CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION MEMO

CLINICAL STUDIES

NDA/BLA #:	NDA207155
Supplement #:	SDN: 0 / eCTD SN:0000
Drug Name:	Evomela ™ (Captisol® –enabled melphalan HCl)
Indication(s):	Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation
Applicant:	Spectrum Pharmaceuticals, Inc.
Receipt Date:	12/23/2014
PDUFA Goal Date:	10/23/2015
Review Priority:	Standard
Biometrics Division:	DB5
Statistical Reviewer:	Yaping Wang
Concurring Reviewers:	Yuan-Li Shen
Medical Division:	Division of Hematology Products (DHP)
Clinical Team:	Pat Dinndorf Albert Deisseroth
Project Manager:	Rachel McMullen

Keywords:

Clopper-Pearson method; Kaplan-Meier estimates.

There was nothing for statistical team to review during this review cycle. Please refer to the previous statistical review signed off on 9/23/2015 (for submission eCTD SN:0000; submitted on 12/23/2014).

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

/s/

YAPING WANG
03/08/2016

YUAN L SHEN
03/08/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA207155
Supplement #:	SDN: 0 / eCTD SN:0000
Drug Name:	Evomela ™ (Captisol® –enabled melphalan HCl)
Indication(s):	Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation
Applicant:	Spectrum Pharmaceuticals, Inc.
Receipt Date:	12/23/2014
PDUFA Goal Date:	10/23/2015
Review Priority:	Standard
Biometrics Division:	DB5
Statistical Reviewer:	Yaping Wang
Concurring Reviewers:	Yuan-Li Shen Rajeshwari Sridhara
Medical Division:	Division of Hematology Products (DHP)
Clinical Team:	Pat Dinndorf Albert Deisseroth Ann Farrell
Project Manager:	Rachel McMullen

Keywords:

Clopper-Pearson method; Kaplan-Meier estimates.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The applicant has submitted a single arm trial, Study CDX-353-002, to seek an indication for Captisol-enabled Melphalan HCL (CE-Melphalan HCl) for use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell Transplantation (ASCT) in patients with multiple myeloma (MM). The purpose of this review was to evaluate the efficacy of CE-Melphalan HCl as a myeloablative conditioning regimen in MM patients undergoing ASCT based on this single arm study.

Study CDX-353-002 is a phase 2b, multicenter, open-label, safety and efficacy study of high dose Captisol-enabled Melphalan HCl for myeloablative conditioning in multiple myeloma patients undergoing autologous transplantation. The primary efficacy endpoint is MM response rate (according to International Myeloma Working Group [IMWG] uniform response criteria).

The MM response rates (partial response or better) was 79% (95% CI= [68.4, 89.0] %) at Pre-treatment (Day -30 to Day -4, from 30 to 4 days before patients receiving an autologous graft) and 95% (95% CI = [89.7, 100] %) on Day +90/Day +100 (90 or 100 days after patients receiving an autologous graft). The Overall Complete Response (CR) Rate was 10% Pre-treatment and 31% on Day +90/Day +100. The number of patients with a stringent CR was 0% at Pre-treatment and 16% on Day +90/Day +100. Myeloablation was achieved in all 61 (100%) patients in this study. The median Time to Myeloablation was 5.0 days (range = [4, 6]; with one patient had myeloablation occurred at day -1). Neutrophil Engraftment and Platelet Engraftment were achieved by all 61 (100%) patients in this study. The median time to Neutrophil Engraftment was 12.0 days (range = [10, 16]) and to Platelet Engraftment was 13.0 days (range = [10, 28]). None of the patients in this study had Non-engraftment.

In summary, the study appears to demonstrate a difference in MM response rate between pre-treatment and Day +90/Day +100 for CE-Melphalan HC1. 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. However, the final decision on the benefit-risk evaluation of CE-Melphalan HC1 is deferred to the clinical review team.

2 INTRODUCTION

2.1 Overview

Study CDX-353-002 is a phase 2b, multicenter, open-label, safety and efficacy study of high dose Captisol-enabled Melphalan HCl (CE-Melphalan HCl) for injection (Propylene Glycol - Free) for myeloablative conditioning in multiple myeloma patients undergoing autologous transplantation.

The applicant's proposed indication in the package insert (PI) is shown here:

(b) (4)

(b) (4) *indicated for:*

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

The primary objective of this study is to determine the safety and toxicity profile of high-dose Captisol-enabled Melphalan HCl (CE-Melphalan HCl) as a myeloablative conditioning regimen in multiple myeloma (MM) patients undergoing autologous stem cell transplantation (ASCT).

The secondary objectives are

- To evaluate the efficacy of CE-Melphalan HCl in this patient population as measured by MM response rate (according to International Myeloma Working Group [IMWG] uniform response criteria), myeloablation, and engraftment rates.
- To determine covariates that affect CE-Melphalan HCl PK parameters using a population PK approach.

