CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

MEDICAL REVIEW(S)

FILE MEMORANDUM

Submission:	207155 Resubmission / Class 2
Submission Date:	11/9/15
Submitted by:	Spectrum Pharmaceuticals, Inc
Date Review Completed:	2/19/16
FROM:	Patricia Dinndorf, MD, Medical Officer; Division of Hematology Products (DHP), OHOP; CDER
THROUGH:	Albert Deisseroth, MD, PhD, Team Leader: Division of Hematology Products (DHP), OHOP; CDER
SUBJECT:	NDA 207155/Original 1 and 2 EVOMELA(melphalan) for Injection, 50 mg(free base)/vial Resubmission 11/9/15

On October 22, 2015 the FDA issued a complete response letter to Spectrum Pharmaceuticals, Inc for NDA 207155 Original 1, (High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma) and Original 2 (Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate). The following product quality issues were cited:

1. Your application referenced Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on (b) (4). These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. Submit a toxicological risk assessment of (b) (4) leachable from the (b) (4)

The primary clinical review of this application was completed and filed on 8/24/15. The recommended regulatory action from clinical was approval.

Recommendation on Regulatory Action
I recommend approval of this 505(b)(2) NDA for EVOMELA (Captisol ® enabled melphalan HCl / CE-Melphalan HCl) for the following indications:

- 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

This new formulation of melphalan incorporates β-cyclodextrin sulfobutyl ether sodium salts which improves the solubility, and thus eliminates the need for propylene glycol as the diluent. The applicant has conducted a bioequivalence trial demonstrating bioequivalence of CE-Melphalan HCl to the currently approved formulation of melphalan HCl (Alkeran for injection).

High-dose Conditioning Treatment in Patients with Multiple Myeloma

To support the new transplant indication the applicant cited extensive literature evidence, including randomized studies, documenting the efficacy and safety of melphalan at a dose of 100 g/m^2 for 2 days as a preparative regimen for autologous stem cell transplantation following initial induction therapy for multiple myeloma. The applicant conducted a safety and efficacy trial in 61 patients undergoing autologous transplant as treatment of multiple myeloma. The trial demonstrated improvement in overall response rate from 79% pretreatment to 95% at day 90 to 100 post transplant. In addition 100% of patients met criteria for myeloablation, and demonstrated prompt platelet and neutrophil engraftment.

Palliation of Patients with Multiple Myeloma

The bioequivalence study supports approval of the existing label indication in the reference product.

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/s/

PATRICIA A DINNDORF
02/19/2016

ALBERT B DEISSEROTH
02/19/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA #	207155
Applicant Name	Spectrum Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) Name	Evomela™ Captisol®-enabled Melphalan Hydrochloride
Dosage Forms / Strength	Powder for Injection, 50 mg per vial [5 mg/mL when reconstituted]
Proposed Indications	• High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma • Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Patricia Dinndorf, M.D./Albert Deisseroth, M.D., Ph.D.
Statistical Review	Yaping Wang, Ph.D./Yuan-Li Shen, Ph.D./Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Brenda Gehrke, Ph.D./Christopher M. Sheth, Ph.D.
CMC Review/OBP Review	Bapu Gaddam, Ph.D. and Ying Lin, Ph.D. (DMF reviewers)/ Maziar Kahki, Ph.D. (Biopharmaceutics)/Amit Mitra, Ph.D. (Drug Product)/Hari Sarker, Ph.D. (Drug Substance)/ Lin Qi, Ph.D. (Process)/Donald Oberhuber (Facilities Inspection)/ Vinayak Pawar, Ph.D. (Microbiology)/ Janice Brown, M.S. (Lead)
Clinical Pharmacology Review	Christy S. John, Ph.D./Justin Earp, Ph.D./Gene Williams, Ph.D.
OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D.
OSIS/DNDBE	Li-Hong Yeh, Ph.D./Charles Bonapace, Pharm.D.
CDTL Review	Albert Deisseroth, M.D., Ph.D.
OMP/DMPP/OPDP	Rachel Conklin, M.S./Nathan Caulk, B.S.N., M.S./LaShawn Griffiths, M.S.H.S.-P.H., B.S.N./Barbara Fuller, M.S.N.

OND=Office of New Drugs
OMP=Office of Medical Policy
OSE= Office of Surveillance and Epidemiology
OSIS=Office of Study Integrity and Surveillance
OPDP=Office of Prescription Drug Promotion
OMEPRM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Melphalan, also known as L-phenylalanine mustard, is a phenylalanine derivative of nitrogen mustard, an alkylating agent. The current melphalan product for parenteral use, Alkeran® (melphalan hydrochloride) for Injection, is approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. Evomela™ (Captisol®-enabled melphalan hydrochloride) for Injection is a new melphalan hydrochloride product that contains Captisol as excipient instead of propylene glycol. NDA 207155 has been submitted as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug. The Applicant is pursuing two indications for Evomela, the current palliative treatment indication for Alkeran and a new indication of high-dose conditioning prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

2. Background

There are several classes of agents that have demonstrated activity in relapsed or refractory multiple myeloma, such as alkylating agents (melphalan, cyclophosphamide, CCNU, anthacyclines), immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib), corticosteroids, and monoclonal antibodies. These agents are administered alone or in two- or three-drug combinations. An important modality is autologous stem cell transplantation (ASCT), often recommended in medically fit patients as first line standard of care after initial induction therapy because of long sustained remissions and low transplant-related mortality. High-dose melphalan is used as conditioning agent in ASCT. Total body irradiation regimens have been largely superseded by 200 mg/m^2 melphalan divided in two 100 mg/m^2 doses and administered on Days -3 and -2 prior to autologous stem cell transplant.

3. CMC/Device

Application Technical Lead recommended Complete Response. "A Complete Response is recommended for NDA 207155 from a product quality standpoint". There are two issues:
1) this NDA references two Drug Master Files. One of the two DMFs was found inadequate to support the submission and a nine item deficiency letter was sent to the DMF holder on (b) (4),
2) the drug product manufacturing facility, (b) (4). received an overall NOT APPROVAL recommendation.

"Satisfactory resolution of these deficiencies is required before this application may be approved."

I concur with the conclusions reached by the chemistry reviewers regarding the unacceptability of the manufacturing of the drug product and drug substance. I concur with the recommendation of Complete Response.

4. Nonclinical Pharmacology/Toxicology

To support the proposed indications, the Sponsor submitted literature of the nonclinical studies conducted with melphalan, an *in vitro* hemolysis studies of the vehicle, and a bridging pharmacokinetic study comparing Evomela to Alkeran in rats. The vehicle containing Captisol® (betadex sulfobutyl ether sodium) produced no hemolysis and the Alkeran vehicle produced minor hemolysis in rat and human red blood cells. The results of the pharmacokinetic study were summarized as follows: "No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following a single intravenous administration of melphalan in the (b) (4)% (w/v) Captisol or Captisol-free formulations." "The nonclinical studies submitted to this NDA and the previous findings of safety and efficacy for the listed drug Alkeran provide sufficient information to support the use of Evomela (Captisol®-enabled melphalan hydrochloride) for the proposed indications."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Sponsor submitted the results of two studies. Study CDX-353-001 was a comparative bioavailability and bioequivalence, Phase 2a single-center, open-label, randomized, cross-over 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 2b, Multi-center, 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 100mg/m^2 on Days -3 and -2 [Adjusted Ideal Body Weight for patients with > 130% ideal body weight]. CE-Melphalan produced clinically meaningful increases in overall multiple myeloma response rates: 95% versus 79% response rate post-treatment versus pre-treatment, respectively. Myeloablation was achieved in all 24 patients on CE-Melphalan between Days 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 the two studies to build population PK models. Simulations based on the final model indicated that it was not necessary to adjust CE-Melphalan dose for patients with renal impairment. The Clinical Pharmacology review team concluded that NDA 207155 is acceptable for approval from a clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

The applicant is relying on consensus treatment recommendations and published literature to support the proposed ASCT indication and the proposed dose. NCCN evidence-based guidelines for treatment of multiple myeloma (2014), the British Society of Hematology Guidelines and the European Myeloma network all recommend ASCT following induction therapy as the first-line standard of care in medically fit patients, and high-dose melphalan 200 mg/m^2 as standard conditioning medium prior to ASCT. In addition the applicant conducted a comprehensive literature review of high-dose melphalan followed by ASCT. The median PFS/EFS were significantly higher with high-dose melphalan followed by ASCT in 4 of the 7 studies. In 2 other studies the median PFS was higher but did not achieve significant difference. Overall Survival was significantly longer in 3 of the 7 studies.

Statistical review of Study CDX-353-002 (described above in Clinical Pharmacology) concluded "In summary, the study appears to demonstrate a difference in Multiple Myeloma response rate between pre-treatment and Day +90/Day +100 for CE-Melphalan HCl. This finding appears to be consistent across the age, gender, race and geographic subgroups. This result was also supported by overall complete response rate and the observation that all patients appear to achieve myeloablation and engraftment by Day +90/Day +100."

The applicant uses the bioequivalence study (described above in Clinical Pharmacology) to support palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

8. Safety

No additional safety issues were identified in the reviews of CDX-353-001 and CDX-353-002 compared to Center for International Blood and Marrow Transplant Research registry experience.

9. Advisory Committee Meeting

This NDA was not presented at an Advisory Committee meeting.

10. Pediatrics

This application was presented to the Pediatric Research Committee (PeRC) on September 23, 2015. The Applicant has received Orphan Drug designation for the Evomela for the indication

of high-dose conditioning treatment for hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. Full waiver was granted for the second indication of palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. PeRC concurred with the Division's comments and agreed with the granting of waiver.

11. Other Relevant Regulatory Issues

The Office of Study Integrity and Surveillance inspected the clinical portion of Study CDX-353-001. The Recommendation following review of the inspectional findings was "I recommend that the clinical data for study CDX-353-001 be accepted for Agency review if the unreported adverse events and use of concomitant medication (Zometa) did not impact the study outcome." Final classification was VAI.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name of Evomela was agreed upon with concurrence with OSE/DMETS.
- Physician labeling. This was a PLR conversion largely based on the Alkeran label.
- Carton and immediate container labels (if problems are noted) were reviewed by Division of Medical Policy Programs and Office of Prescription Drug Promotion.
- Patient labeling review was assisted by Division of Medical Policy Programs and Office of Prescription Drug Promotion.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response due to product quality deficiencies.
- Risk Benefit Assessment: N/A because of Complete Response regulatory action.
- Recommendation for Postmarketing Risk Management Activities: N/A.
- Recommendation for other Postmarketing Study Commitments: N/A.

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/s/

EDVARDAS KAMINSKAS
10/20/2015

CDTL (Cross Discipline Team Leader) Review

Date	October 16, 2015
From	Albert Deisseroth, MD, PhD
Subject	Cross Discipline Team Leader Review
BLA Number	NDA 207155
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Established/Proprietary Name	Captisol®-enabled Melphalan HCl/Evomela™ (proposed)
Dosage Regimen	1. 100 mg/m^2/day IV for 2 days (for preparative regimen for ASCT) 2. 16 mg/m^2 q 2 seeks for 4 doses (for palliation)
Dosage Form/Strength	Powder/50 mg (free base)/vial
Approved Indication	1: high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma (ORPHAN) 2. for the palliative treatment of patients with Multiple Myeloma for whom oral therapy is not appropriate (Non-ORPHAN)
Recommendation:	Non-Approval (Complete Response)

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Patricia Dinndorf, MD
Clinical Pharmacology	John Christy, Ph.D., and Gene Williams, PhD.
CMC (Drug Product)	Amit Mitra, PhD and Janice Brown, PhD
CMC (Drug Substance)	Haripada Sarker PhD and Janice Brown, PhD
CMC (Microbiology)	Vinayak Pawar, PhD and Janice Brown, PhD
CMC (Biopharm)	Maziar Kakhi, PhD and Elsbeth Chikhale, PhD
Nonclinical	Brenda Gehrke, PhD, and Christopher Sheth, PhD
Biostatistics	Yaping Wang, PhD and Yuan Li Shen, PhD
DMEPA	Kevin Wright, PhD
Project Manager	Rachel McMillan

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY: (This section was derived in part from the reviews of Dr. Patricia Dinndorf).

On December 23, 2014, Spectrum Pharmaceuticals, Inc. submitted the 505(b)(2) NDA 207155 for EVOMELA (Captisol ®-enabled melphalan HCl/CE-Melphalan HCl) for the following indications:

a. Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma;
b. The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate

This is a new formulation of melphalan which incorporates β-cyclodextrin sulfobutyl ether sodium salts which improves the solubility, and thus eliminates the need for propylene glycol as the diluent. The applicant has conducted a bioequivalence trial (CDX-353-001) demonstrating of CE-Melphalan HCl to the currently approved formulation of melphalan HCl (Alkeran for injection).

Clinical Data Supporting the Indication for High-dose Conditioning Treatment in Patients with Multiple Myeloma: To support the new transplant indication, the applicant cited extensive literature evidence, including randomized studies, documenting the efficacy and safety of melphalan at a dose of $100g/m^2$ for 2 days as a preparative regimen for autologous stem cell transplantation following initial induction therapy for multiple myeloma.

The applicant also conducted a safety and efficacy trial (CDX-353-002) in 61 patients undergoing autologous transplant as treatment of multiple myeloma. The trial demonstrated improvement in overall response rate from 79% pretreatment to 95% at day 90 to 100 post transplant. In addition 100% of patients met criteria for myeloablation, and demonstrated prompt platelet and neutrophil engraftment.

Bioequivalence Study Supports The Indication for Palliation of Patients with Multiple Myeloma: The bioequivalence study supports approval of the existing label indication in the reference product.

