schematically in **Figure 3** and estimated PK parameters are shown in **Table 1.**

Ko

V1

CL

Q

V2

Where:
Ko = Zero-order input (intravenous infusion)
CL = Systemic Elimination Clearance
Q = Distributional Clearance
V1 = Volume of Central Compartment
V2 = Volume of Peripheral Compartment

Figure 3. Population PK Two Compartment Model
(Source: Applicant's POP PK Report, Figure 1)

Table 1. Final PK Parameter estimates

Parameter	Estimate	RSE (%)	IIV (%CV)
CL (L/h)	27.07	2.5	21
V1 (L)	20.29	6.2	37
Q (L/h)	23.22	6.5	38
V2 (L)	14.61	3.0	14
Effect of creatinine clearance on CL (power model)	0.169	26.4	
SD of the additive residual component (ng/mL)	0.036		
%CV of the proportional residual component	9.4		

RSE: Relative standard error = SE/Estimate

(Source: Applicant's POP PK Report , Table 7)

3.1.3 Applicant's base model diagnostic plots
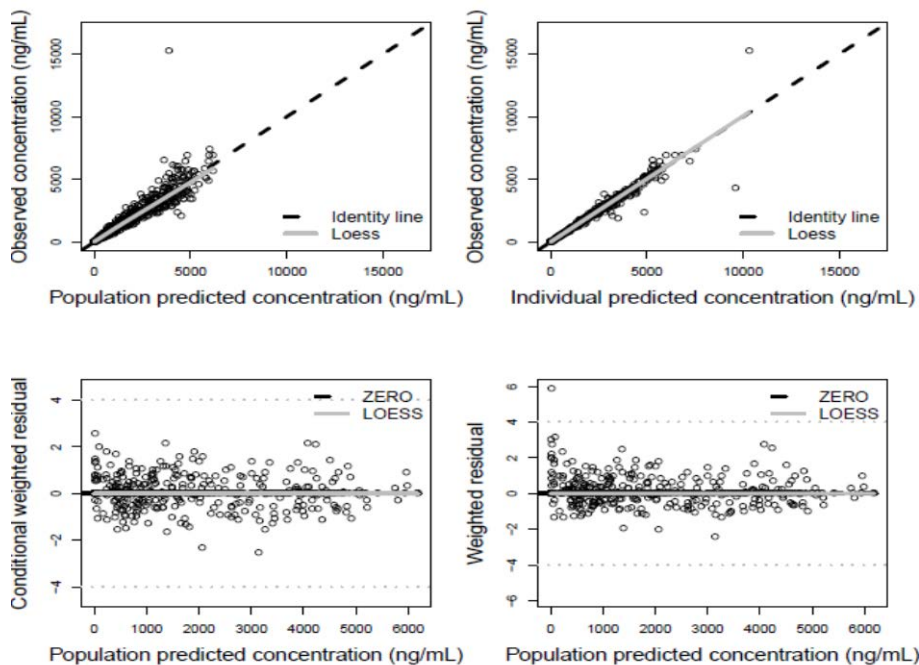
Figure 4. Final model diagnostic plots
(Source: Applicant's POP PK Report , Figure 2)

3.1.4 Simulations to Evaluate Dosing Recommendation for Renal Impairment.

To investigate if dose-adjustment is recommended in subjects with renal impairment, simulations using the final PK model were performed. The dose for all simulations was fixed at 185 mg with an infusion duration of 32 minutes consistent with the median dose and infusion duration across studies CDX-353-001 and CDX-353-002. The fat free mass was either fixed at its mean value of 56 kg or was allowed to vary between 30 kg and 84 kg, the observed range in studies CDX-353-001 and CDX-353-002. For estimated creatinine clearance, (Cockcroft-Gault) the following renal function categories were used based on the FDA draft guidance on renal studies:

• Normal: at least 90 mL/min,

• Mild: between 60 mL/min and 89 nL/min,

• Moderate: between 30 mL/min and 59 mL/min, and

• Severe: between 15 mL/min and 29 mL/min

Based on population PK results, estimated creatinine clearance and fat free mass were identified as influential covariates for plasma elimination clearance (CL). It was estimated that a decrease in estimated creatinine clearance from 100 mL/min to 30 mL/min resulted in an 18.4% reduction in CL for a typical person with a fat-free mass of 58.3 kg. A decrease in fat-free mass from 90 kg to 60 kg and 30 kg resulted in a 26.1% and 55.8% decrease of melphalan CL, respectively. In addition, based on the simulations of 400 patients, the median model predicted exposure (AUC or Cmax) did not differ greatly between patients with severe renal impairment and patients with

normal renal function (**Figure 1** and **Figure 2**). **No dose adjustment is considered necessary for patients with different stages of renal impairment.**