There were 5 sites in the United States (US) enrolled patients into the study. The trial contains three distinct evaluation periods: pre-treatment period, study period/on treatment period and follow-up period (details will be presented in the Study Design and Endpoint session).

The primary endpoints of this study is the overall safety and toxicity profile of high dose CE-Melphalan HC1 in this patient population as assessed through analysis of the following safety endpoints:

- Treatment-related mortality (TRM [death without relapse or progression]) during the first +90/Day +100 days after ASCT
- Tolerability and toxicity as evaluated by AEs, serious AEs (SAEs), and laboratory parameters.

The secondary endpoints include:

- MM Response Rates according to IMWG criteria Day +90/Day +100 after ASCT in the Intent-to-treat Population; this endpoint was also analyzed in the Evaluable Population.
- Myeloablation - defined as an ANC <0.5 x 10^9/L, ALC <0.1 x 10^9/L, or platelet count <20,000/mm^3 (bleeding can occur without myeloablation and is not pertinent).
- Neutrophil Engraftment (ANC >0.5 x 10^9/L x 3 consecutive daily assessments).
- Platelet Engraftment (untransfused platelet measurement >20,000/mm^3 x 3 consecutive daily assessments).
- Nonengraftment (failure to reach an ANC >0.5 x 10^9/L x 3 consecutive daily assessments by Day +90/Day + 100).

An independent Data Safety Monitoring Board (DSMB) was established to review the safety data.

The first patient was enrolled on 2/20/2013 and started the treatment on 3/4/2013. The last patient's last visit was on 2/6/2014. The database was locked on 8/27/2014.

Some key information for the supporting study is summarized in the following table:

Table 1 Summaries of the Key Information for the Supporting Phase II Study

Phase and Design	a phase 2b, multicenter, open-label, safety and efficacy study
Pre-treatment Period **(Day -30 to Day -4)**	Baseline assessments, including tests for organ function (pulmonary and cardiac) and Baseline disease assessments, were conducted after completion of the MM induction regimen. These assessments did not need to be repeated during the **Pre-treatment Period** as long as they were completed within 8 weeks prior to start of conditioning. Additional Baseline assessments were collected within 30 days of dosing with **CE-Melphalan HCl**, after the patient had signed the informed consent form (ICF).
Treatment Period **(Day -3 to Day +30)**	Patients received doses of CE-Melphalan HCl at 100 mg/m^2 each on **Day-3** and **Day-2**. Following 1 day of rest after myeloablative conditioning (Day-1), patients received an ASCT
Follow-up Period **(Day +31 to Day +90/ Day +100)**	Patients were evaluated twice at the transplant center by the Principal Investigator or their designee; the first visit occurred around **Day +60** (±7 days) and the final follow-up assessment occurred approximately 1 month later **(Day +90/Day +100)**.

Number of Subjects	A total of 76 patients were screened for this Phase 2b study and 61 patients were enrolled.
Study Population	Patients (≥18 years)

2.2 Data Sources

The application's data (including raw and analysis datasets) are located at the following link: \\CDSESUB1\evsprod\NDA207155\0000\m5\datasets\cdx-353-002\analysis\legacy, \\CDSESUB1\evsprod\NDA207155\0000\m5\datasets\cdx-353-002\tabulations\sdtm.
The original submission only contains one ADaM file (ADSL). After an information request (on 1/29/2015), the applicant submitted additional ADaM files on 2/3/2015 and 3/23/2015, and the data are included in the following links, respectively:
\\CDSESUB1\evsprod\NDA207155\0002\m5\datasets\cdx-353-002\analysis\adam\datasets, \\CDSESUB1\evsprod\NDA207155\0006\m5\datasets\cdx-353-002\analysis\adam\datasets.

The SAS programs that were used to derive the analysis datasets and perform the analysis were also provided.

The clinical study reports and the statistical analysis plan for this study are located in the following link:
\\CDSESUB1\evsprod\NDA207155\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud.

3 STATISTICAL EVALUATION

The original protocol for study CDX-353-002 was finalized on 8/1/2012 and subsequently has undergone one amendments on 7/24/2013 The items that were revised and may affect the efficacy evaluation are listed below:
Amendment 1 (7/24/2013)

- Revise the ITT population from all enrolled patients to all enrolled patients who signed the informed consent and received a dose of Melphalan HCl for Injection (Propylene Glycol-Free);
- Revised the MM Response-Evaluable Population to add patients who had a follow-up MM response assessment at Day+90/+100 to the original definition (i.e. all patients

with measurable disease at baseline according to the IMWG criteria who received the full dose of Melphalan HCl for Injection [Propylene Glycol-Free]);

- Clarified that the sample size provides for a 95% confidence interval having a width of ±13% to estimate an AE incidence rate;
- Expand assessment window from 100 days to +90/+100 days after ASCT;
- Clarify the timing of the assessment of the MM response and nonengraftment from 100 days to be based on Day +90/Day+100 assessments;
- Change timing of the analysis of treatment related mortality (TRM [death without relapse or progression]) from 100 days to be based on +90/+100 days;
- Clarify the definition and timing of myeloablation and engraftment.