CMC Deficiencies:

1. NDA submission referenced Drug Master File (b) (4) which was found inadequate to support the submission due to 9 deficiencies.
2. The drug product manufacturing facility: (b) (4) received an overall not approval recommendation.
3. The CMC review division concluded that these deficiencies rendered the NDA 207155 unapprovable until corrected and recommended a Complete Response (non approvable).

Regulatory Recommendation of the CDTL Reviewer: Non-Approval (complete response).

2. BACKGROUND: (This section was derived in part from the review of Dr. Patricia Dinndorf).

Proposed Indication #1: Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Proposed Dosage and Administration: 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).

Proposed Indication #2: The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Proposed Dosage and Administration: 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.

The currently available formulation of melphalan, Alkeran® for injection (Melphalan HCl), requires a propylene glycol (b) (4) diluent. Melphalan has marginal solubility and the Alkeran formulation with propylene glycol diluent has limited chemical stability upon reconstitution and dilution.

Propylene glycol diluent has been associated with toxic effects including hyperosmolality, increased anion gap metabolic acidosis, acute kidney injury, sepsis-like syndrome, hemolysis, cardiac arrhythmia, seizure and coma, and agitation. The CE-Melphalan HCl formulation eliminates potential formulation toxicity due to propylene glycol. The applicant has submitted data in the submission to demonstrate CE-Melphalan HCl formulation has improved chemical stability upon reconstitution and dilution.

Summary: Melphalan is the agent of choice as a preparative regimen for autologous stem celltransplant in patients with multiple myeloma. Alkeran® for injection (Melphalan HCl), is the only other presentation of melphalan available in the US.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC): (This section was exerpted from the CMC review of Dr. Janice Brown. For details, see the review of Dr. Janice Brown.)

Executive Summary:

1. The NDA submission referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support the Applicant's submission and a nine item deficiency letter was sent to the DMF holder on (b) (4).
2. The drug product manufacturing facility, (b) (4) received an overall not approval recommendation.
3. Action letter language, related to critical issues such as expiration date.
4. The Applicant's application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support the NDA submission and a deficiency letter was sent to the DMF holder on (b) (4). These deficiencies must be adequately addressed before this application can be approved. As part of the response to this letter, the Applicant should include the date the DMF holder amended their DMF to address the deficiencies.
5. During a recent inspection of the (b) (4) manufacturing facility for this application, the FDA field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
6. The Applicant should submit a toxicological risk assessment of (b) (4) leachable (b) (4).

Regulatory Recommendation of the CMC Division: Complete Response (non-approval).

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

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin is a phenylalanine derivative of nitrogen mustard and an alkylating agent. The current melphalan product, Alkeran® (melphalan hydrochloride) for Injection, is approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Evomela™ (Captisol®-enabled melphalan hydrochloride) for Injection is a new melphalan hydrochloride product that contains Captisol as an excipient instead of propylene glycol. NDA 207155 has been submitted as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug. With the submission of NDA 207155, Spectrum Pharmaceuticals Inc. is pursuing two indications for Evomela, the current palliative treatment indication for Alkeran and a new indication of high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

To support the proposed indications, the Applicant has submitted literature of the nonclinical studies conducted with melphalan, an in vitro hemolytic study of the vehicle, and a bridging pharmacokinetic study comparing Evomela to Alkeran in rats. Additionally, the Applicant is relying on the FDA's previous finding of safety and efficacy for Alkeran.

Results: An in vitro hemolytic study of rodent and human red blood cells from fasted subjects was conducted to determine the hemolytic potential of the melphalan vehicle containing Captisol and the Alkeran vehicle in rodent and human blood. The vehicle containing Captisol produced no hemolysis and the Alkeran vehicle produced minor hemolysis in rat and human red blood cells. A pharmacokinetic study containing data following intravenous administration of melphalan in the presence or absence of Captisol in the delivery vehicle to male Sprague Dawley rats was submitted as a bridging pharmacokinetic study comparing Evomela to Alkeran.

Commercial Alkeran vials were used for both formulations. The Captisol-free formulation was prepared as per the product insert for the commercial Alkeran injectable formulation using the sterile diluent that is provided with the Alkeran product, while in the Captisol formulation, Alkeran was reconstituted with a Captisol solution resulting in a final formulation with (b) (4) (w/v) Captisol. No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following a single intravenous administration of melphalan in the (b) (4) (w/v) Captisol or Captisol-free formulations.

Regulatory Recommendation of the Pharmacology/Toxicology Review Team: The nonclinical studies submitted to this NDA and the previous findings of safety and efficacy for the listed drug Alkeran provide sufficient information to support the use of Evomela (Captisol®-enabled melphalan hydrochloride) for the proposed indications.

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

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/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 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) CEMelphalan HCl and Melphalan HCl (Alkeran for Injection, FDA approved drug). The applicant demonstrated that the new formulation was equivalent (80 -125% for AUC and CMAX) 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.

Regulatory Recommendation of Clinical Pharmacology Team: Approval

6. EFFICACY: (This section is excerpted from the reviews of Dr. Patricia Dinndorf, MD. For details, please see the primary review of Dr. Dinndorf.)

Preparative Regimen for Autologous Stem Cell Transplantation: The applicant uses published literature to support this new indication. This includes consensus recommendations from 3 groups; the National Comprehensive Cancer Network (NCCN), the British Society of Hematology, and the European Myeloma Network. The applicant has provided confirmation the agent used in key supportive literature studies is the reference product, Alkeran (Melphalan HCl).

To establish the bridge from Alkeran to CE-Melphalan HCl, the applicant conducted 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.”

To provide safety information regarding the new formulation, the sponsor conducted 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."

The benchmarks used to establish safety in this single arm trial are supplied by a Center for International Blood and Marrow Transplant Research (CIBMTR) report of descriptive statistics and post-autologous stem cell transplant engraftment and overall mortality rates for adult multiple myeloma patients who received a first autologous stem cell transplant in the United States between 2008 and 2013.

Review of CDX-353-001: Palliative Treatment of Patients with Multiple Myeloma for Whom Oral Therapy is Not Appropriate. The applicant uses the bioequivalence study of CDX-001 to support the existing label indication in the reference product.

Conclusions from results: (copied from Study Report Section 5.3.1.2 page 137/692) . In conclusion, CE-Melphalan HCl for Injection (Propylene Glycol-Free) was shown to be bioequivalent to Alkeran for Injection. Based on the overall results of this study, the efficacy (myeloablation and engraftment) and safety profile were consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous stem cell transplantation in patients with multiple myeloma.

Review of CDX-353-002: Safety of CE-Melphalan HCL in Multiple Myeloma ASCT Population:
Eligibility Criteria:
a. Patients with symptomatic multiple myeloma, based on International Myeloma Working Group (IMWG) guidelines, requiring treatment who are eligible for ASCT.
b. Patients who are 70 years of age or younger at time of transplant. Patients older than 70 years of age may be enrolled on a case-by-case basis.
c. Patients with an adequate autologous stem cell collection, defined as an unmanipulated, cryopreserved, peripheral blood stem cell collection containing at least 2 × 106 CD34+ cells/kg based on patient body weight.
d. Patients with adequate organ function (cardiac, hepatic, renal, pulmonary).
e. ECOG 0 to 2.

Efficacy Conclusion: (copied from submission Section 5.3.5.2 CDX-002 Study Report page 85 of 1084): CE-Melphalan high dose treatment of patients (N=61) with symptomatic multiple myeloma requiring treatment and eligible for ASCT, including 7% of patients with prior ASCT, produced clinically meaningful increases in Overall multiple myeloma Response Rates from 79% Pre-treatment to 95% at Day +90/Day +100. Importantly, there was also an increase in the overall complete response rate from 10% to 31%, with the number of patients with a stringent complete response rate increasing from 0% Pretreatment to 16% at Day +90/Day +100.

In addition, CE-Melphalan HCl high dose therapy resulted in:

a. Myeloablation in all 61 (100%) patients meeting the protocol-defined criteria, and as reflected by the development of severe neutropenia with ANCs $<0.5\times10^9$/L;
b. median time to myeloablation was 5 days.
c. Neutrophil engraftment was achieved in all 61 (100%) patients in this study, with a median time of 12 days.
d. Platelet engraftment was achieved in all 61 (100%) patients in this study, with a median time to platelet engraftment of 13 days.
e. No (0%) patients had non-engraftment of neutrophils by Day +90/Day +100.

Regulatory Recommendation. Approval.

7. SAFETY: (This section was derived in part from the review of Dr. Patricia Dinndorf).

Safety Conclusions for CDX-001: CE-Melphalan HCl for Injection (Propylene Glycol-Free) was shown to be bioequivalent to Alkeran for Injection. Based on the overall results of this study, myeloablation and engraftment and safety profile were consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous stem cell transplantation in patients with multiple myeloma.

Safety Conclusions for CDX-002: CE-Melphalan HCl was generally safe and well-tolerated in the MM patient population of this study with no deaths or discontinuations due to AEs. All Grade 3 and 4 AEs were reversible and no unexpected safety signals were identified. Clinically relevant increases in multiple myeloma response rates, including increases in CR and sCR rates were seen following CEMelphalan HCl. High dose therapy induced myeloablation in all patients and allowed for timely engraftment of both neutrophils and platelets; no patients had non-engraftment following ASCT. Overall, CE-Melphalan HCl was effective in preparing symptomatic multiple myeloma patients for ASCT.

Regulatory Recommendation for Safety: Approval.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. REGULATORY RECOMMENDATION OF THE CDTL REVIEWER: Non-Approval (Complete Response).

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/s/

ALBERT B DEISSEROTH
10/16/2015

Secondary (Team Leader) Review

Date	September 23, 2015
From	Albert Deisseroth, MD, PhD
Subject	Secondary Team Leader Review
BLA Number	NDA 207155
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Established/Proprietary Name	Captisol-enabled Melphalan HCl/Evomela
Dosage Form/Strength	Powder/50 mg (free base)/vial
Approved Indication	1: high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma (ORPHAN) 2. for the palliative treatment of patients with Multiple Myeloma for whom oral therapy is not appropriate (Non-ORPHAN)
Recommendation:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Patricia Dinndorf, MD
Clinical Pharmacology	John Christy, Ph.D., and Gene Williams, PhD.
CMC DTP (Product Quality)	Janice Brown, PhD
Nonclinical	Brenda Gehrke, PhD, and C. Sheth, PhD
Biostatistics	Yaping Wang, PhD and Yuan Li Shen, PhD
DMEPA	Kevin Wright, PhD
Project Manager	Rachel McMullen

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1. EXECUTIVE SUMMARY: (This section was derived in part from the reviews of Dr. Patricia Dinndorf).

On December 23, 2014, Spectrum Pharmaceuticals, Inc. submitted the 505(b)(2) NDA 207155 for EVOMELA (Captisol ®-enabled melphalan HCl/CE-Melphalan HCl) for the following indications:

a. Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma;
b. The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate

This is a new formulation of melphalan which incorporates β-cyclodextrin sulfobutyl ether sodium salts which improves the solubility, and thus eliminates the need for propylene glycol as the diluent. The applicant has conducted a bioequivalence trial (CDX-353-001) demonstrating of CE-Melphalan HCl to the currently approved formulation of melphalan HCl (Alkeran for injection).

High-dose Conditioning Treatment in Patients with Multiple Myeloma: To support the new transplant indication, the applicant cited extensive literature evidence, including randomized studies, documenting the efficacy and safety of melphalan at a dose of $100g/m^2$ for 2 days as a preparative regimen for autologous stem cell transplantation following initial induction therapy for multiple myeloma.

The applicant also conducted a safety and efficacy trial (CDX-353-002) in 61 patients undergoing autologous transplant as treatment of multiple myeloma. The trial demonstrated improvement in overall response rate from 79% pretreatment to 95% at day 90 to 100 post transplant. In addition 100% of patients met criteria for myeloablation, and demonstrated prompt platelet and neutrophil engraftment.

Palliation of Patients with Multiple Myeloma: The bioequivalence study supports approval of the existing label indication in the reference product.

Regulatory Recommendation of the Secondary Reviewer: Approval

2. BACKGROUND: (This section was derived in part from the review of Dr. Patricia Dinndorf).

Proposed Indication #1: Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Proposed Dosage and Administration: 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).

Proposed Indication #2: The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Proposed Dosage and Administration: 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.

The currently available formulation of melphalan, Alkeran® for injection (Melphalan HCl), requires a propylene glycol (b) (4) diluent. Melphalan has marginal solubility and the Alkeran formulation with propylene glycol diluent has limited chemical stability upon reconstitution and dilution.

Propylene glycol diluent has been associated with toxic effects including hyperosmolality, increased anion gap metabolic acidosis, acute kidney injury, sepsis-like syndrome, hemolysis, cardiac arrhythmia, seizure and coma, and agitation. The CE-Melphalan HCl formulation eliminates potential formulation toxicity due to propylene glycol. The applicant has submitted data in the submission to demonstrate CE-Melphalan HCl formulation has improved chemical stability upon reconstitution and dilution.

Summary: Melphalan is the agent of choice as a preparative regimen for autologous stem celltransplant in patients with multiple myeloma. Alkeran® for injection (Melphalan HCl), is the only other presentation of melphalan available in the US.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC): For details, see the review of Drs. Janice Brown.