Individual subject PK parameters based on the final model were used to assess potential relationships between systemic exposure and various PD endpoints. Three exposure metrics (AUC, Cmax, and Cmin) were assessed for potential relationships with white blood cell (WBC) count, platelet (PLAT) count and therapeutic response. PK/PD relationships were investigated graphically and statistically, as appropriate. For continuous PD endpoints such as WBC and PLAT, a linear regression was performed for data collected pre-ASCT and for data collected at follow-up.

Reviewer's Comments:

The applicant's model appears appropriate. The applicant's population pharmacokinetic analysis is also consistent with the previously published results [Nath, C. E., et al. "Population pharmacokinetics of melphalan in patients with multiple myeloma undergoing high dose therapy." Br J Clin Pharmacol 69(5): 484-497; 2010]. The population estimate/typical value for plasma clearance from the central compartment by applicant was determined to be approximately 27 L/h, which is the same as the total melphalan clearance published value, 27 L/h. A two-compartment model adequately described individual concentration–time data following single-dose administration.

3.2 Sensitivity Analysis for Ideal Body Weight

Drug dosing is based on weight or ideal body weight and not fat free mass. We therefore, requested that sponsor conduct an analysis based on ideal body weight.

An information request (IR) was sent by clinical pharmacology to the applicant to **re-run the model using ideal body weight (IBW) rather than fat-free mass (FFM) as the metric for patient size. Perform sensitivity analyses to assure that using IBW rather than FFM results in essentially unchanged relationships for the effects of patient size and CrCl.**
Using the model to derive, please submit the CL (not % changes but mL/min) for:
IBW 60 kg @ CrCl of 100, 90 and 30 mL/min,
IBW 70 kg @ CrCl of 100, 90 and 30 mL/min.
Using the model to derive, please submit the CL (not % changes but mL/min) for IBW 100 kg, 70 kg and 60 kg.

The sponsor responded back and modified the existing population PK model to be consistent with dosing recommendations for patients using IBW as the metric for patient size. The final model included Clearance (Cl) as a function of IBW and Volume of Distribution as function of FFM. Changing the predictor from FFM (FFM Model) to IBW (Mixed Model) had little effect on parameter estimates. Similarly, the predicted clearances for a simulated population based on the mixed model were correlated with those of FFM model.

Estimates for melphalan clearance, based on the FFM Model and IBW Model (Mixed Model), are provided for IBW of 100, 70, and 60 kg for CrCl of 30, 90, and 100 mL/min in **Table 2**.

Table 2. Mean (SD) Creatinine Clearance by Ideal Body Weight

Population	FFM Model Predicted Cl (mL/min)	IBW Model Predicted Cl (mL/min)
IBW=60 kg		
CrCl = 30 mL/min	279 (61)	337 (84)
CrCl = 90 mL/min	527 (114)	457 (114)
CrCl = 100 mL/min	565 (122)	469 (118)
IBW=70 kg		
CrCl = 30 mL/min	316 (68)	377 (93)
CrCl = 90 mL/min	576 (121)	515 (124)
CrCl = 100 mL/min	610 (129)	524 (128)

Population	FFM Model Predicted Cl (mL/min)	IBW Model Predicted Cl (mL/min)
IBW=100 kg		
CrCl = 30 mL/min	315 (65)	490 (117)
CrCl = 90 mL/min	565 (119)	657 (160)
CrCl = 100 mL/min	617 (123)	693 (159)

(Source: Clinical Pharmacology/Response To Information Request, Rec'd 9/2/2015)

Assessment of IBW as a predictor of clearance for Melphalan HCL in Autologous Stem Cell Transplantation (ASCT) for Multiple Myeloma, using IBW rather than FFM to predict melphalan Cl resulted in small differences in the relationship between body size and Cl. By objective measures, the model using IBW to predict Cl fit the data less well than the model using FFM. Differences in predicted individual Cl between the FFM model and the IBW model were small, with a root mean square error (RMSE) of 10.3%. While the model based on IBW seems to be less predictive of melphalan clearance than the model based on FFM, the IBW model is consistent with the proposed label.