The original statistical analysis plan (SAP) for study CDX-353-002was dated on 8/1/2012. It was amended on 7/24/2013 (on the same date as the protocol amendment) and the final one was signed off by the applicant on 2/10/2014.

3.1 Data and Analysis Quality

The applicant submitted raw datasets in SDTM (Study Data Tabulation Model) and analysis data sets in ADaM (Analysis Data Model Implementation) formats, the defined files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The reviewer was able to duplicate the analysis results based on the applicant's submitted datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study CDX-353-002 is a phase 2b, multicenter, open-label, safety and efficacy study of high dose Captisol -enabled Melphalan HCl (CE-Melphalan HCl) for injection (Propylene Glycol - Free) for myeloablative conditioning in multiple myeloma patients undergoing autologous transplantation.

The primary objective of this study is to determine the safety and toxicity profile of high-dose Captisol -enabled Melphalan HCl (CE-Melphalan HCl) as a myeloablative conditioning regimen in Multiple Myeloma (MM) patients undergoing autologous stem cell transplantation (ASCT).

The secondary objectives are

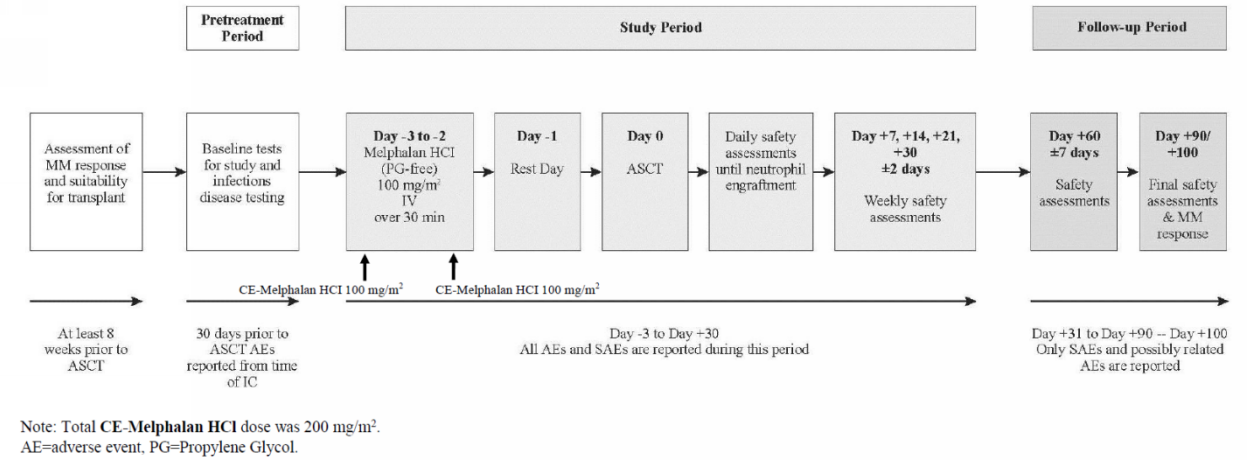
- To evaluate the efficacy of CE-Melphalan HCl in this patient population as measured by MM response rate (according to International Myeloma Working Group [IMWG] uniform response criteria), myeloablation, and engraftment rates.
- To determine covariates that affect CE-Melphalan HCl PK parameters using a population PK approach.

There were 5 sites in the United States (US) enrolled patients into the study. The trial contains three distinct evaluation periods:

- Pre-treatment Period (Day -30 to Day -4): Baseline assessments were performed.
- Study Period/On treatment period (Day -3 to Day +30): patients received doses of CE-Melphalan HCl at 100 mg/m^2 each on **Day -3** and **Day -2**. Following 1 day of rest after myeloablative conditioning (**Day -1**), patients received an autologous stem cell graft with a minimum cell dose of 2×10^6 CD34+ cells/kg of patient body weight (**Day 0**). Cryopreservation, thawing, and infusion of product were conducted consistent with Foundation for the Accreditation of Cellular Therapy (FACT) standards and local institutional practice. Starting on **Day +5**, granulocyte colony stimulating factor (G-CSF) was administered at a dose of 5 µg/kg/day, or another alternative colony stimulating factor (e.g., pegfilgrastim or sargramostim) at an equivalent dose was used, until neutrophil engraftment was achieved. Patients were hospitalized and received standard of care treatment, along with daily laboratory tests required until Neutrophil engraftment and weekly safety evaluations required until Day +30.
- Follow-Up Period (Day +31 to Day +90/Day +100) : patients were evaluated twice at the transplant center : the first visit occurred around **Day +60** (±7 days) and the final follow-up assessment occurred approximately 1 month later (**Day +90**/**Day+100**).