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

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin is a phenylalanine derivative of nitrogen mustard and an alkylating agent. The current melphalan product, Alkeran® (melphalan hydrochloride) for Injection, is approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

Evomela™ (Captisol®-enabled melphalan hydrochloride) for Injection is a new melphalan hydrochloride product that contains Captisol as an excipient instead of propylene glycol. NDA 207155 has been submitted as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug. With the submission of NDA 207155, Spectrum Pharmaceuticals Inc. is pursuing two indications for Evomela, the current palliative treatment indication for Alkeran and a new

indication of high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

To support the proposed indications, the Applicant has submitted literature of the nonclinical studies conducted with melphalan, an in vitro hemolytic study of the vehicle, and a bridging pharmacokinetic study comparing Evomela to Alkeran in rats. Additionally, the Applicant is relying on the FDA's previous finding of safety and efficacy for Alkeran.

Results: An in vitro hemolytic study of rodent and human red blood cells from fasted subjects was conducted to determine the hemolytic potential of the melphalan vehicle containing Captisol and the Alkeran vehicle in rodent and human blood. The vehicle containing Captisol produced no hemolysis and the Alkeran vehicle produced minor hemolysis in rat and human red blood cells. A pharmacokinetic study containing data following intravenous administration of melphalan in the presence or absence of Captisol in the delivery vehicle to male Sprague Dawley rats was submitted as a bridging pharmacokinetic study comparing Evomela to Alkeran.

Commercial Alkeran vials were used for both formulations. The Captisol-free formulation was prepared as per the product insert for the commercial Alkeran injectable formulation using the sterile diluent that is provided with the Alkeran product, while in the Captisol formulation, Alkeran was reconstituted with a Captisol solution resulting in a final formulation with (b) (4) (w/v) Captisol. No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following a single intravenous administration of melphalan in the (b) (4) (w/v) Captisol or Captisol-free formulations.

Regulatory Recommendation of the Pharmacology/Toxicology Review Team: The nonclinical studies submitted to this NDA and the previous findings of safety and efficacy for the listed drug Alkeran provide sufficient information to support the use of Evomela (Captisol®-enabled melphalan hydrochloride) for the proposed indications.

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

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/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 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) CEMelphalan HCl and Melphalan HCl (Alkeran for Injection, FDA approved drug). The applicant demonstrated that the new formulation was equivalent (80 -125% for AUC and CMAX) 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.

Regulatory Recommendation of Clinical Pharmacology Team: Approval

6. EFFICACY: (This section is excerpted from the reviews of Dr. Patricia Dinndorf, MD. For details, please see the primary review of Dr. Dinndorf.)

Preparative Regimen for Autologous Stem Cell Transplantation: The applicant uses published literature to support this new indication. This includes consensus recommendations from 3 groups; the National Comprehensive Cancer Network (NCCN), the British Society of Hematology, and the European Myeloma Network. The applicant has provided confirmation the agent used in key supportive literature studies is the reference product, Alkeran (Melphalan HCl).

To establish the bridge from Alkeran to CE-Melphalan HCl, the applicant conducted 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."

To provide safety information regarding the new formulation, the sponsor conducted 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."

The benchmarks used to establish safety in this single arm trial are supplied by a Center for International Blood and Marrow Transplant Research (CIBMTR) report of descriptive statistics and post-autologous stem cell transplant engraftment and overall mortality rates for adult multiple myeloma patients who received a first autologous stem cell transplant in the United States between 2008 and 2013.

Review of CDX-353-001: Palliative Treatment of Patients with Multiple Myeloma for Whom Oral Therapy is Not Appropriate. The applicant uses the bioequivalence study of CDX-001 to support the existing label indication in the reference product.

Conclusions from results: (copied from Study Report Section 5.3.1.2 page 137/692) . In conclusion, CE-Melphalan HCl for Injection (Propylene Glycol-Free) was shown to be bioequivalent to Alkeran for Injection. Based on the overall results of this study, the efficacy (myeloablation and engraftment) and safety profile were consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous stem cell transplantation in patients with multiple myeloma.

Review of CDX-353-002: Safety of CE-Melphalan HCL in Multiple Myeloma ASCT Population:
Eligibility Criteria:
a. Patients with symptomatic multiple myeloma, based on International Myeloma Working Group (IMWG) guidelines, requiring treatment who are eligible for ASCT.
b. Patients who are 70 years of age or younger at time of transplant. Patients older than 70 years of age may be enrolled on a case-by-case basis.
c. Patients with an adequate autologous stem cell collection, defined as an unmanipulated, cryopreserved, peripheral blood stem cell collection containing at least 2 × 106 CD34+ cells/kg based on patient body weight.
d. Patients with adequate organ function (cardiac, hepatic, renal, pulmonary).
e. ECOG 0 to 2.

Efficacy Conclusion: (copied from submission Section 5.3.5.2 CDX-002 Study Report page 85 of 1084): CE-Melphalan high dose treatment of patients (N=61) with symptomatic multiple myeloma requiring treatment and eligible for ASCT, including 7% of patients with prior ASCT, produced clinically meaningful increases in Overall multiple myeloma Response Rates from 79% Pre-treatment to 95% at Day +90/Day +100. Importantly, there was also an increase in the overall complete response rate from 10% to

31%, with the number of patients with a stringent complete response rate increasing from 0% Pretreatment to 16% at Day +90/Day +100.

In addition, CE-Melphalan HCl high dose therapy resulted in:

a. Myeloablation in all 61 (100%) patients meeting the protocol-defined criteria, and as reflected by the development of severe neutropenia with ANCs $<0.5\times10^9$/L;
b. median time to myeloablation was 5 days.
c. Neutrophil engraftment was achieved in all 61 (100%) patients in this study, with a median time of 12 days.
d. Platelet engraftment was achieved in all 61 (100%) patients in this study, with a median time to platelet engraftment of 13 days.
e. No (0%) patients had non-engraftment of neutrophils by Day +90/Day +100.

Regulatory Recommendation. Approval.

7. SAFETY: (This section was derived in part from the review of Dr. Patricia Dinndorf).

Safety Conclusions for CDX-001: CE-Melphalan HCl for Injection (Propylene Glycol-Free) was shown to be bioequivalent to Alkeran for Injection. Based on the overall results of this study, myeloablation and engraftment and safety profile were consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous stem cell transplantation in patients with multiple myeloma.

Safety Conclusions for CDX-002: CE-Melphalan HCl was generally safe and well-tolerated in the MM patient population of this study with no deaths or discontinuations due to AEs. All Grade 3 and 4 AEs were reversible and no unexpected safety signals were identified. Clinically relevant increases in multiple myeloma response rates, including increases in CR and sCR rates were seen following CEMelphalan HCl. High dose therapy induced myeloablation in all patients and allowed for timely engraftment of both neutrophils and platelets; no patients had non-engraftment following ASCT. Overall, CE-Melphalan HCl was effective in preparing symptomatic multiple myeloma patients for ASCT.

Regulatory Recommendation for Safety: Approval.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. LABELLING: Currently under negotiation with the Applicant.

10. REGULATORY RECOMMENDATION OF THE SECONDARY REVIEWER:
Approval

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/s/

ALBERT B DEISSEROTH
09/23/2015

CLINICAL REVIEW

Application Type	NDA (505(b)(2))
Application Number(s)	207155
Priority or Standard	Standard
Submit Date(s)	12/23/14
Received Date(s)	12/30/14
PDUFA Goal Date	10/23/15
Division / Office	DHP/OHOP
Reviewer Name(s)	Patricia Dinndorf
Review Completion Date	8/17/15
Established Name	Captisol®-enabled Melphalan HCl
(Proposed) Trade Name	EVOMELA™
Therapeutic Class	Alkylating Agent
Applicant	Spectrum Pharmaceuticals, Inc.
Formulation(s)	Injectable Melphalan HCl with β-cyclodextrin sulfobutyl ether sodium salts (CE)
Dosing Regimen	100 mg/m^2/day IV for 2 days 16 mg/m^2 q 2 wk for 4 doses
Indication(s)	Preparative regimen ASCT Palliation
Intended Population(s)	Patients with multiple myeloma undergoing transplant Palliative treatment of patients with multiple myeloma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this 505(b)(2) NDA for EVOMELA (Captisol ®-enabled melphalan HCl / CE-Melphalan HCl) for the following indications:

- 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

This new formulation of melphalan incorporates β-cyclodextrin sulfobutyl ether sodium salts which improves the solubility, and thus eliminates the need for propylene glycol as the diluent. The applicant has conducted a bioequivalence trial demonstrating bioequivalence of CE-Melphalan HCl to the currently approved formulation of melphalan HCl (Alkeran for injection).

<u>High-dose Conditioning Treatment in Patients with Multiple Myeloma</u>
To support the new transplant indication the applicant cited extensive literature evidence, including randomized studies, documenting the efficacy and safety of melphalan at a dose of 100g/m^2 for 2 days as a preparative regimen for autologous stem cell transplantation following initial induction therapy for multiple myeloma. The applicant conducted a safety and efficacy trial in 61 patients undergoing autologous transplant as treatment of multiple myeloma. The trial demonstrated improvement in overall response rate from 79% pretreatment to 95% at day 90 to 100 post transplant. In addition 100% of patients met criteria for myeloablation, and demonstrated prompt platelet and neutrophil engraftment.

<u>Palliation of Patients with Multiple Myeloma</u>
The bioequivalence study supports approval of the existing label indication in the reference product.

1.2 Risk Benefit Assessment

Table 1: Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of evidence**: Multiple myeloma is a fatal disease	**Conclusions (implications for decision):** Stem cell transplant with melphalan 200mg/m^2 as initial therapy is the treatment of choice for patients with MM. CE-Melphalan HCl formulation has superior properties compared to Alkeran.
Unmet Medical Need	**Summary of evidence**: Alkeran has marginal solubility and stability. Alkeran is reconstituted with propylene glycol, which contributes to side effects of treatment.	**Conclusions (implications for decision):** The formulation of melphalan that incorporates β-cyclodextrin sulfobutyl ether sodium salts: 1. Allows omitting propylene glycol as the diluent 2. Allows use of normal saline as diluent. 3. Improves the solubility, and stability of melphalan. Formulation simplifies logistics of administration, provides flexibility of infusion duration, avoids propylene glycol toxicity
Clinical Benefit	**Summary of evidence**: Bioequivalence to of CE-Melphalan HCl demonstrated in CDX-353-001 study. Efficacy and safety in 61 patient CDX-353-002 study comparable to known efficacy and safety demonstrated in large transplant registry population.	**Conclusions (implications for decision):** Efficacy and safety demonstrated.
Risk	**Summary of evidence**: There does not appear to be any additional risks with the CE-Melphalan HCL and safety profile is likely to be superior to Alkeran	**Conclusions (implications for decision):** No clinical risks identified.
Risk Management	**Summary of evidence**: No clinical risks identified.	**Conclusions (implications for decision):** No clinical risks identified.
Benefit-Risk Summary and Assessment The risk benefit analysis supports approval. The CE-Melphalan HCl has superior characteristics of solubility, stability and avoids propylene glycol. The formulation simplifies the logistics of administration, provides flexibility of infusion duration, avoids propylene glycol toxicity. No new safety s gnals were identified.		

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: CE-Melphalan HCl
Reference Listed Product: Alkeran® for Injection (Melphalan HCl)
Proprietary Name: EVOMELA
Applicant: Spectrum Pharmaceuticals, Inc.
Pharmacological Class: Alkylating agent

Proposed Indication:

- Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Proposed Dosage and Administration:

- 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).

Proposed Indication:

- The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate

Proposed Dosage and Administration:

- 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.

CE-Melphalan HCl is an injectable formulation of melphalan HCl (Alkeran for Injection) that incorporates the Captisol brand of β-cyclodextrin sulfobutyl ether sodium salts into a (b) (4) product. Melphalan, is a phenylalanine derivative of nitrogen mustard. It is a bifunctional alkylating agent of the bischloroethylamine type that is active against selected human neoplastic diseases.

2.2 Tables of Currently Available Treatments for Proposed Indications

Preparative Regimen for ASCT
(Derived from UpToDate)
Autologous stem cell transplant performed either at the time of initial diagnosis or at relapse, is considered the standard of care for younger patients (less than 70 years of age) with newly diagnosed multiple myeloma. The standard conditioning regimen used for hematopoietic cell transplantation in myeloma is melphalan at a dose of 200 mg/m^2, with dose reductions based on age and renal function. The use of this dose is primarily based upon two randomized trials that have compared melphalan 200 mg/m^2 with a lower dose of melphalan, with or without radiation therapy, in preparation for ASCT. In

two other randomized studies, the use of more intensive preparative regimens, such as thiotepa, busulfan, and cyclophosphamide or high-dose idarubicin, cyclophosphamide, and melphalan did not result in better outcomes than melphalan at a dose of 200 mg/m^2.

Formulation Issues

The currently available formulation of melphalan, Alkeran® for injection (Melphalan HCl), requires a propylene glycol (b) (4) diluent. Melphalan has marginal solubility and the Alkeran formulation with propylene glycol diluent has limited chemical stability upon reconstitution and dilution. Propylene glycol diluent has been associated with toxic effects including hyperosmolality, increased anion gap metabolic acidosis, acute kidney injury, sepsis-like syndrome (Zar 2007), hemolysis, cardiac arrhythmia, seizure and coma, and agitation. (Wilson 2005)

The CE-Melphalan HCl formulation eliminates potential formulation toxicity due to propylene glycol. The applicant has submitted data in the submission to demonstrate CE-Melphalan HCl formulation has improved chemical stability upon reconstitution and dilution.

Summary

Melphalan is the agent of choice as a preparative regimen for autologous stem cell transplant in patients with multiple myeloma. Alkeran® for injection (Melphalan HCl), is the only other presentation of melphalan available in the US.