Changing the predictor covariate for Cl from FFM (FFM model) to IBW (mixed model) had little effect on the parameter estimates (Table 3). Similarly, the predicted clearances for a simulated population based on the mixed model were correlated with those from the FFM model, (0.82 for Cl, 1.0 for Volume). The mean for Cl was 469 mL/min for the FFM model, and 450 mL/min for the mixed model, with a bias of -4.1%. The root mean square error percent for Typical value Cl (not individual values, just based on body size and CrCl) from the FFM model vs. Typical value Cl from the mixed model was 10.3%.
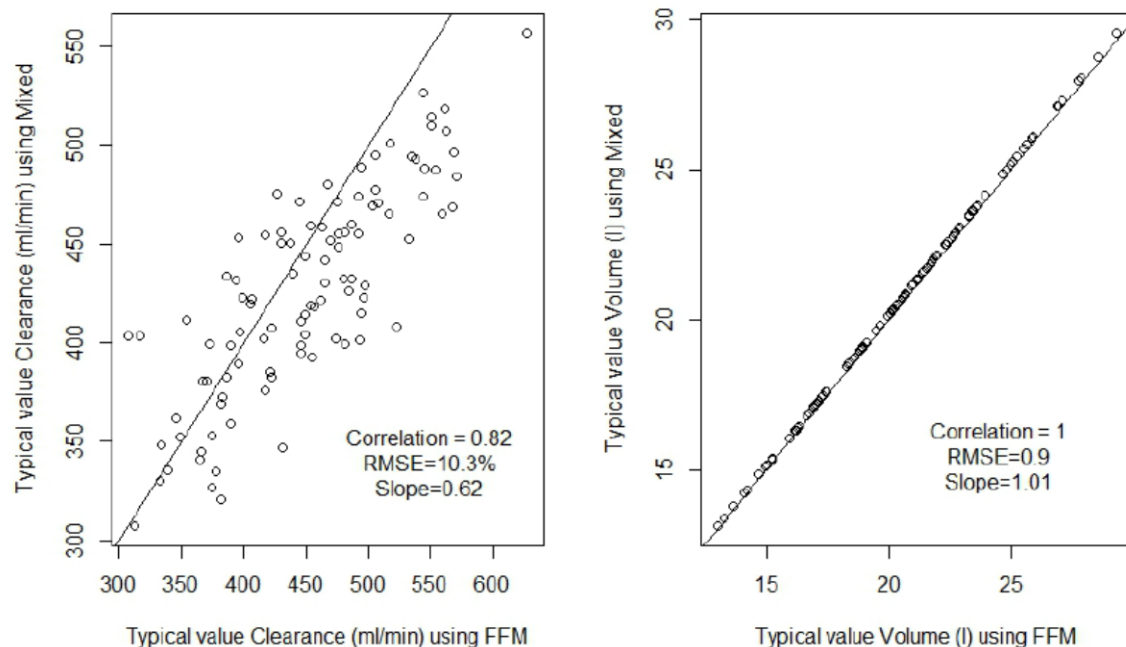
Figure 5. Clearance and Volume for Model using FFM and Model with Mixed IBW and FFM. Solid line is line of unity (intercept=0, slope=1)
(Source: Clinical Pharmacology/Response to Information Request, Rec'd 9/2/2015)

Reviewer's Comments:

The applicant's model appears appropriate. Ideal body weight is a more common method of dosing and was used for the clinical trial as well. The POP PK sensitivity results showed that fat free mass model converged better that ideal body weight as the objective function value was about 400 points lower than ideal body weight model. However the differences in estimated PK parameters between the two models were not significantly different.

3.3 Exposure-Response Analysis for White Blood Cell and Platelet Counts

Exploratory PK/PD analyses showed that there were no statistically significant trends between Melphalan HCl exposure (AUC, Cmax, or Cmin) and changes from baseline in white blood cell count or platelet count. In addition, there were no exposure-response trends between Melphalan HCl exposure and the efficacy response rate as defined by the International Myeloma Working Group Guidelines for Multiple Myeloma Response score. Finally, there was also no visually evident trend between any of the Melphalan HCl exposure metrics with the adverse events (AEs) of interest, namely mucositis, diarrhea, nausea, and fatigue.