A detailed study Scheme is presented in the following figure:

Figure 1 Study Scheme



Note: Total **CE-Melphalan HCl** dose was 200 mg/m².
AE=adverse event, PG=Propylene Glycol.

Source: Section 9.1.4 of Study Report Body for CDX-353-002 (P26 of 1082)

Patients who were 70 years of age or younger at time of transplant (patients who were older than 70 years old may be enrolled based on medical monitor's discretion) , who had symptomatic MM, requiring treatment who are eligible for ASCT, who had an adequate autologous stem cell collection, defined as an un-manipulated, cryopreserved, peripheral blood stem cell collection containing at least 2×106 CD34+ cells/kg based on patient body weight, who had adequate organ function and had Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 were eligible to be enrolled.

Patients who had smoldering MM not requiring therapy, who had plasma cell leukemia, systemic amyloid light chain amyloidosis, uncontrolled hypertension, active bacterial, viral, or fungal infection., who had a life expectancy of <6 months, had prior malignancies (except resected basal cell carcinoma or treated cervical carcinoma in situ. cancer treated with curative intent >5 years previously were allowed per medical monitor's discretion) and female who were pregnant or breastfeeding or had childbearing potential, who were unwilling to use adequate contraceptive techniques, who had seropositive for human immunodeficiency virus (HIV), who received other concurrent anticancer therapy within 21 days prior to the ASCT and who had not adequately recovered from the side effects of previous chemotherapy agents prior to dosing as well patients who were unwilling to provide informed consent, etc., were excluded from the study.

All patients enrolled in the study received CE-Melphalan HCl at 100 mg/m2 on Day -3 and Day -2 prior to ASCT. Following reconstitution, CE-Melphalan HCl was further diluted with normal saline to a concentration of no greater than 0.45 mg/mL and infused over 30 minutes (±3 minutes) via a central venous catheter. Patients who received other chemotherapy agents greater than 21 days prior to the first dose had to have documentation in the eCRF that they had adequately recovered from the side effects of these agents. Any maintenance therapies to be given after ASCT were not started until after completion of the final study assessments at Day +90/Day +100).

The primary endpoints of this study is the overall safety and toxicity profile of high dose CE-Melphalan HC1 in this patient population as assessed through analysis of the following safety endpoints:

- Treatment-related mortality (**TRM** [death without relapse or progression]) during the first +90/**Day +100** days after ASCT
- Tolerability and toxicity as evaluated by AEs, serious AEs (SAEs), and laboratory parameters.

The secondary endpoints include:

- MM Response Rates according to IMWG criteria on **Day +90/Day +100** after ASCT
- Myeloablation - defined as an ANC <0.5 x 10^9/L, ALC <0.1 x 10^9/L, or platelet count <20,000/mm^3 (bleeding can occur without myeloablation and is not pertinent).
- Neutrophil Engraftment (ANC >0.5 x 10^9/L x 3 consecutive daily assessments).
- Platelet Engraftment (untransfused platelet measurement >20,000/ mm^3 x 3 consecutive daily assessments).
- Nonengraftment (failure to reach an ANC >0.5 x 10^9/L x 3 consecutive daily assessments by **Day +90**/**Day + 100**).

Note: ANC: Absolute neutrophil count; ALC: Alanine aminotransferase.

Reviewer's comment:
For the purpose of this statistical review, only efficacy evaluation will be presented. So MM response rate will be considered as the primary efficacy endpoint and the rest of the efficacy endpoints will be considered as exploratory secondary efficacy endpoints.

3.2.2 Sample Size Calculation

A sample size of 60 patients is planned for this study in order to adequately assess the safety profile of Melphalan HCl for Injection (Propylene Glycol-Free) in this patient

population. A study size of 60 subjects would provide for a 95% confidence interval having a width of ±13% to estimate an AE incidence rate.

3.3 Statistical Analysis Methods

3.3.1 Analysis Population

Efficacy analyses were performed based on the following analysis populations:

- **Intent-to-Treat Population (ITT):** The **ITT Population**, which was defined as all patients who signed the informed consent and received a dose of **CE-Melphalan HCl,** consisted of all enrolled patients.
- **MM Response-Evaluable Population:** The population evaluable for MM response included all patients with measurable disease at Baseline according to the IMWG criteria who received the full dose of **CE-Melphalan HCl** and had a follow-up MM response assessment at **Day +90/Day +100**.
- **Safety Population:** The **Safety Population** consisted of all patients who received any amount of **CE-Melphalan HCl**.

3.3.2 Efficacy Analyses

The efficacy analyses of this trial are primarily based on summaries of rates and time-to-event analysis results. The 95% confidence interval (CI) will be provided for the rate and median survival time estimates.