Palliative Treatment of Patients with Multiple Myeloma for Whom Oral Therapy is Not Appropriate

Due to the number of approved agents for treatment of multiple myeloma that have become available since the original approval of melphalan, melphalan is not a common choice for this indication.

(Derived from UpToDate)

There are a plethora of agents that have demonstrated activity in relapsed or refractory multiple myeloma. The main treatment options for relapsed or refractory disease are bortezomib, lenalidomide, carfilzomib, alkylators, thalidomide, anthracyclines, and corticosteroids, administered alone, or more commonly as part of two or three drug combinations. The most common regimens recommended for the treatment of relapsed or refractory myeloma include lenalidomide plus dexamethasone, bortezomib with cyclophosphamide and dexamethasone, bortezomib plus lenalidomide and dexamethasone, carfilzomib plus lenalidomide and dexamethasone, and pomalidomide plus dexamethasone.

2.3 Availability of Proposed Active Ingredient in the United States

Alkeran® for injection (Melphalan HCl), is the only other presentation of melphalan available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Boxed Warning
Severe bone marrow suppression with resulting infection or bleeding may occur. Controlled trials comparing IV to oral melphalan have shown more myelosuppression with the IV formulation. Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received the IV formulation. (b) (4) Melphalan produces chromosomal aberrations *in vitro* and *in vivo* and, (b) (4) should be considered potentially (b) (4) in humans.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2: Presubmission Regulatory Activity

Date	Item
7/23/07	Pre IND Meeting IND (b) (4) Sponsor: (b) (4) • Discussed 505(b)(2) pathway for palliation of patients with MM • Discussed appropriate PK/PD bioequivalence study • Discussed manufacturing plan, impurities, stability • Agreed the plan to rely on pre-clinical date from Alkeran® (Melphalan Hydrochloride) for Injection, NDA 020207 and Type V Drug Master File (DMF # (b) (4)) entitled, (b) (4)
12/1/2008	Received orphan-drug designation of mephalan hydrochloride as a "high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation."
5/27/2009	Pre IND Meeting IND 104925 • Discussed plans to submit a 505(b)(2) application for high-dose (200 mg/m^2) conditioning treatment prior to ASCT for patients with MM • FDA agreed a 505(b)(2) application could be an acceptable approach • FDA advised the applicant the proposed study must be redesigned to establish pharmacokinetic comparability of melpahlan (propylene glycol-free) and Alkeran at the proposed recommended dose • FDA commented the acceptability of literature to support the would be review issue and if literature did not provide sufficient support a trial to establish efficacy would be required • Discussed need for additional preclinical studies at proposed doses for the transplant indication. The applicant stated these were not feasible because of the LD50 in rats of the proposed dose. FDA advised additional studies may be necessary, and should be performed at the highest feasible dose.
8/13/09	Advice Letter • Bioequivalence trial should be modified to make AUC_{0-T}, rather than $AUC_{0-\infty}$, the primary AUC endpoint to conclude comparability. • A single bioequivalence study is not adequate to support the application. In order to support safety a clinical study in at least 60 patients will be required.
4/17/13	Spectrum Pharmaceuticals acquired development and commercialization rights for Ligand Pharmaceuticals' Melphalan HCl for Injection (Propylene Glycol-Free) formulation. The IND was transferred.
1/3/14	Type C meeting is to discuss the adequacy of the bridging pharmacokinetic and/or toxicology studies
4/16/14	CMC Meeting to discuss CMC studies to support application
6/23/14	Pre-NDA Meeting • FDA advised the applicant verification that the formulation of melphalan in literature reports supporting the application was Alkeran • FDA gave detailed advice on the presentation and content of clinical pharmacology data.

2.6 Other Relevant Background Information

CE-Melphalan HCl was granted Orphan Drug Designation for use as a high-dose conditioning treatment prior to hematopoietic autologous stem cell transplantation in patients with multiple myeloma. Due to this orphan designation this indication is not subject to the Pediatric Research Equity Act (PREA). The applicant is requesting waiver for the palliative treatment of patients with multiple myeloma indication.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was of adequate quality to allow for filing of the NDA and for the clinical review to be conducted.

3.2 Compliance with Good Clinical Practices

The study report for CDX-353-002 includes the statement: This study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines.

The study report for CDX-353-001 includes the statement: This study was conducted in compliance with the protocol, the Declaration of Helsinki, applicable U.S. FDA regulations, and GCP guidelines.

3.3 Financial Disclosures

The applicant checked the first box of form 3454.

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No approvability issues were identified by the product quality review team at the midcyle review.

4.2 Clinical Microbiology

No approvability issues were identified at the midcycle review.

4.3 Preclinical Pharmacology/Toxicology

No pharmacology/toxicology concerns with the NDA were identified at the midcycle review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Melphalan, is a phenylalanine derivative of nitrogen mustard. It is a bifunctional alkylating agent of the bischloroethylamine type.

4.4.2 Pharmacodynamics

Trial CDX-353-002 demonstrated improvement in overall response rate from 79% pretreatment to 95% at day 90 to 100 post transplant. In addition 100% of patients met criteria for myeloablation, and demonstrated prompt platelet and neutrophil engraftment.

4.4.3 Pharmacokinetics

No approvability issues were identified at the midcycle meeting. Pharmacokinetic evaluation under review at the midcycle review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

(copied from submission 2.5 Clinical overview page 25/118)

Table 3: Summary of Key Supportive Efficacy Data

Data Source	Compound	Data Type	Efficacy Endpoints
Key Efficacy Data			
Sponsor-initiated Studies - CDX-353-002	CE-Melphalan HCl	Clinical Study	MM Response Rate, Myeloablation, Engraftment
Key Literature Studies - Randomized, controlled studies; key uncontrolled studies (US)	Melphalan HCl	Melphalan Published Literature	MM Response Rate, OS, EFS/PFS, Engraftment
CIBMTR Report **(Module 5.3.5.4)**	Melphalan HCl	Clinical Database	MM Response Rate, Engraftment
Supportive Efficacy Data			
Sponsor-initiated Studies - CDX-353-001	CE-Melphalan HCl	Clinical Study	Myeloablation, Engraftment
Other Literature Studies - Controlled and Uncontrolled Prospective Studies	Melphalan HCl	Melphalan Published Literature	MM Response Rate, OS, EFS/PFS, Engraftment
Other Literature Studies - Controlled and Uncontrolled Retrospective Studies	Melphalan HCl	Melphalan Published Literature	MM Response Rate, OS, EFS/PFS, Engraftment
Other Literature Studies in Special Patient Subpopulations- Prospective and Retrospective Studies (elderly, renal impairment)	Melphalan HCl	Melphalan Published Literature	MM Response Rate, OS, EFS/PFS, Engraftment

5.2 Review Strategy

Preparative Regimen for Autologous Stem Cell Transplantation

The applicant uses published literature to support this new indication. This include consensus recommendations from 3 groups; the National Comprehensive Cancer Network (NCCN), the British Society of Hematology, and the European Myeloma Network. The applicant has provided confirmation the agent used in key supportive literature studies is the reference product, Alkeran (Melphalan HCl).

- To establish the bridge from Alkeran to CE-Melphalan HCl the applicant conducted 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." See Section 5.3.1.
- To provide safety information regarding the new formulation the sponsor conducted 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." See Section 5.3.2. The benchmarks used to establish safety in this single arm trial are supplied by a Center for International Blood and Marrow Transplant Research (CIBMTR) report of descriptive statistics and post-autologous stem cell transplant engraftment and overall mortality rates for adult multiple myeloma patients who received a first autologous stem cell transplant in the United States between 2008 and 2013. See Section 5.3.3.

The review of the literature and consensus recommendations is summarized in Section 6 Efficacy Summary. The reviews of CDX-353-001 and CDX-353-002 are presented in Section 5.3 Discussion of Individual Studies/Clinical Trials.

Palliative Treatment of Patients with MM for Whom Oral Therapy is Not Appropriate

The applicant uses the bioequivalence study of CDX-001 to support the existing label indication in the reference product. The reviews of CDX-353 -001 is presented in Section 5.3 Discussion of Individual Studies/Clinical Trials.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 CDX-353-001 Bioequivalence CE-Melphalan HCl and Alkeran

Number/Clinical Trial Title: 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

Dose: CE-Melphalan HCl 100 mg/m^2 and Alkeran 100 mg/m^2 (crossover) Day -3 and -2

Route: IV infusion over 30 minutes ± 3 minutes

Population:

- Patients with symptomatic MM requiring treatment at diagnosis or anytime thereafter
- Patients who qualify for ASCT therapy and who have received appropriate primary induction therapy for transplantation
- Age ≥ 18 years ≤ 70 years
- Patients with an adequate autologous graft, that is at least 2 × 10^6 CD34+ cells/kg
- Patients with adequate organ function (cardiac, hepatic, renal, pulmonary)

Enrollment:

- A total of 40 patients were screened, and 24 patients were enrolled

Date of Study: First patient enrolled 2/4/10; Last patient completed 6/8/11

Results:

Demographics and Baseline Characteristics:

Table 4: CDX-353-001 Demographic & Baseline Characteristics

Demographics and Baseline Characteristics CDX-353-001	
	n=24
Gender n (%)	
Male	13 (54)
Female	11 (46)
Age in Years	
Mean	57
Median	58
Range	48 to 65
Race n (%)	
White	19 (79)
Black African Heritage or African American	4 (17)
Asian	1 (4)
ECOG Score	
0 – Fully active	12 (50)
1 – Restricted strenuous activity but ambulatory	12 (50)
Multiple Myeloma Stage at Study Entry	
II	9 (38)
III	15 (63)
Years Since Multiple Myeloma Diagnosis	
Mean	1.6
Median	0.8
Range	0 to 6

Exposure:

(copied from Study Report Section 5.3.1.2 page 73/692)
All 24 enrolled patients received both formulations of melphalan (Alkeran for injection and Melphalan HCl for Injection (Propylene Glycol-Free), and no patients discontinued prematurely in this study.

All subjects were treated with identical doses (100 mg/m^2) of Alkeran and CE-Melphalan HCl. The dose of melphan was calculated based on actual body weight or ideal body weight (IBW) if the actual body weight was >130% of the IBW. Approximately one-half of the patients were dosed based on a BSA that was determined from their IBW rather than their actual body weight.

Disposition:

(copied from Study Report Section 5.3.1.2 page 73/692)
All 24 enrolled patients received both formulations of melphalan (Alkeran for injection and Melphalan HCl for Injection (Propylene Glycol-Free), and no patients discontinued prematurely in this study.

Pharmacodynamic Efficacy Results:

The efficacy endpoints for study were myeloablation and engraftment.

Myeloablation

Myeloablation was defined as an absolute neutrophil count (ANC) <0.5 × 10^9/L, absolute lymphocyte count (ALC) <0.1 × 10^9/L, platelet count <20 x 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. The results are a summarized in Table 5.

(copied from submission Section 5.3.1.2 CDX-001 Study Report page 168/692)

Table 5: CDX-353-001 Summary of Time and Rate of Myeloablation

Experienced Myeloablation	Yes	24(100%)
Time to Myeloablation (Study Days)	n	24
	Mean	2.9
	SD	1.21
	Median	3.0
	Min	0
	Max	5

Engraftment

Engraftment was defined as neutrophil (ANC >0.5 × 10^9/L × on the first of 3 consecutive daily assessments) and platelet (untransfused platelet measurement >20 x 10^9/L on the first of 3 consecutive daily assessments). All 24 subjects met criteria for engraftment between day 9 to day 13. The results are a summarized in Table 6.

(copied from submission Section 5.3.1.2 CDX-001 Study Report page 169/692)

Table 6: CDX-353-001 Summary of Time and Rate of Engraftment

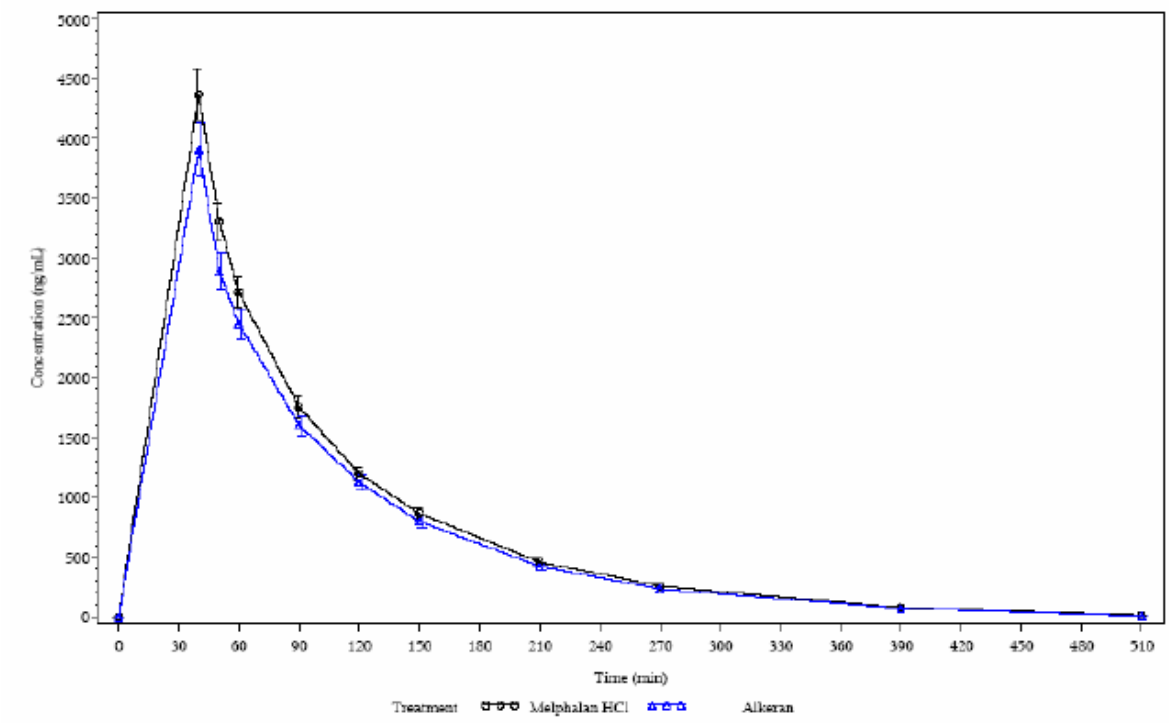
Experienced Engraftment	Yes	24(100%)
Time to Engraftment (Study Days)	n	24
	Mean	11.0
	SD	1.08
	Median	11.0
	Min	9
	Max	13

Pharmacokinetic Results:

Mean melphalan plasma concentrations for CE-Melphalan HCl versus Alkeran are summarized for each time point in Figure 1.