Exploratory PK/PD analysis was performed on several PD endpoints of interest. For continuous PD endpoints, possible linear exposure-response relationships were investigated between the PK metrics (AUC, Cmax, and Cmin) and the change from baseline (or percent change from baseline) in WBC count and PLAT count. It should be noted that AUC and Cmax were derived from an analytical (closed-form) solution of a two-compartment model; however, Cmin was the

minimum of the predicted Melphalan HCL concentration from the final population PK model. Figure 7 to Figure 12 present the relationships between each of the PK metrics and the change from baseline (or percent change from baseline) WBC count or PLAT count prior to ASCT.
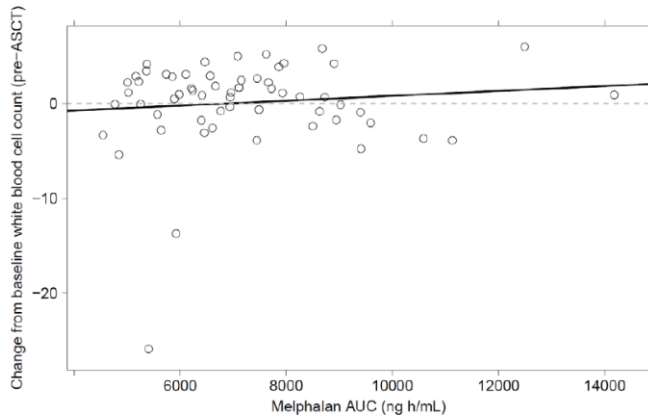
Figure 6. Change from baseline WBC vs melphalan AUC (pre-ASCT)
(Source: Applicant's POP PK Report , Figure 17)
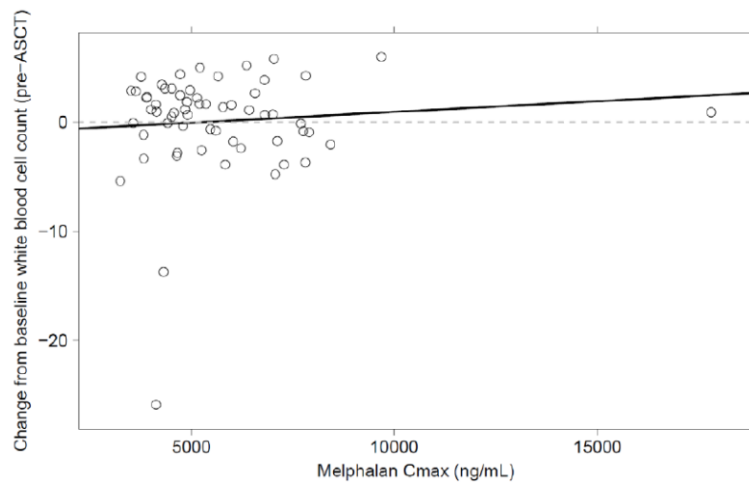
Figure 7. Change from baseline WBC vs melphalan Cmax (pre-ASCT)
(Source: Applicant's POP PK Report , Figure 19)
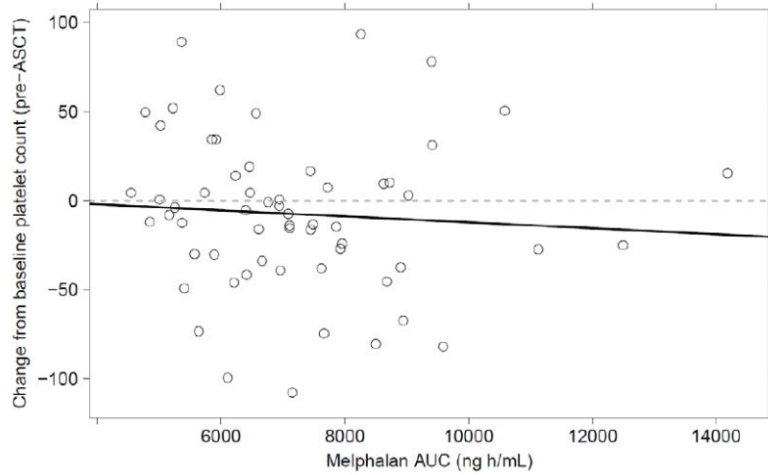
Figure 8. Change from baseline platelet vs melphalan AUC (pre-ASCT)
(Source: Applicant's POP PK Report , Figure 22)
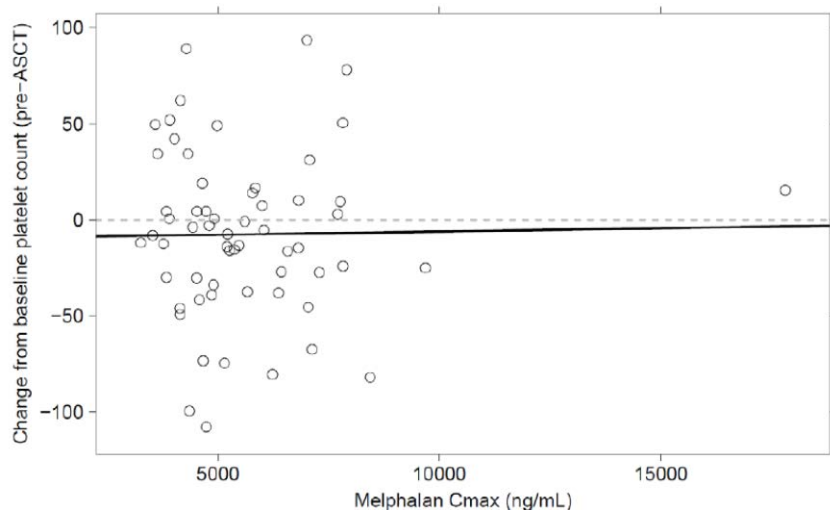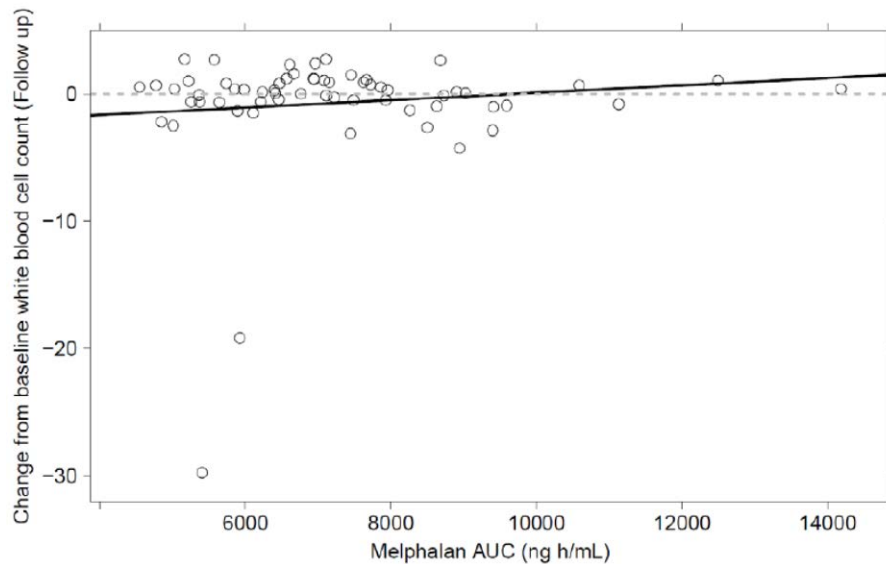