Primary efficacy Analysis

The myeloma disease response rate was assessed using the IMWG uniform response criteria. These samples were analyzed by investigators on Day +90/Day +100.

Multiple myeloma response rates according to each category of response (stringent complete response, complete response, very good partial response, partial response, stable disease, and progressive disease) were summarized by the proportion (with 95% confidence intervals) of patients meeting each criterion.

Handling Drop Out or Missing Values

In cases of incomplete dates (e.g. AE, concomitant medication, and medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed

for study day computations (i.e. treatment-emergent status, etc.). If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month components.

If multiple numeric assessments are collected at a given time point, then the mean will be used in the summary tables and all values will be presented in the data listings. If multiple categorical assessments are collected at a given time point, then the "worst" assessment will be used in the summary tables and all values will be presented in the data listings.

Subgroup Analyses for the Primary Efficacy Endpoints

No pre-specified subgroup was provided.

Secondary Efficacy Analysis

Two-sided 95 CI's were presented for the secondary efficacy endpoints involved proportions. The protocol specified that Kaplan-Meier (KM) cumulative distribution curves with 2-sided 95% CI will be generated for time-to-event secondary endpoints. However, summaries based on mean/median with standard deviation or ranges were provided in the clinical study report.

Myeloablation, Neutrophil Engraftment, and Platelet Engraftment were measured by the collection of daily CBCs with differential until neutrophil and platelet counts met the engraftment criteria. These samples were analyzed by local laboratories at the investigative site. The laboratory reports were reviewed and adjudicated by the Principal Investigator to determine the onset and time of Myeloablation, Neutrophil Engraftment and Platelet Engraftment.

CBC with differential (include RBC count, hemoglobin, hematocrit, platelet count, and WBC count with differential.) was measured at pretreatment period, daily from day -3 until neutrophil and platelet engraftment, then weekly until day 30, day +60 and day +90/+100.

Time to Myeloablation was calculated for each patient as the time from the date of the ASCT to the Date of Myeloablation and summarized using Kaplan-Meier estimates. The rates of myeloablation during the 30 day On-Treatment Period were calculated and summarized by the proportion (with 95% confidence intervals) of patients meeting the criteria. The rates of engraftment (neutrophil and platelets) and Non-engraftment in the study population were

determined using standard Center for International Blood and Marrow Transplant Research (CIBMTR) criteria.

Interim Analysis

There was no planned efficacy interim analysis in this trial. However, an independent Data Safety Monitoring Board (DSMB), composed of 2 physicians (1 of whom was an oncologist) and a statistician was establish to review the safety data. The first meeting of the DSMB occurred after the first 5 patients had been treated and follow-up data had been obtained through Day +30 for each of those patients. Following the initial meeting on 5/22/2013, the second and final meeting of the DSMB occurred on 9/9/2013. Both meetings ended with the DSMB recommending the study continue as planned.

3.4 Results and Conclusions

The first patient was enrolled on 2/20/2013 and the study was ended on 2/6/2014.

Among a total of 76 patients screened, only 61 patients were enrolled into the study and received medication. It is noted that 6 patients had major protocol deviation, mainly due to not meeting inclusion/exclusion criteria.

Table 2 Applicant's Summary of Patient Disposition

Patient population	**Overall N=76 (%) ***
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

*total patients screened

The median patient age was 62.0 years and there were more males (57%) than female (43%) in the study. The majority of patients were White (80%).

Table 3 Summary of Patient Demographic Information

Characteristics	Number (%) of evaluable patients N=61
Age (years) Median (range) **<65 years** **≥ 65 years**	 62.0 (32, 73) 43 (70%) 18 (30%)
Sex, n (%) Male Female	 35 (57%) 26 (43%)
Race, n (%) White Black Asian	 49 (80%) 11 (18%) 1 (2%)

The International Staging System for Multiple Myeloma was used to determine the stage of MM in patients: 28 (47%) patients were diagnosed with Stage I MM, 16 (27%) were diagnosed with Stage II MM, and 15 (25%) were diagnosed with Stage III MM. Approximately 97% of patients entered the study with an ECOG performance status of 0-1; no patients had an ECOG performance status of 3 or 4. The median number of prior primary systemic therapies was 1 (range 1-4). Before entering this study, 53 (87%) patients had 1 prior therapy, 5 (8%) patients had 2 prior therapies, 2 (3%) patients had 3 prior therapies, and 1 (2%) patient had 4 prior therapies. Four patients (7%) received a stem cell transplant prior to enrollment in this study. A summary of disease history and characteristics is shown in the following table:

Table 4 Applicant's Summary of Patient Disease History and Characteristics

characteristics	n (%) N=61
Multiple Myeloma Stage- by ISS Criteria and Response by IMWG Criteria at Screening, n (%) Stage I Stage II Stage III Other not available	 28 (47%) 16 (27%) 15 (25%) 2 (3%)
ECOG Performance Status, n (%) 0 1 2	 36 (59%) 23 (38%) 2 (3%)
Median Time (months) from Last Disease Progression to Study Entry Median (Range)	 2.7 (1.3, 12.9)
Number of Prior Systemic Therapies Median (Range)	 1 (1, 4)
Prior treatment 1 prior therapy	 53 (87)