(copied from submission Section 5.3.1.2 CDX-001 Study Report page 77/692)

Figure 1: Mean Plasma Melphalan Concentration CE-Melphalan versus Alkeran



Noncompartmental Analysis Melphalan Pharmacokinetic Parameters

(copied from Study Report Section 5.3.1.2 page 79/692)

Table 7: Noncompartmental Analysis of PK Parameters CE-Melphalan v Alkeran

Parameter	Melphalan HCl (PG-Free) N = 24	Alkeran N = 24
C_{max} (ng/mL)	4374 ± 1050	3931 ± 1034
AUC_{0-t} (min·ng/mL)	376,577 ± 93,401	341,183 ± 91,349
$AUC_{0-\infty}$ (min ng/mL)	381,443 ± 93,494	345,945 ± 91,347
T_{max} (min)	40.0 ± 0.00	40.4 ± 2.04
$t_{1/2}$ (min)	67.7 ± 6.25	67.6 ± 5.46
k_{el} (/min)	0.0103 ± 0.00095	0.0103 ± 0.00079

Noncompartmental Bioequivalence Analysis

The geometric mean ratios for the noncompartmental analysis estimates of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 112.00%, 110.90%, and 110.77%, respectively, and the

associated 90% CIs were contained within 80.00 to 125.00% as summarized in Table 8.

(copied from Study Report Section 5.3.1.2 page 80/692)

Table 8: Statistical Analysis of PK Parameters (Noncompartmental) CE-Melphalan v Alkeran

Parameter	Estimate	90% Confidence Interval[a]	
C_{max}	112.00	105.58	118.80
AUC_{0-t}	110.90	105.13	116.98
$AUC_{0-\infty}$	110.77	105.08	116.78

Compartmental Analysis Melphalan Pharmacokinetic Parameters

(copied from Study Report Section 5.3.1.2 page 80/692)

Table 9: Compartmental Analysis of PK Parameters CE-Melphalan v Alkeran

Parameter[a]	Melphalan HCl (PG-Free) N = 24	Alkeran N = 24
C_{max} (ng/mL)	5839 ± 1485	5406 ± 2001
$AUC_{0-\infty}$ (min·ng/mL)	450,997 ± 109,230	416,118 ± 116,779
$t_{1/2}$ (min)	68.7 ± 6.60	72.3 ± 16.8
k_{el} (min)	0.0012 ± 0.0010	0.0012 ± 0.0010

Compartmental Bioequivalence Analysis

The geometric mean ratios for the model-estimated C_{max} and $AUC_{0-\infty}$ were 111.42% and 109.40% and the associated 90% CIs were contained within 80.00 to 125.00% as summarized in Table 10.

(copied from Study Report Section 5.3.1.2 page 81/692)

Table 10: Statistical Analysis of PK Parameters (Compartmental) CE-Melphalan v Alkeran

Parameter	Geometric Mean Ratio (%)[a]		
	Estimate	90% Confidence Interval	
C_{max}	111.42	101.36	122.48
$AUC_{0-\infty}$	109.40	103.50	115.62

Safety Results:
An overall summary of the adverse events is presented in Table 11.

(copied from Study Report Section 5.3.1.2 page 81/692)
Table 11: CDX-353-001 Overall Summary of Treatment Emergent Adverse Events (TEAE)

Type of Adverse Event	n (%) of Patients Total (N = 24)
Patients With at Least 1 TEAE	24 (100%)
Patients With at Least 1 Treatment-Related TEAE	24 (100%)
Patients With at Least 1 Grade 3 to 4 TEAE	17 (71%)
Patients With at Least 1 Grade 3 to 4 Treatment-Related TEAE	16 (67%)
Patients With at Least 1 Serious TEAE	7 (29%)
Patients With at Least 1 Serious Treatment-Related TEAE	6 (25%)
Patients With a TEAE Leading to Discontinuation of Study Drug	0 (0%)

Deaths
No patients died during this study.

Adverse Events Leading to Discontinuation
None.

Serious Adverse Events (SAE)

Table 12 summarizes the SAEs reported on this study. These are expected event associate with ASCT. All the reported SAEs were considered related to treatment except for left bundle branch block was reported on the second day of study treatment (Day -2) prior to the patient receiving CE-Melphalan HCl.

(copied from Study Report Section 5.3.1.2 page 242/692)

Table 12: CDX-353-001 Serious Adverse Events

Subject ID/ Gender/ Race/ Age	System Organ Class/ Preferred Term/ Verbatim Term	Prior/ Start Date/ End Date/ Ongoing/ Duration	Phase/ Study Day/ Treatment Seq/ First Trt Date	Study Drug Action/ Treatment Required/ Outcome	Relation/ Severity/ Serious
007/ Male/ White/ 62	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS/ MUCOSAL INFLAMMATION/ hospitalization with mucositis	No/ 13JUL2010/ 20JUL2010/ No/ 8d	Follow-up Period/ 4/ Melphalan-Alkeran/ 06JUL2010	None/ Concomitant Medications/ Resolved w/Sequelae	Probably Related/ Severe/ Yes
009/ Female/ Black African Heritage or African American/ 61	CARDIAC DISORDERS/ BUNDLE BRANCH BLOCK LEFT/ left bundle branch block	No/ 18AUG2010/ 18AUG2010/ No/ 12h	Study Period/ -2/ Alkeran-Melphalan/ 17AUG2010	None/ None/ Resolved	Not Related/ Severe/ Yes
010/ Male/ White/ 50	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS/ MUCOSAL INFLAMMATION/ Hospitalization due to mucositis	No/ 23SEP2010/ 28SEP2010/ No/ 6d	Follow-up Period/ 7/ Melphalan-Alkeran/ 13SEP2010	None/ Concomitant Medications and Non-Drug Therapies/ Resolved	Possibly Related/ Severe/ Yes
015/ Female/ White/ 57	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS/ FATIGUE/ extreme fatigue	No/ 21DEC2010/ 23DEC2010/ No/ 3d	Follow-up Period/ 5/ Melphalan-Alkeran/ 13DEC2010	None/ Non-Drug Therapies/ Resolved	Probably Related/ Severe/ Yes
022/ Female/ White/ 65	BLOOD AND LYMPHATIC SYSTEM DISORDERS/ FEBRILE NEUTROPENIA/ Febrile Neutropenia	No/ 11APR2011/ 20APR2011/ No/ 10d	Follow-up Period/ 4/ Alkeran-Melphalan/ 04APR2011	None/ Concomitant Medications and Non-Drug Therapies/ Resolved	Probably Related/ Severe/ Yes
023/ Female/ White/ 52	BLOOD AND LYMPHATIC SYSTEM DISORDERS/ FEBRILE NEUTROPENIA/ neutropenic fever	No/ 12MAY2011/ 16MAY2011/ No/ 5d	Follow-up Period/ 7/ Melphalan-Alkeran/ 02MAY2011	None/ Concomitant Medications/ Resolved	Probably Related/ Severe/ Yes
024/ Female/ White/ 57	INFECTIONS AND INFESTATIONS/ SEPSIS/ Sepsis	No/ 06JUN2011/ 09JUN2011/ No/ 4d	Post Follow-up/ 11/ Melphalan-Alkeran/ 23MAY2011	None/ Concomitant Medications and Non-Drug Therapies/ Resolved	Possibly Related/ Life threatening or disabling/ Yes

Conclusion:

(copied from Study Report Section 5.3.1.2 page 137/692)

In conclusion, CE-Melphalan HCl for Injection (Propylene Glycol-Free) was shown to be bioequivalent to Alkeran for Injection. Based on the overall results of this study, the efficacy (myeloablation and engraftment) and safety profile were consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous stem cell transplantation in patients with multiple myeloma.

5.3.2 CDX-353-002 Safety of CE-Melphalan HCl in MM ASCT Population

Number/Clinical Trial Title: 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

Dose: CE-Melphalan HCl 100 mg/m^2 Day -3 and -2 [Adjusted Ideal Body Weight (AIBW) for patients with > 130% ideal body weight]

Route: IV infusion over 30 minutes

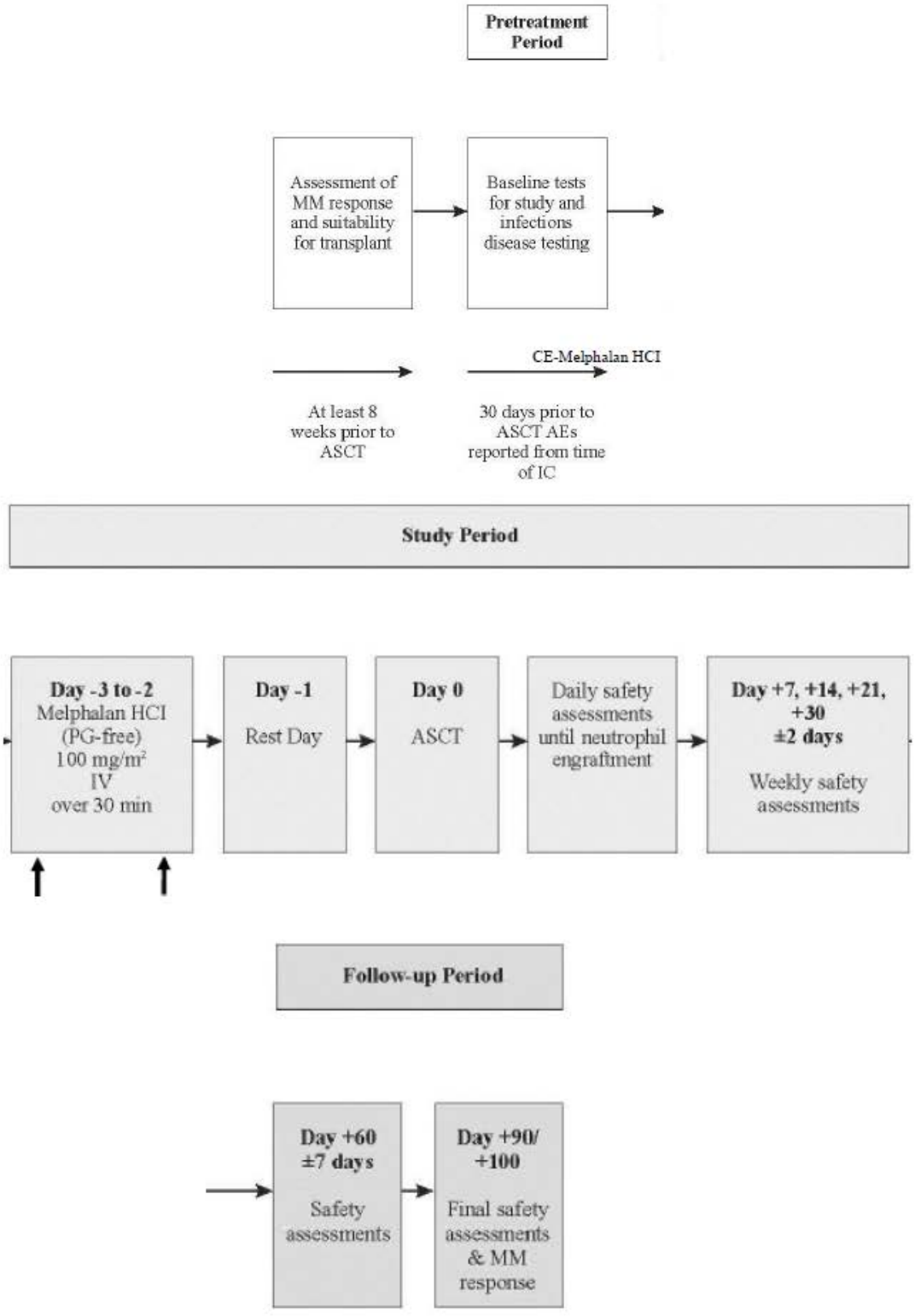
Population:

- Patients with symptomatic MM, based on International Myeloma Working Group (IMWG) guidelines, requiring treatment who are eligible for ASCT.
- Patients who are 70 years of age or younger at time of transplant. Patients older than 70 years of age may be enrolled on a case-by-case basis.
- Patients with an adequate autologous stem cell collection, defined as an unmanipulated, cryopreserved, peripheral blood stem cell collection containing at least 2 × 10^6 CD34+ cells/kg based on patient body weight.
- Patients with adequate organ function (cardiac, hepatic, renal, pulmonary)
- ECOG 0 to 2

Enrollment: There were 76 patients screened. Planned number of patients was 60. The actual number of patients enrolled was 61.