Figure 9. Change from baseline platelet vs melphalan Cmax (pre-ASCT)
(Source: Applicant's POP PK Report , Figure 24)

Figure 10. Change from baseline in WBC vs melphalan AUC (Follow up)
(Source: Applicant's POP PK Report , Figure 28)
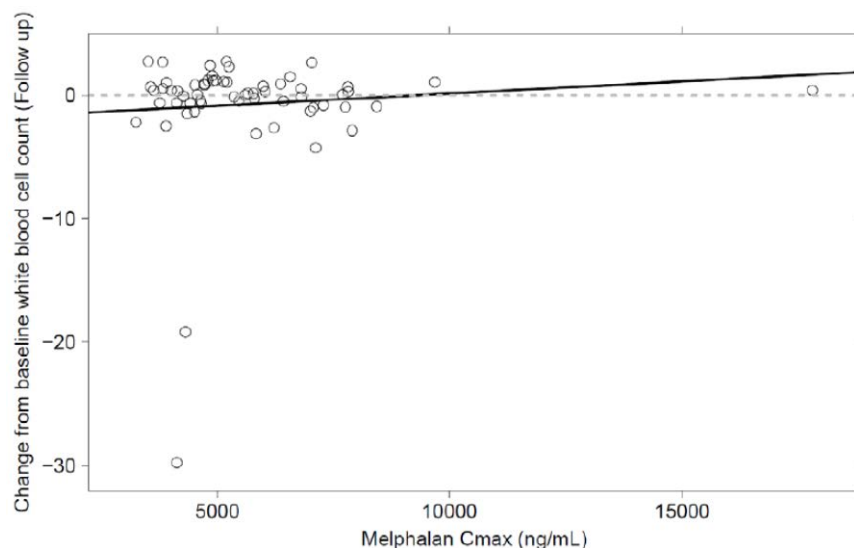
Figure 11. Change from baseline in WBC vs melphalan Cmax (follow up)
(Source: Applicant's POP PK Report , Figure 30)