2 prior therapies 3 prior therapies 4 prior therapies	5(8) 2 (3) 1 (2)
Prior Autologous stem cell transplant Prior autologous transplant	4 (7%)
Complete or partial response to any prior therapy **Yes** **No**	48 (79) 13(21)
Response to the most recent pre-transplant therapy Stringent Complete Response (CR) CR Very good Partial Response (VGPR) PR Stable Disease (SD) Progressive Disease (PDP Unknown	1(2) 5(8) 21(34) 14(23) 14(23) 3(5) 3(5)

Assessment of Baseline neutrophil, lymphocytes and platelet counts are presented in the following table.

Table 5 Applicant's Summary of baseline Laboratory Assessments

Description	n N=61
Neutrophils (%) n Median (range)	61 68 (43, 86)
Absolute Neutrophils Count ($\times 10^9$/L) Median (range)	61 3.1 (0.72, 9.7)
Platelet Count ($\times 10^9$/L) Median (range)	61 198 (27, 376)
Lymphocytes (%) Median (range)	61 17 (3,39)
Absolute Lymphocytes Count ($\times 10^9$/L) Median (range)	59 0.74 (0.0, 2.3)

3.4.1 Efficacy Endpoint Analyses

MM response rate on Day +90/+100

MM response rates (partial response or better) was 79% (95% CI= [68.4, 89.0] %) at pre-treatment, and 95% on Day +90/Day +100 (95% CI = [89.7, 100]%). The Overall Complete Response (CR) Rate was 10% at pre-treatment and 31% on Day +90/Day +100. The number of patients with a stringent CR was 0% at Pre-treatment and 16% on Day +90/Day +100; the Overall PR Rate was 69% Pre-treatment and 64% on Day +90/Day +100. Some patients with PR at pre-treatment had CR on Day +90/Day +100.

Table 6 Reviewer's Summaries of Complete MM Response Rate

MM Response Assessment, N=61	n (%)	95% CI *
Pre-Treatment (Day -30 to Day -4)		
Overall Response Rate	48 (79)	(68.4, 89.0)
Overall Complete Response Rate, n (%)	6 (10)	(2.4, 17.3)
Stringent Complete Response	0	(0, 0)
Complete Response	6 (10)	(2.4, 17.3)
Overall Partial Response Rate	42 (69)	(57.2, 80.5)
Very Good Partial Response	22 (36)	(24.0, 48.1)
Partial Response	20 (33)	(21.0, 44.6)
Stable Disease	8 (13)	(4.6, 21.6)
Progressive Disease	5 (8)	(1.3, 15.1)
Follow-Up Period Day 100 (Day +90 to Day +100)		
Overall Response Rate	58 (95)	(89.7, 100)
Overall Complete Response Rate	19 (31)	(19.5, 42.8)
Stringent Complete Response	10 (16)	(7.1, 25.7)
Complete Response	9(15)	(5.9, 23.7)
Overall Partial Response Rate	39 (64)	(51.9, 76.0)
Very Good Partial Response	26 (43)	(30.2, 55.0)
Partial Response	13 (21)	(11.0, 31.6)
Stable Disease	2 (3)	(-1.2, 7.7)
Progressive Disease	1 (2)	(-1.5, 4.8)

*: 95% CI was calculated based on a large sample assumption.

Myeloablation was achieved in all 61 (100%) patients in this study. The median Time to Myeloablation was 5.0 days (range = [4, 6]; with one patient had myeloablation occurred at day -1). Neutrophil Engraftment and Platelet Engraftment were achieved by all 61 (100%) patients in this study. The median time to Neutrophil Engraftment was 12.0 days (range = [10, 16]) and to Platelet Engraftment was 13.0 days (range = [10, 28]).

Table 7 Reviewer's Summary of Time to Key secondary end points

Time to Event	**Median days, [min, max]***
Time to Myeloablation Range	**5 [4, 6]**
Time to Neutrophil Engraftment Range	**12 [10, 16]**
Time to Platelet Engraftment Range	**13 [10, 28]**

*. Median days and 95% CI were calculated based on K-M estimates

3.5 Evaluation of Safety

The safety evaluation was not performed in this statistical review. Please refer to the clinical review for more details for the safety assessments. Treatment-related Mortality (TRM) was a primary endpoint of this study. There were no deaths during the study, thus, TRM was 0%. No analysis by demographic subgroups was performed since there was no TRM.