Date of Study: Initiation 2/20/13; End 2/6/14

Schema:


Pretreatment Period
Assessment of MM response and suitability for transplant
Baseline tests for study and infections disease testing
CE-Melphalan HCl
At least 8 weeks prior to ASCT
30 days prior to ASCT AEs reported from time of IC
Study Period
Day -3 to -2
Melphalan HCl
(PG-free)
100 mg/m²
IV
over 30 min
Day -1
Rest Day
Day 0
ASCT
Daily safety assessments until neutrophil engraftment
Day +7, +14, +21, +30
±2 days
Weekly safety assessments
Follow-up Period
Day +60
±7 days
Safety assessments
Day +90/ +100
Final safety assessments & MM response

Results:

Demographics and Baseline Characteristics:

Table 13: CDX-353-002 Demographic & Baseline Characteristics

Demographics and Baseline Characteristics CDX-353-002	
	n=61
Gender n (%)	
Male	35 (57)
Female	26 (43)
Age in Years	
Mean	59
Median	62
Range	32 to 73
Race n (%)	
White	49 (80)
Black African Heritage or African American	11 (18)
Asian	1 (2)
ECOG Score	
0 – Fully active	35 (57)
1 – Restricted strenuous activity but ambulatory	25 (41)
2 - Ambulatory self-care unable to work	1 (2)
Multiple Myeloma Stage n (%)	
I	28 (46)
II	16 (26)
III	15 (25)
Unknown	2 (3)
Prior Therapy n (%)	
1 Prior Therapy	53 (87)
2-4 Prior Therapies	8 (13)
Prior ASCT	4 (7)
Response to the Most Recent Pre-transplant Therapy n (%)	
Complete Response (CR)	6 (10)
Very Good Partial Response (VGPR)	22 (36)
Partial Response (PR)	20 (33)
Stable Disease (SD)	8 (13)
Progressive Disease (PD)	5 (8)

:

Exposure:

All patients received 2 doses of CE-Melphalan HCl 100 mg/m^2 on day -3 and -2. [Adjusted Ideal Body Weight (AIBW) for patients with > 130% IBW]

Disposition:

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 59 of 1084)

Table 14: CDX-353-002 Disposition

Patient Population	Overall N=76 (%)[a]
Patients Enrolled	61 (80)
Screening Failures	15 (20)
ITT Population	61 (80)
MMRE Population	61 (80)
Safety Population	61 (80)
Completed the Study	61 (80)
Discontinued from the Study	0

Efficacy:

Multiple Myeloma Response Day 90 to 100

MM Response- assessed by Investigators according to IMWG criteria Day +90/Day +100 after treatment. The pre ASCT response of patients compare to response at the final trial assessment is presented in Table 15. Cells with improved status are highlighted in yellow, and cells with worse status are highlighted in blue.

Table 15: CDX-353-002 Comparison Pre ASCT v Day 90 - 100 Response Status

Pretreatment Response Status	Day 90 - 100 Response					
	sCR	CR	VGPR	PR	SD	PD
Pretreatment sCR n=0						
Pretreatment CR n=6	3	2	1			
Pretreatment VGPR n=22	6	5	8	3		
Pretreatment PR n=20		2	10	6	2	
Pretreatment SD n=8	1		5	2		
Pretreatment PD n=5			2	2		1
Total n=61	10 (16%)	9 (15%)	16 (26%)	13 (21%)	2 (3%)	1 (2%)

sCR – stringent complete response; CR - complete response; VGPR – very good partial response; PR - partial response; SD – stable disease; PD – progressive disease

Prior to ASCT, 48 (79%) of the patients were categorized as PR or better; at the day 90 to 100 evaluation, 58 (95%) of the patients were categorized as PR or better. There was an increase in the overall CR Rate from 10% to 31%, with the number of patients with a sCR increasing from 0% Pre-treatment to 16% at Day +90/Day +100.

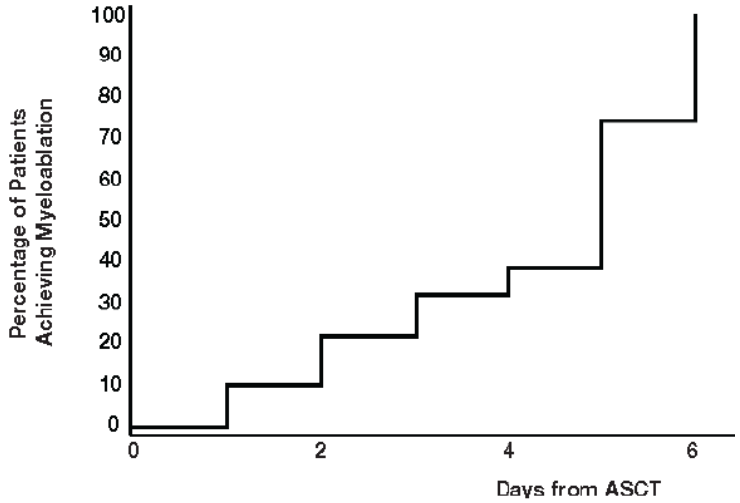
Myeloablation

Myeloablation- defined as any of the following: ANC <0.5×10^9/L, ALC <0.1×10^9/L, or platelet count <20 x 10^9/L.

Myeloablation was achieved by all 61 (100%) patients in this study. The median time to myeloablation was 5.0 days (range - day -1, day +6). See Figure 2.

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 79 of 1084)

Figure 2: CDX-353-002 Time to Myeloablation



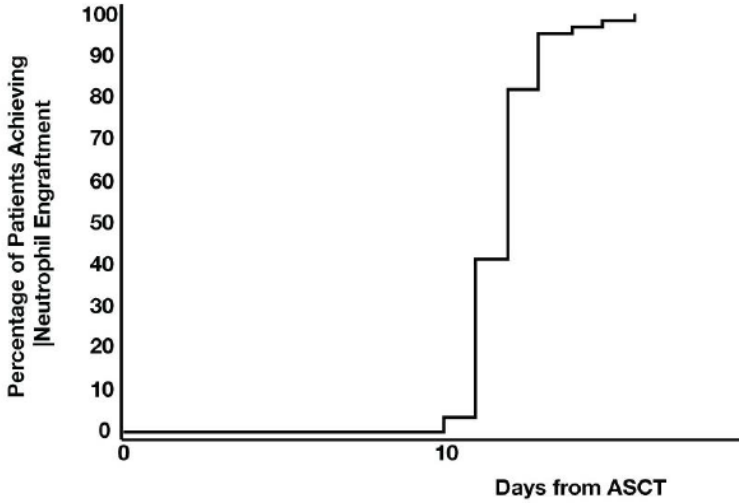
Engraftment

Neutrophil Engraftment- defined as an ANC >0.5×10^9/L×3 consecutive daily assessments.

Neutrophil engraftment was achieved by all 61 (100%) patients in this study. The median time to neutrophil engraftment was 12 days (range 10 to 16). See Figure 3.

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 82 of 1084)

Figure 3: CDX-353-002 Time to Neutrophil Engraftment

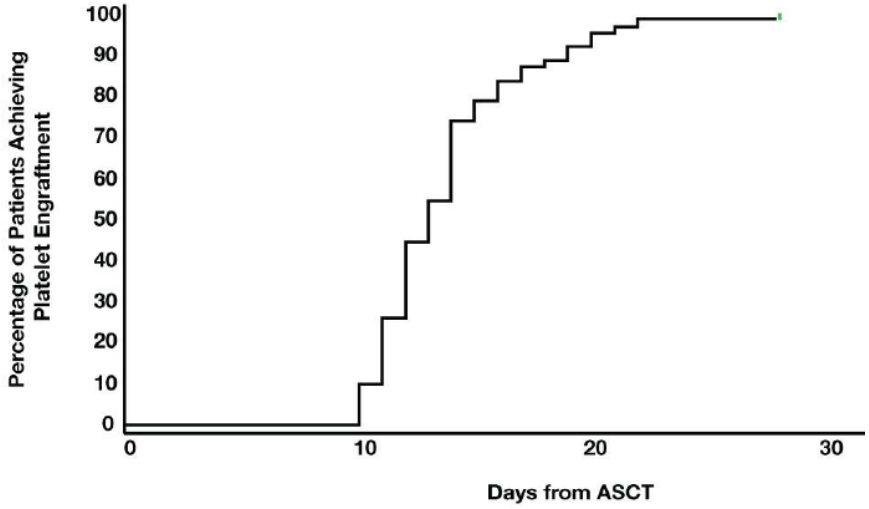


Platelet Engraftment- defined as an untransfused platelet measurement >20 x 10^9/L ×3 consecutive daily assessments.

Platelet engraftment was also achieved by all 61 (100%) patients in this study. The median time to platelet engraftment was 13 days (10, 28)

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 83 of 1084)

Figure 4: CDX-353-002 Time to Platelet Engraftment



Non-engraftment- defined as a failure to reach an ANC >0.5×10^9/L×3 consecutive daily assessments by Day +90/Day +100.

None of the patients in this study had non-engraftment.

Efficacy Conclusion
(copied from submission Section 5.3.5.2 CDX-002 Study Report page 85 of 1084)
CE-Melphalan high dose treatment of patients (N=61) with symptomatic MM requiring treatment and eligible for ASCT, including 7% of patients with prior ASCT, produced clinically meaningful increases in Overall MM Response Rates from 79% Pre-treatment to 95% at Day +90/Day +100. Importantly, there was also an increase in the Overall CR Rate from 10% to 31%, with the number of patients with a sCR increasing from 0% Pre-treatment to 16% at Day +90/Day +100.

In addition, CE-Melphalan HCl high dose therapy resulted in:

- Myeloablation in all 61 (100%) patients meeting the protocol-defined criteria, and as reflected by the development of severe neutropenia with ANCs $<0.5\times10^9$/L; median time to myeloablation was 5 days.
- Neutrophil engraftment was achieved in all 61 (100%) patients in this study, with a median time of 12 days.
- Platelet engraftment was achieved in all 61 (100%) patients in this study, with a median time to platelet engraftment of 13 days.
- No (0%) patients had non-engraftment of neutrophils by Day +90/Day +100.

Pharmacokinetic Results:
Population pharmacokinetics were characterized in patients with MM undergoing ASCT utilizing samples from CDX-353-001 and CDX-353-001. See the clinical pharmacology review for an analysis of this data.

Pharmacokinetic Conclusion:
(copied from submission Section 5.3.5.2 CDX-002 Study Report page 89 of 1084)
The final 2-compartment pharmacokinetic model was shown to adequately describe individual concentration-time data following single-dose administration, and was consistent with previously published results.

- The final population pharmacokinetic model was able to characterize the pharmacokinetics of CE-Melphalan HCl in MM patients undergoing ASCT The population estimate for melphalan plasma CL from the central compartment was ~27 L/h, which corresponds to previously published values; diagnostic plots revealed no apparent time- or concentration-dependencies
- Fat-free mass was determined to be an influential covariate on each model parameter: CL, Q, V1, and V2
- Creatinine clearance was identified as an influential covariate on CL
- There was no statistically significant correlation between melphalan exposure and safety or efficacy

REVIEWER COMMENT:
Agree with efficacy conclusions.

Safety Results

An overall summary of the adverse events is presented in Table 16.

Table 16: CDX-353-002 Overall Summary of Adverse Events

Type of Adverse Event	n (%) of Patients Total n=61
Patients with at Least 1 TEAE	61 (100)
Patients with at Least 1 Treatment-Related TEAE	61 (100)
Patients with at Least 1 Grade 3 to 4 TEAE	61 (100)
Patients with at Least 1 Grade 3 to 4 Treatment-Related TEAE	61 (100)
Patients with at Least 1 Serious TEAE	12 (20)
Patients with at Least 1 Serious Treatment-Related TEAE	7 (11)
Patients with a TEAE Leading to Discontinuation of Study Drug	0

Deaths

Treatment-related Mortality (TRM) was a primary endpoint of this study. No patients died during this study, thus, thus TRM was 0%.

Adverse Events Leading to Discontinuation

None.

Serious Adverse Events

Table 17: CDX-353-002 Non Hematologic Serious Adverse Events Excluding Hematologic

SOC	PT	Grade 3	Grade 4	Total
CARDIAC DISORDERS	ATRIAL FIBRILLATION	**1**		**1**
GASTROINTESTINAL DISORDERS	DIARRHEA	**1**		**1**
	HAEMATOCHEZIA	1	1	2
	ORAL PAIN	1		1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	MUCOSAL INFLAMMATION	1		1
	PYREXIA	2		5
INFECTIONS AND INFESTATIONS	OSTEOMYELITIS	1		1
	STAPHYLOCOCCAL INFECTION	1		1
	CELLULITIS	1		1
METABOLISM AND NUTRITION DISORDERS	DEHYDRATION	1		1
NERVOUS SYSTEM DISORDERS	PRESYNCOPE	1		1
RENAL AND URINARY DISORDERS	RENAL FAILURE ACUTE	2		2

Grade 3 and 4 Adverse Events Excluding Hematologic and Metabolic

Table 18: CDX-353-002 Grade 3 & 4 Adverse Events Excluding Hematologic and Metabolic

SOC	PT	Grade 3	Grade 4	Total
CARDIAC DISORDERS	ATRIAL FIBRILLATION	1		1
GASTROINTESTINAL DISORDERS	CAECITIS	1		1
	DIARRHEA	3		3
	HAEMATOCHEZIA	1	1	2
	NAUSEA	1		1
	ORAL PAIN	1		1
	STOMATITIS	3		3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	EDEMA	1		1
	FATIGUE AGGRAVATED	1		1
	MALAISE	1		1
	MUCOSAL INFLAMMATION	6		6
	PYREXIA	2		2
INFECTIONS AND INFESTATIONS	BACTEREMIA	1		1
	CELLULITIS	1		1
	DEVICE RELATED INFECTION	2		2
	ESCHERICHIA INFECTION	1		1
	OSTEOMYELITIS	1		1
	SEPSIS		2	2
	STAPHYLOCOCCAL INFECTION	1		1
	URINARY TRACT INFECTION	2		2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BONE PAIN	1		1
NERVOUS SYSTEM DISORDERS	SYNCOPE	1		1
	PRESYNCOPE	1		1
RENAL AND URINARY DISORDERS	OLIGURIA	1		1
	RENAL FAILURE ACUTE	2		2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	HICCUPS	1		1
VASCULAR DISORDERS	HYPERTENSION	4	1	5

Common Adverse Events

Demonstration of myeloablation was an efficacy endpoint for tis trial. All subjects achieved myeloablation, this included leukopenia, anemia, thrombocytopenia, neutropenia, and lymphopenia. “Febrile Neutropenia” was reported for 26 patients (maximum grade 1 - n=7, maximum grade 2 - n=1, maximum grade 3 - n=17).