Figure 6 to **Figure 11** present the graphical relationships between each of the PK metrics and the change from baseline (or percent change from baseline) WBC count or PLAT count at the follow-up visit. There was no statistically significant exposure-response relationship between any of the PK metrics and the WBC or the PLAT count. For the exposure-safety, the graphs comparing mucositis severity as a function of AUC, Cmax, and Cmin are provided in **Figure**

12., **Figure 13**., respectively, and revealed no trends or obvious relationships for increased severity or duration in subjects with elevated exposure metrics.
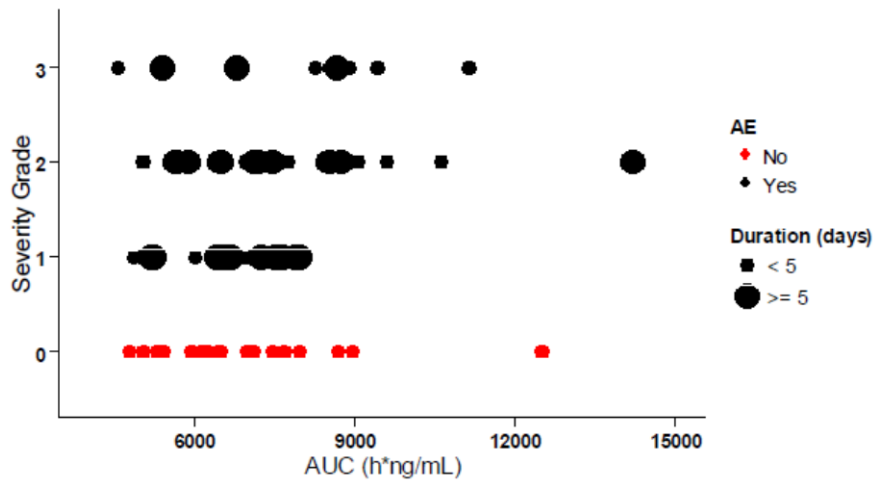
Figure 12. Bubble plots of AUC values by mucositis severity and duration (Source: Applicant's POP PK Report , Figure 49)
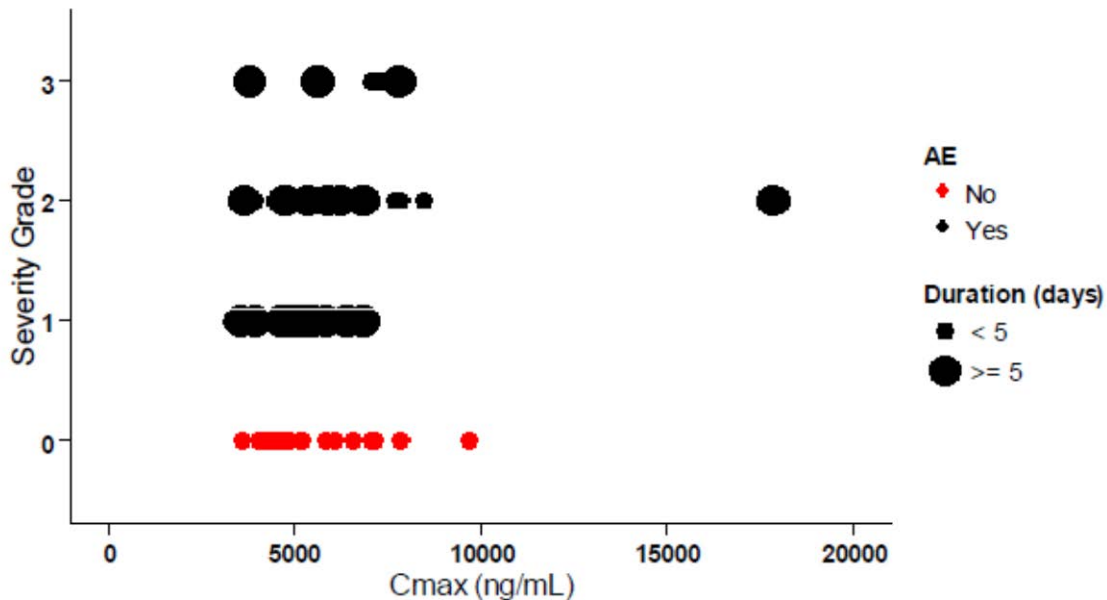
Figure 13. Bubble plots of Cmax values by mucositis severity and duration (Source: Applicant's POP PK Report , Figure 50)