3.6 Benefit-Risk Assessment

The benefit-risk assessment was not performed in this statistical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, ECOG Score, and Region

4.1.1 Gender

In study CDX-353-002, a difference in MM Response Rates Pre-treatment versus Follow-up was noted across both gender categories. The overall MM Response Rates at Follow-up between gender subgroups were comparable; males, 97%; females 92%.

For male patients, there was an increase in MM Response Rates at Follow-up. At Pre-treatment, 29 (83%) patients showed a response (PR or better). At Follow-up, 34 (97%) patients showed a response.

For female patients, there was a difference in MM Response Rates at Follow-up. At Pre-treatment, 19 (73%) patients showed a response (PR or better). At Follow-up, 24 (92%) patients showed a response.

Table 8 Reviewer's Summary of MM Response Rates by Gender

MM Response Assessment, N=61	Total [%], 95% CI [a]	Male [%], 95% CI [a]	Female [%], 95% CI [a]
n	61	35	26
Pre-Treatment (Day -30 to Day -4)			
Overall Response Rate	48 [79], (68.4, 89.0)	29 [83], (70.4, 95.3)	19 [73], (56.0, 90.1)
Stringent Complete Response	0, (0, 0)	0, (0, 0)	0, (0, 0)
Complete Response	6 [10], (2.4, 17.3)	4 [11], (0.9, 22.0)	2 [8], (-2.6, 17.9)
Follow-Up Period Day 100 (Day +90 to Day +100)			
Overall Response Rate	58 [95], (89.7, 100)	34 [97], (91.6, 100)	24 [92], (82.1, 100)
Stringent Complete Response	10 [16], (7.1, 25.7)	5 [14], (2.7, 25.9)	5 [19], (4.1, 34.4)
Complete Response	9 [15], (5.9, 23.7)	5 [14], (2.7, 25.9)	4 [15], (1.5, 29.3)

(a) Represents a 2-sided 95% large sample confidence interval for the proportion of patients at each MM Response Assessment.
(b) Overall Response is categorized as Partial Response or better. Any 95% CI over 100% has been truncated to 100%.

4.1.2 Race

An increase in MM Response Rates Pre-treatment versus Follow-up was noted across both race categories. The overall MM Response Rates at Follow-up by race were comparable across subgroups; White, 94%; Non-white 100%.

For Whites, there was an increase in MM Response Rates at Follow-up. At Pre-treatment, 40 (82%) patients showed a response (PR or better). At Follow-up, 46 (94%) patients showed a response. For non-White, there was an increase in MM Response Rates demonstrated an overall improvement in response at Follow-up (Table 19). At Pre-treatment, 8 (67%) patients showed a response (PR or better). At Follow-up, 12 (100%) patients showed a response.

Table 9 Reviewer's Summary of MM Response Rates by Race

MM Response Assessment, N=61	Total [%], 95% CI [a]	White [%], 95% CI [a]	Non-white [%], 95% CI [a]
N	61	49	12
Pre-Treatment (Day -30 to Day -4)			
Overall Response Rate	48 [79], (68.4, 89.0)	40 [82], (70.8, 92.5)	8 [67], (40.0, 93.3)
Stringent Complete Response	0, (0, 0)	0, (0, 0)	0, (0, 0)
Complete Response	6 [10], (2.4, 17.3)	5 [10], (1.7, 18.7)	1 [8], (-7.3, 24.0)
Follow-Up Period Day 100 (Day +90 to Day +100)			
Overall Response Rate	58 [95], (89.7, 100)	46 [94], (87.2, 100)	12 [100], (100, 100)
Stringent Complete Response	10 [16], (7.1, 25.7)	7 [14], (4.5, 24.1)	3 [25], (0.5, 49.5)
Complete Response	9 [15], (5.9, 23.7)	9 [18], (7.5, 29.2)	0, (0, 0)

(a) Represents a 2-sided 95% large sample confidence interval for the proportion of patients at each MM Response Assessment.
(b) Overall Response is categorized as Partial Response or better. Any 95% CI over 100% has been truncated to 100%.

4.1.3 Age

An increase in MM Response Rates Pre-treatment versus Follow-up was noted across both age categories. The overall MM Response Rates at Follow-up by age were comparable across subgroups.

Table 10 Reviewer's Summary of MM Response Rates by Age

MM Response Assessment, N=61	Total [%], 95% CI [a]	<65 [%], 95% CI [a]	≥65 [%], 95% CI [a]
N	61	43	18
Pre-Treatment (Day -30 to Day -4)			
Overall Response Rate	48 [79], (68.4, 89.0)	34 [79], (64.0, 90.0)	14 [78], (52.4, 93.6)
Stringent Complete Response	0, (0, 0)	0, (0, 0)	0, (0, 0)
Complete Response	6 [10], (2.4, 17.3)	6 [14], (5.3, 27.9)	0 [0], (0, 0)
Follow-Up Period Day 100 (Day +90 to Day +100)			
Overall Response Rate	58 [95], (89.7, 100)	41 [95], (84.1, 99.4)	17 [94.4], (72.7, 99.9)
Stringent Complete Response	10 [16], (7.1, 25.7)	8 [17], (8.4, 33.4)	2 [11], (1.4, 34.7)

Complete Response	9 [15], (5.9, 23.7)	5 [12], (3.9, 25.1)	4[22.2], (6.4, 47.6)

(a) Represents a 2-sided 95% large sample confidence interval for the proportion of patients at each MM Response Assessment.
(b) Overall Response is categorized as Partial Response or better. Any 95% CI over 100% has been truncated to 100%.