Non-hematologic adverse events that were reported in ≥ 10% of patients are presented in Table 19.

Table 19: CDX-353-002 Non-hematologic Adverse Events Reported in ≥ 10% of Patients

PT	Grade 1	Grade 2	Grade 3	Grade 4	Total
DIARRHEA	32 (52)	23 (38)			57 (93)
NAUSEA	28 (46)	26 (43)	1 (2)		55 (90)
FATIGUE	24 (39)	22 (36)	1 (2)		47 (77)
HYPOKALAEMIA	13 (21)	15 (25)	16 (26)	1 (2)	45 (74)
VOMITING	30 (49)	12 (20)			39 (64)
DECREASED APPETITE	18 (30)	12 (20)			30 (49)
HYPOPHOSPHATEMIA		1 (2)	25 (41)	4 (7)	30 (49)
CONSTIPATION	24 (39)	5 (8)			29 (48)
PYREXIA	13 (21)	14 (23)	2 (3)		29 (48)
DIZZINESS	21 (34)	2 (3)			23 (38)
MUCOSAL INFLAMMATION	8 (13)	9 (15)	6 (10)		23 (38)
EDEMA PERIPHERAL	15 (25)	5 (8)			20 (33)
ABDOMINAL PAIN	16 (26)	1 (2)			17 (28)
DYSGEUSIA	11 (18)	6 (10)			17 (28)
STOMATITIS	7 (11)	7 (11)	3 (5)		17 (28)
DYSPEPSIA	10 (16)	6 (10)			16 (26)
HYPOMAGNESEMIA	8 (13)	7 (11)			15 (25)
HEADACHE	12 (20)	2 (3)			14 (23)
HYPOPHAGIA	4 (7)	10 (16)			14 (23)
OROPHARYNGEAL PAIN	9 (15)	5 (8)			14 (23)
ALOPECIA	10 (16)	3 (5)			13 (21)
HYPOCALCEMIA	3 (5)	7 (11)	3 (5)		13 (21)
TACHYCARDIA	11 (18)	1 (2)			12 (20)
ASTHENIA	9 (15)	1 (2)			10 (16)
DEHYDRATION	3 (5)	5 (8)	2 (3)		10 (16)
WEIGHT DECREASED	9 (15)	1 (2)			10 (16)
HYPOTENSION	6 (10)	4 (7)			10 (16)
CHILLS	8 (13)	1 (2)			9 (15)
DYSPHAGIA	5 (8)	4 (7)			9 (15)
DYSPNEA	7 (11)	2 (3)			9 (15)
INSOMNIA	7 (11)	2 (3)			9 (15)
SINUS TACHYCARDIA	8 (13)	1 (2)			9 (15)
ENGRAFTMENT SYNDROME		8 (13)			8 (13)
COUGH	5 (8)	5 (8)			7 (11)
DYSPNEA EXERTIONAL	7 (11)				7 (11)
HYPERTENSION	2 (3)	1 (2)	3 (5)	1 (2)	7 (11)
MALAISE	4 (7)	2 (3)	1 (2)		7 (11)
EDEMA	3 (5)	3 (5)	1 (2)		7 (11)
PAIN IN EXTREMITY	3 (5)	4 (7)			7 (11)
ERYTHEMA	5 (8)	1 (2)			6 (10)
FLUSHING	6 (10)				6 (10)
HYPERGLYCEMIA	1 (2)		5 (8)		6 (10)
MUSCULAR WEAKNESS	5 (8)	1 (2)			6 (10)
ORAL CANDIDIASIS	4 (7)	2 (3)			6 (10)

Special Safety Studies Evaluated

Mucositis

Patients (n=57) were prospectively evaluated at baseline and daily until day 15 for mucositis using the World Health Organization (WHO) Mucositis Scoring System. See Table 20. The maximum grade of mucositis identified was grade 0 in 9 (15%), grade 1 in 20 (33%), grade 2 in 19 (31%) and grade 3 in 8 (13%). Only 2 patients used total parenteral nutrition due to severe mucositis. Fifty-two (85%) patients reported opioid usage.

Table 20: World Health Organization Mucositis Scoring System

Grade	0	1	2	3	4
	None	Soreness and erythema	Erythema, ulcers Patient can swallow solid diet	Ulcers, extensive erythema Cannot swallow solid diet	Mucositis to the extent that alimentation is not possible

Electrocardiogram

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 139 of 1084)
A review of the ECG data for this trial of CE-Melphalan HCl demonstrated a large (and not unexpected) increase in heart rate, and no effect on AV conduction or cardiac repolarization. The central tendency analyses of QTcF demonstrated no effect on cardiac repolarization, though the PK-pharmacodynamic model (limited by the small number of observations) suggested a possible small effect of CE-Melphalan HCl on QTcF with a magnitude less than 10 ms. Data from this trial suggest that the QTc liability with CE-Melphalan HCl is at most quite small and is not likely to be clinically relevant.

Safety Conclusion

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 141 of 1084)

- The related AEs and SAEs reported in this study in the Gastrointestinal, Blood and Lymphatic, General Disorders, Investigations SOCs were expected for myeloablative conditioning with melphalan, and no new or increased incidence of AEs was identified for CE-Melphalan HCl.
- SAEs were reported in only 12 (20%) patients with treatment-related SAEs in 7 (11%); all SAE resolved prior to study closure.
- There were no clinically relevant pulmonary AEs, including pulmonary fibrosis, reported during this study.
- There were few clinically relevant treatment-related renal function AEs.

In conclusion, this Phase 2b study confirmed the acceptable safety profile of CE-Melphalan HCl as a conditioning regimen for symptomatic patients with MM undergoing ASCT.

Conclusion:

(copied from submission Section 5.3.5.2 CDX-002 Study Report page 143 of 1084)
In conclusion, CE-Melphalan HCl was generally safe and well-tolerated in the MM patient population of this study with no deaths or discontinuations due to AEs. All Grade 3 and 4 AEs were reversible and no unexpected safety signals were identified. Clinically relevant increases in MM response rates, including increases in CR and sCR rates, were seen following CEMelphalan HCl. High dose therapy induced myeloablation in all patients and allowed for timely engraftment of both neutrophils and platelets; no patients had non-engraftment following ASCT. Overall, CE-Melphalan HCl was effective in preparing symptomatic MM patients for ASCT.

REVIEWER COMMENT:
Agree with conclusions.

5.3.3 CIBMTR Database Review ASCT with Melphalan for Multiple Myeloma

Historical Control to Benchmark Results from CDX-002 Safety Trial
The application included a report from the Center for International Blood and Marrow Transplant Research (CIBMTR) that provides descriptive statistics and post-ASCT engraftment and overall mortality rates for adult patients with multiple myeloma who received a first ASCT in the US between 2008 and 2013 included in the Center for International Blood and Marrow Transplant Research Observational Database.

The report included 1631 adult patients with MM who underwent a first single or tandem autologous peripheral blood ASCT with melphalan at 200 mg/m^2 for conditioning. The best disease response by 100-days post-ASCT patients in the CIBMTR registry control group compared to the results from the CDX-353-002 is presented in Table 21. The response rates in the CDX-353-002 trial compare favorably with the CIBMTR population.

Table 21: Best Response Day 100 CIBMTR v CDX-353-002

		CIBMTR Population Months from Diagnosis to ASCT		CDX-353-002
		0 to 12	**> 12**	
Number Patients		1064	367	61
Subset US centers		95	78	
Best response by 100-days post-ASCT	**CR**	318 (30%)	85 (23%)	19 (31%)
	PR	579 (54%)	211 (57%)	29 (48%)
	SD	106 (10%)	45 (12%)	2 (3%)
	PD	21 (2%)	13 (4%)	1 (2%)
	Unknown	40 (4%)	13 (4%)	

Overall post-HCT engraftment and mortality patients in the CIBMTR registry control group is presented in Table 22. The overall mortality in CDX-353-002 of 0% at 30 and 100 days compares favorably with the CIBMTR results. Neutrophil engraftment in 100% of patients with a median 12 days (range 10 to 16) compares favorably with the CIBMTR results. Platelet engraftment 100% of patients with a median 13 days (range 10 to 28) compares favorably with the CIBMTR results.

(copied from submission Section 5.3.5.4 Literature Review – CIBMT Report page 11 of 11)

Table 22: Overall post-ASCT Engraftment and Mortality CIBMTR

	Time from diagnosis to HCT			
	0-12 months		>12 months	
Outcomes	N Eval[a]	Prob[b] (95% CI)	N Eval[a]	Prob[b] (95% CI)
Overall Mortality	1064		367	
30-days post HCT		0.4 (0.1-0.8)%		0.8 (0.2-2.0)%
100-days post HCT		1.0 (0.5-1.7)%		0.8 (0.2-2.0)%
ANC engraftment (≥ 500/mm^3)	1051		363	
7-days post HCT		1 (0-1)%		1 (1-2)%
14-days post HCT		86 (83-88)%		84 (80-87)%
28-days post HCT		99 (99-100)%		99 (99-100)%
Platelet engraftment (≥ 20 x10^9/L)	1044		364	
7-days post HCT		6 (5-8)%		7 (5-10)%
14-days post HCT		18 (16-21)%		23 (18-27)%
28-days post HCT		93 (91-94)%		92 (89-95)%
Platelet recovery count (≥ 50 x10^9/L)	1026		356	
7-days post HCT		6 (5-8)%		5 (3-8)%
14-days post HCT		12 (11-15)%		13 (9-16)%
28-days post HCT		90 (88-92)%		88 (85-92)%

a. Number evaluable
b. Kaplan-Meier estimation used to evaluate overall mortality. Cumulative incidence estimation was used to evaluate engraftment in order to account for the competing risk of death.

6 Review of Efficacy

Efficacy Summary

Preparative Regimen for Autologous Stem Cell Transplantation (ASCT)
The applicant is relying on consensus treatment recommendations and published literature to support the proposed transplant indication and the proposed dose. To benchmark the efficacy and safety results in the CDX-353-002 (See Section 5.3.2) safety trial, the application provides descriptive statistics and post-ASCT engraftment and overall mortality rates for adult multiple myeloma patients who received an ASCT between 2008 and 2013 included in the Center for International Blood and Marrow Transplant Research Observational Database. See Section 5.3.3. The applicant conducted CDX-353-001, a bioequivalence study, to bridge CE-Melphalan HCl and the reference product Alkeran. See Section 5.3.1.

Consensus Treatment Recommendations
The consensus treatment recommendations include:

- The NCCN evidence-based guidelines for the treatment of MM. (Anderson, 2014) Recommend autologous stem cell transplantation following initial induction therapy for patients suitable for transplant. The studies cited to support this recommendation utilized melphalan containing regimens.
    - The Group Myelome-Autogreffe used lomustine 120 mg/m^2, etoposide 750 mg/m^2, cyclophosphamide 60 mg/kg, and melphalan 140 mg/m^2 with total-body irradiation. (Fermand1998)
    - The Group Myelome-Autogreffe used melphalan 200 mg/m^2 or melphalan 140 mg/m^2 with busulfan 16 mg/kg. (Fermand 2005)
    - Intergroupe Français du Myélome used melphalan 140 mg/m^2 and total-body irradiation. (Attal 1996)
    - Medical Research Council Myeloma VII Trial used melphalan 200 mg/m2 or melphalan 140 mg/m^2 and total-body irradiation. (Child 2003)

  One trial did not result in improved outcome, response rates, PFS or OS, with autologous transplant compared to standard therapy.
    - The US Intergroup Trial used melphalan 140 mg/m^2 and total-body irradiation. (Barlogie 2006)

  The NCCN guidelines also state that although earlier studies of autologous transplant included total body irradiation as a component of the preparative regimen, regimens utilizing chemotherapy only have been shown to have equivalent efficacy and less toxicity than regimens with total body irradiation (melphalan 200 mg/m^2 compared to melphalan 140 mg/m^2 and total body irradiation). (Moreau 2002) In current practice total body irradiation regimens have been abandoned.

- The British Society of Hematology Guidelines for the Management of MM. (Bird 2011) The following table which summarizes results of randomized controlled trials comparing conventional chemotherapy with high dose therapy and autologous stem cell transplantation is copied from this paper.

Table 23: Summary of Trials Supporting British Society of Hematology Guidelines

Trial	*n*	EFS (median, months)	OS (median, months)	References
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The British Society of Hematology Guidelines conclude:

- Autologous stem cell transplantation is the first line standard of care in those deemed biologically fit enough for this option because of the low transplant-related mortality and prolongation of EFS resulting in improved quality of life.
- High dose melphalan 200 mg/m^2 remains the standard conditioning regimen prior to autologous stem cell transplantation.