Reviewer's Comments:
The sponsor studied the relationship between PD endpoints, and the PK metrics (AUC, Cmax, and Cmin) and the change from baseline (or percent change from baseline) in white blood cell (WBC) count and platelet count. There was no significant exposure-response relationship

between any of the PK metrics and the WBC or the platelet counts. Similarly, exploratory analyses of exposure metrics with AEs of interest (mucositis, diarrhea, nausea, and fatigue) also revealed that there were no exposure-response trends.

4   REVIEWER'S ANALYSIS

4.1   Introduction
The applicant's model was used to run the population PK model. The population PK analysis was conducted via nonlinear mixed-effects modeling with the software package NONMEM®, version 7.3.

4.2   Objectives
The objective of this review was to investigate if dose-adjustment is necessary in patients with renal impairment administered high doses of CE-melphalan prior to ASCT.

4.2.1   Data Sets
Data sets used are summarized in Table 1.

Table 1. Analysis Data Sets

Study Number	Name	Link to EDR
CDX-353-001	Bioequivalence Study	\\CDSESUB1\evsprod\NDA207155\
CDX-353-002	Safety, Efficacy and POP PK Study	\\CDSESUB1\evsprod\NDA207155\

4.2.2   Software
The population PK analysis was conducted via nonlinear mixed-effects modeling with the software package NONMEM®, version 7.2 (ICON plc, 7250 Parkway Drive, Suite 430, Hanover, MD, 21076, USA) with its library subroutines (ADVAN and its appropriate TRANS).

4.2.3   Models
No independent PK or PK/PD models were developed as part of this review. The sponsor's control stream was used.

4.3   Results
Plots of inter-individual variability as a function of model covariates were utilized to evaluate the necessity of the covariate relationship in the population PK model. The plot showed there was not much dependence on creatinine clearance as a covariate. This is consistent with the small increase in the exposure. This magnitude (20%) does not necessitate dose adjustment in patients with renal impairment. **Figure 14** shows that for creatinine clearance the exclusion of the parameter from the model leads to a trend that would suggest this covariate is relevant. **Figure 15** shows that for free fat mass, inclusion of this covariate in the model appears relevant.
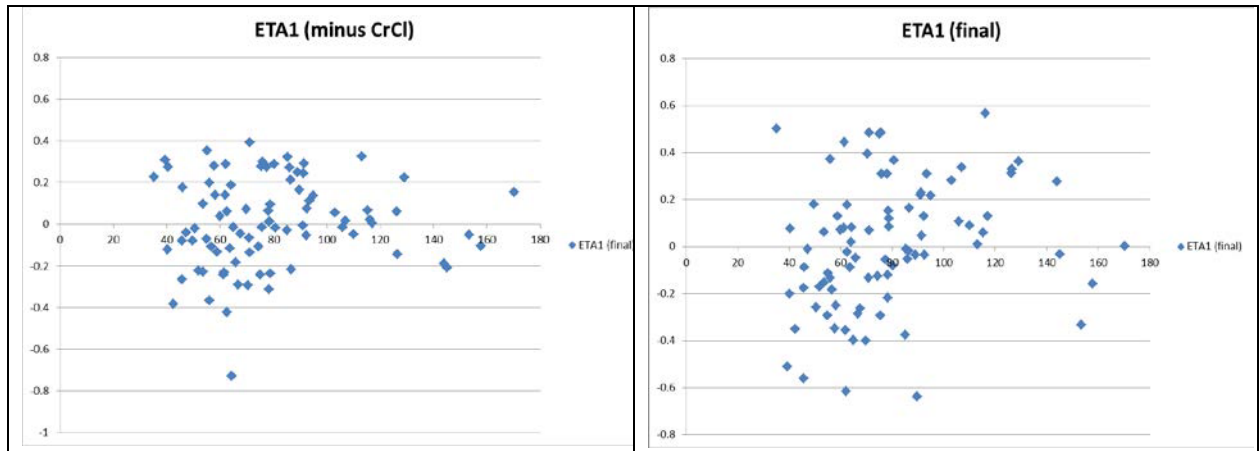
Figure 14. Eta(CL) versus estimated creatinine clearance for the applicant's final model (right panel) and final model minus estimated creatinine clearance covariate (left panel).
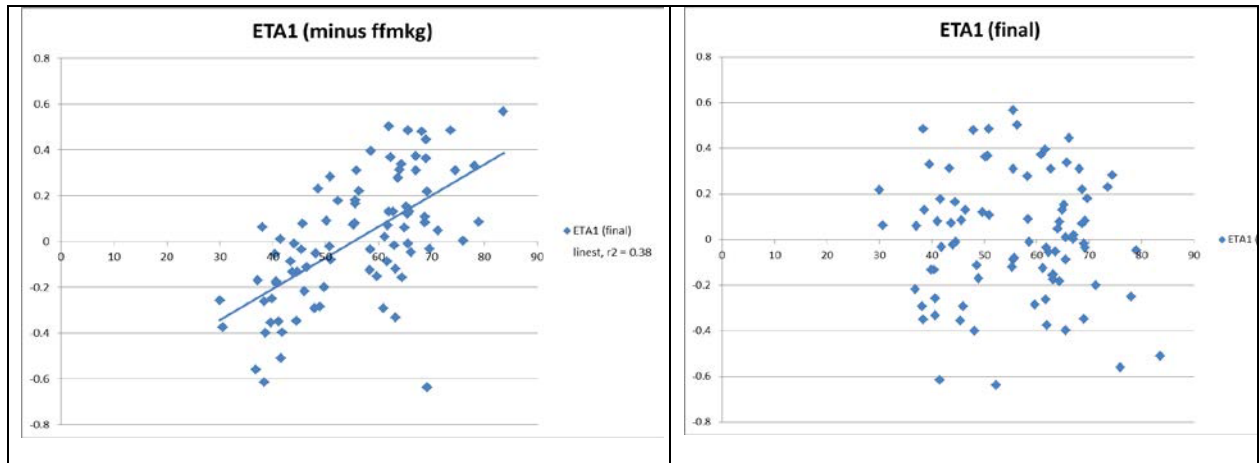
Figure 15. Eta(CL) versus fat free mass for the applicant's final model (left panel) and final model minus fat free mass covariate (right panel).