4.1.4 Baseline ECOG Score

An increase in MM Response Rates Pre-treatment versus Follow-up was noted across fully active and restricted ECOG scores categories.

Table 11 Reviewer's Summary of MM Response Rates by Baseline ECOG Score

MM Response Assessment, N=61	Fully Active [c] [%], CI [a]	Restricted [c] [%], CI [a]	Ambulatory [c] [%], CI [a]
n	36	23	2
Pre-Treatment (Day -30 to Day -4)			
Overall Response Rate	30 [83], (71.2, 95.5)	16 [70], (50.8, 88.4)	2 [100], (100, 100)
Stringent Complete Response	0, (0, 0)	0, (0, 0)	0, (0, 0)
Complete Response	2 [6], (-1.9, 13.0)	3 [13], (-0.7, 26.8)	1 [50], (-19, 119)
Follow-Up Period Day 100 (Day +90 to Day +100)			
Overall Response Rate	33 [92], (82.6, 101)	23 [100], (100, 100)	2 [100], (100, 100)
Stringent Complete Response	6 [17], (4.5, 28.8)	4 [17], (1.9, 32.9)	0, (0, 0)
Complete Response	3 [8], (-0.7, 17.4)	5 [22], (4.9, 38.6)	1 [50], (-19, 119)

a Represents a 2-sided 95% large sample confidence interval for the proportion of patients at each MM Response Assessment.

b No patients had a Baseline ECOG score of 3-Capable of only limited self-care or 4-Completely disabled.

c. fully active : ECOG score= []; restricted: ECOG score=[]; ambulatory: ECOG score=[].

4.1.5 Region

Since all the sites are in the United States. The subgroup analysis based on region is not applicable.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The reviewer was able to confirm the primary and some secondary efficacy analysis results. There is no significant statistical issue identified. Based on study CDX-353-002, Overall response rate (partial response or better) was 79% at Pre-treatment, and 95% at Day +90/Day +100. The Overall CR Rate was 10% at pre-treatment and 31% on Day +90/Day +100. The number of patients with a stringent CR was 0% at Pre-treatment and 16% on Day +90/Day +100; similar differences in response rates were observed in patients with all stages of MM and across various demographic subgroups. Considering other chemo therapy and the transplant, it is possible the response rates may be confounded.

Table 12 Reviewer's Summary of Efficacy results – Study CDX-353-002

	n (%)	95% CI
Pre-Treatment (Day -30 to Day -4), N=61		
Overall MM Response Rate	48 (79)	(68.4, 89.0)
Overall Complete Response Rate, n (%)	6 (10)	(2.4, 17.3)
Overall Partial Response Rate	42 (69)	(57.2, 80.5)
Follow-Up Period Day 100 (Day +90 to Day +100)		
Overall MM Response Rate	58 (95)	(89.7, 100)
Overall Complete Response Rate, n (%)	19 (31)	(19.5, 42.8)
Overall Partial Response Rate	39 (64)	(51.9, 76.0)

Myeloablation was achieved in all 61 (100%) patients in this study. The median Time to Myeloablation was 5.0 days (with one myeloablation occurred at Day -1). Neutrophil Engraftment and Platelet Engraftment were achieved by all 61 (100%) patients in this study. The median time to Neutrophil Engraftment was 12.0 days and to Platelet Engraftment was 13.0 days. None of the patients in this study had Non-engraftment.

5.2 Conclusions and Recommendations

In conclusion, this statistical reviewer confirms the applicant's results submitted. Whether the results demonstrate an overall favorable benefit to risk ratio in supporting an indication of the Evomela as a myeloablative conditioning in Multiple Myeloma patients undergoing autologous transplantation is deferred to the clinical review team.

Yaping Wang, Ph.D.
Mathematical Statistician
Date: September 22, 2015

Concur: Dr. Shen, Team Leader
Cc:
PM/ McMullen, Rachel
DHP/ Dinndorf, Patricia
DHP/ Deisseroth, Albert
DBV/ Shen, Yuan-Li
DBV/ Gwise, Thomas
DBV/ Sridhara, Rajeshwari
OB/ Patrician, Lillian

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

/s/

YAPING WANG
09/23/2015

YUAN L SHEN
09/23/2015

RAJESHWARI SRIDHARA
09/23/2015