- The European Myeloma Network recommendations for management of patients with MM. (Engelhardt 2014)
  - Novel-agent-based induction and upfront autologous stem cell transplantation in medically fit patients lead to sustained remission and continues to be the standard of care in this patient cohort.
  - High dose melphalan is the standard preparative regimen at this time.

Published Literature

The applicant conducted a comprehensive literature review of high-dose melphalan followed by autologous stem cell transplant in patients with multiple myeloma. The primary objective of the literature review was to demonstrate that high-dose melphalan (200 mg/m^2 over 2 days) followed by autologous stem cell transplant is effective in inducing clinically meaningful responses (Complete Response [CR] or Very Good Partial Response [VGPR]) compared to conventional dose chemotherapy regimens in newly diagnosed patients with multiple myeloma based on studies available in the literature. The results prospective randomized trials in newly diagnosed patients with multiple myeloma will be the focus of my review.

The applicant identified 13 "Key Literature Studies," these include 7 multicenter prospective randomized studies in newly diagnosed patients with multiple myeloma using conventional dose chemotherapy as the control. These exclude Cook 2014 – relapsed refractory, Moreau 2002 no conventional dose chemotherapy control Barlogie 1997 used historical conventional dose chemotherapy control, Roussel 2014 + Barlogie 1999 + Vesole, 1999 not randomized controlled.

(copied from submission 5.3.5.4 Literature review Melphalan page 20/284)

Table 24: Design Characteristics of Key Literature Studies

Citation	Multicenter/ Prospective	Randomized/ Controlled	Patients with MM Receiving ASCT	MEL200 or MEL140+TBI as Conditioning Regimen	Comparison of HDT vs. CDT	Efficacy Endpoints	Safety Endpoints
Palumbo, 2014	Yes/Yes	Yes/Yes	Yes	Yes	Yes	MM response[a], OS	AEs, SPM, TRM
Cook, 2014	Yes/Yes	Yes/Yes	Yes	Yes	Yes	MM response[a], OS	AEs, SPM, TRM
Attal, 1996	Yes/Yes	Yes/Yes	Yes	Yes	Yes	OS	TRM
Moreau, 2002	Yes/Yes	Yes/Yes	Yes	Yes	MEL200 vs. MEL140+TBI	OS, Engraftment	AEs, TRM
Blade, 2005	Yes/Yes	Yes/Yes	Yes	Yes	Yes	OS	SPM, TRM
Barlogie, 2006	Yes/Yes	Yes/Yes	Yes	Yes	Yes	OS, Engraftment	TRM
Child, 2003	Yes/Yes	Yes/Yes	Yes	Yes	Yes	OS	TRM
Fermand, 2005	Yes/Yes	Yes/Yes	Yes	Yes	Yes	OS	TRM
Palumbo, 2004	Yes/Yes	Yes/Yes	Yes	Yes (MEL100 x 2)	Yes	OS, Engraftment	AEs, TRM
Barlogie, 1997[c]	No/Yes	Yes/Yes	Yes	Yes	Yes (Historical CDT data)	OS	TRM
Roussel, 2014[b]	Yes/Yes	No/No	Yes	Yes	No	MM response[a], OS	AEs, TRM
Barlogie, 1999[c]	No/Yes	No/No	Yes	Yes	No	OS	AEs, TRM
Vesole, 1999[c]	Yes/Yes	No/No	Yes	Yes	No	OS	AEs, TRM

AE=adverse event; ASCT=autologous stem cell transplant; CDT=conventional dose therapy; HDT=high dose therapy; MEL=melphalan; MM=multiple myeloma; OS=overall survival; SPM=second primary malignancy; TBI=total body irradiation; TRM=treatment related mortality.
(a) Efficacy endpoint of MM response is only included if IMWG criteria were used.
(b) Included as key study even though not randomized controlled since it represents a recent study in the proposed indication and dosing.
(c) Studies considered to provide bridging data to the proposed indication and dosing.

Response Evaluation

The response evaluation in the 7 multicenter prospective randomized studies in newly diagnosed patients with multiple myeloma using conventional dose chemotherapy as the control are summarized in Table 25. Overall Response Rate and/or CR rate was significantly higher in patients who received high dose chemotherapy with melphalan autologous stem cell transplant compared with conventional dose chemotherapy in 4 prospective, controlled studies.

Table 25: Response Melphalan (HDT) v Conventional Chemotherapy (CDT)

Study ID Population/ MEL Regimen	ORR	CR	VGPR	PR
Palumbo, 2014 Newly diagnosed MEL200	CR+PR+VGPR: HDT: 92.9% CDT: 90.9%	CR: HDT: 23.4% CDT: 18.2%	VGPR: HDT: 35.5% CDT: 44.7%	PR: HDT: 34.0% CDT: 28.0%
IFM-90 (Attal,1996) Previously untreated MEL140+TBI	CR+PR+VGPR: HDT: 81% CDT: 57% p<0.001	CR: HDT: 22% CDT: 5%	VGPR: HDT: 16% CDT: 9%	PR: HDT: 43% CDT: 43%
PETHEMA (Blade, 2005) Newly diagnosed MEL200 or MEL140+TBI	NR	CR: HDT: 30% CDT: 11% p=0.002	NA	NR
Intergroup S9321 (Barlogie, 2006) Newly diagnosed MEL140+TBI	NR	CR: HDT: 17% CDT: 15% P=NS	NA	NR
MRC VII (Child, 2003) Previously untreated MEL200	CR+PR: HDT: 86% CDT: 48%	CR: HDT: 44% CDT: 8% p<0.001	NA	PR: HDT: 42% CDT: 40% p=0.72
GMA (Fermand, 2005) Newly diagnosed MEL200 or MEL140+BUS	CR/MRD+PR: HDT: 62% CDT: 58.5%	CR/MRD: HDT: 36% CDT: 20%	NA	PR: HDT: 26% CDT: 38.5%
IMMSG/ M97G (Palumbo, 2004) Newly diagnosed MEL100 × 2	CR+PR: HDT × 1: 78% HDT × 2: 85%* CDT: 52%* (*p=0.001)	CR: HDT × 1: 25% HDT × 2: 40% CDT: NR	NA	NR

Survival Evaluation

The evaluation of survival (OS, PFS/EFS) in the 7 multicenter prospective randomized studies in newly diagnosed patients with multiple myeloma using conventional dose chemotherapy as the control are summarized in Table 26. The median follow-up times ranged from 37 months to 120 months, with 4 of the studies with follow-up times of at least 4 years. The probability of OS or median OS in the high dose chemotherapy with melphalan group was significantly higher compared with the conventional dose chemotherapy group in 4 of the 7 studies.

The median PFS/EFS was significantly higher with high dose chemotherapy with melphalan autologous stem cell transplant compared with conventional dose chemotherapy in 4 of the 7 studies. Although median PFS was higher in the high dose chemotherapy with melphalan groups in the other 2 studies, there was no significant difference between treatments.

Table 26: OS, PFS/EFS Melphalan (HDT) v Conventional Chemotherapy (CDT)

Study ID	Median (Range) F/U	OS	PFS/EFS	Treatment Comparisons
Palumbo, 2014	51.2 mo	4 yr OS: CDT: 65.3% HDT: 81.6%	Median PFS: CDT: 22.4 mo HDT: 43.0 mo	4 yr OS: HR: 0.55 (95% CI: 0.32, 0.93) p=0.02 PFS: HR: 0.44 (95% CI: 0.32 to 0.61) p<0.001
IFM-90	CDT: 37 mo (26 to 60 mo) HDT: 41 mo (22 to 60 mo)	Median OS: CDT: 37 mo HDT: not reached OS 5 yr Probability: CDT: 12% HDT: 52%	Median EFS: CDT: 18 mo HDT: 27 mo EFS 5 yr Probability: CDT: 10% HDT: 28%	OS: p=0.03 EFS: p=0.01
PETHEMA	56 mo	Median OS: HDT: 61 mo CDT: 66 mo	Median PFS: HDT: 42 mo CDT: 33 mo	OS: p=NS PFS: p=NS
Intergroup S9321	76 mo	OS 7 yr Probability: HDT: 38% CDT: 38%	PFS 7 yr Probability: HDT: 17% CDT: 14%	OS: p=NS PFS: p=NS
MRC VII	42 mo (9 to 96 mo)	Median OS: HDT: 54.1 mo (95% CI: 44.9,65.2) CDT: 42.3 mo (95% CI: 33.1, 51.6)	Median PFS: HDT: 31.6 mo (95% CI: 27.4, 38.0) CDT: 19.6 mo (95% CI: 16.2, 21.8)	OS: p=0.04 (log rank) p=0.03 (Wilcoxin) PFS: p<0.001 (log rank) p<0.001 (Wilcoxin)
GMA	120 mo	Median OS: HDT: 47.8 mo CDT: 47.6mo	Median EFS: HDT: 25 mo CDT: 19 mo	OS: p=0.91 EFS: p=0.07
IMMSG/ M97G	HDT: 41 mo (2.9 to 64.5 mo) CDT: 39 mo (10 to 65.9 mo)	Median OS: HDT × 2: not reached (62+) CDT: 48 mo	Median EFS: HDT × 2: 49 mo CDT: 22 mo	OS: p=0.01 EFS: p=0.0001

Bridge from Literature to Bioequivalence Study

The melphalan formulation used in the Key Literature Studies that were reviewed for this literature summary was not always specified in the original publications. Alkeran for Injection (Melphalan HCl) was the only commercially available formulation of melphalan until 2009. The applicant concludes all studies conducted prior to 2009 used the Alkeran for Injection formulation. The Alkeran for Injection (Melphalan HCl) formulation that is available in the United States is also the same composition as the Alkeran for Injection formulation marketed and sold in other countries. The application includes direct confirmation the following studies were conducted with Alkeran (Melphalan HCl).

(copied from submission 5.3.5.4 Literature review Melphalan page 265/284)

Table 27: Key Studies Confirmed to Be Conducted with Alkeran (Melphalan HCl)

Literature Reference
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Palliative Treatment of Patients with MM for Whom Oral Therapy is Not Appropriate

The applicant uses the bioequivalence study to support this indication.

7 Review of Safety

Safety Summary

No additional safety issues were identified in the reviews of CDX-353-001 (section 5.3.1) and CDX-353-002 (section 5.3.2) compared to CIBMTR experience (section 5.3.3).

- Myeloablation was documented by day 5 in 100% of patients.
- Neutrophil engraftment and platelet engraftment was documented in 100% of patients by day 20.
- 100% of patients survived to day 100.
- There was no evidence of loss of effectiveness based on the response rate compare to the CIBMTR experience. See Table 21
- Avoidance of propylene glycol diluent improves the safety profile of the product

8 Postmarket Experience

None.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This was a PLR conversion largely based on the Alkeran label. The following revisions to sections 6 and 14 were made based on the clinical review of the studies conducted by the sponsor.

Section 6.

The table presenting adverse reactions that occurred in more than 25% in the CDX-353-002 study was revised to exclude hematologic adverse reactions as this is expected and desired in patients undergoing myeloablation.

Section 14. The tables were removed and the text was revised to include the relevant information the sponsor included in the tables.

Sponsor's proposal:

CLINICAL STUDIES

(b) (4)

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

FDA Revision:
An open-label, single-arm, non-randomized trial of Evomela was conducted at 5 US centers. There were 61 patients with symptomatic multiple myeloma with at least 2 × 10^6 CD34+ cells/kg cryopreserved stem cells available enrolled on the trial. The median age was 62 years (range 32 to 73); 57% male, 80% white, 18% black, 2% Asian. Evomela was administered at 100 mg/m2/day over 30 minutes by IV infusion for two consecutive days (ASCT days -3 and -2) prior to ASCT (ASCT day 0).

The objective of the trial was to determine the overall safety and toxicity profile of 200 mg/m^2 of Evomela in patients with multiple myeloma undergoing ASCT. [See Clinical Trials Experience (6.2)] The efficacy was evaluated by the International Myeloma Working Group response criteria comparing the disease response immediately prior to the ASCT procedure to the disease response assessed 90 to 100 days post -transplant. In addition, successful myeloablation, and time to engraftment were evaluated.
The overall response rate (partial response or better) improved from 79% (48 of 61) prior to the ASCT procedure to 95% (58 of 61) at 90 to 100 days post-transplant. There was also an increase in the number of patients with a stringent complete response from 0 patients prior to the ASCT procedure to 16% (10 of 61) at 90 to 100 days post-transplant.

Myeloablation and engraftment were evaluated by complete blood cell count tests daily until neutrophil and platelet engraftment, and then weekly until day 30, and at day 60 and day 90-100. Myeloablation was defined as any of the following: absolute neutrophil count (ANC) < $500/mm^3$, absolute lymphocyte count < $100/mm^3$, or platelet count < $20,000/mm^3$). Neutrophil engraftment was defined as ANC > $500/mm^3$ × 3 consecutive daily assessments. Platelet engraftment was defined as untransfused platelet counts > $20,000/mm^3$ × 3 consecutive daily assessments). Nonengraftment was defined as failure to reach an ANC > $500/mm^3$ × 3 consecutive daily assessments 90 to 100 days post -transplant.

Myeloablation, neutrophil engraftment and platelet engraftment were achieved by all 61 patients. The median time to myeloablation was 8 days which occurred on ASCT day 5 (range ASCT days -1 to 6). The median time to neutrophil engraftment was 12 days (range ASCT days 10 to 16). The median time to platelet engraftment was 13 days (range ASCT days 10 to 28).

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

/s/

PATRICIA A DINNDORF
08/24/2015

ALBERT B DEISSEROTH
08/24/2015