APPENDIX 4.2   OCP FILING FORM

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

Office of Clinical Pharmacology			
New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**207-155**	**Brand Name**	**EVOMELA** (Captisol®-enabled Melphalan HCl) for Injection
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	Melphalan
Medical Division	**OHOP/DHP**	**Drug Class**	
OCP Reviewer	**Christy S John, Ph.D.**	**Indication(s)**	Captisol®-enabled Melphalan-HCl for injection (propylene-glycol free) (CE-Melphalan) is an alkylating agent indicated for: use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.
OCP Team Leader	**Gene Williams, Ph.D.**	**Dosage Form**	For injection: 50 mg of melphalan free base, lyophilized powder in single-use vial for reconstitution.

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

Pharmacometrics Reviewer		Dosing Regimen	For **Conditioning Treatment**, the recommended dose of CE-Melphalan is 100 mg/m2/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0). For **Palliative Treatment**, the recommended dose of CE-Melphalan is 16 mg/m2 administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.
Date of Submission	December 23, 2014	Route of Administration	IV Injection
Estimated Due Date of OCP Review	August 7, 2015	Sponsor	Spectrum Pharmaceuticals, Inc.
Medical Division Due Date	August 23, 2015	Priority Classification	1S
PDUFA Due Date	October 23, 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			

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

Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) **-**				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				

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

solution as reference:				
alternate formulation as reference:				
Bioequivalence studies –				
traditional design; single / multi dose:	**X**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**7**		The applicant has cited several literature studies in support of the label.
Total Number of Studies		**11**		

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

No	Content Parameter	Yes	No	N/A	Comment
	Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements				
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			
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		ONDQA biopharm to review
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			

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

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?				
	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	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?			N/A	

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

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____X__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A

Christy S John, Ph.D.

Reviewing Clinical Pharmacologist   Date

Gene Williams, Ph.D.

Team Leader/Supervisor   Date

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

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

/s/

CHRISTY S JOHN

02/19/2015

GENE M WILLIAMS

02/19/2015

I concur with the recommendations

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

/s/

CHRISTY S JOHN
09/18/2015

JUSTIN C EARP
09/18/2015

GENE M WILLIAMS
09/18/2015
I concur with the recommendations