CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-311

STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22,311 / 000
Drug Name:	Mozobil™ (plerixafor injection)
Indication(s):	To enhance the mobilization of hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma
Applicant:	Genzyme
Date:	6/16/2008
Review Priority:	Priority
Biometrics Division:	V (HFD-715)
Statistical Reviewer:	Weishi (Vivian) Yuan
Concurring Reviewers:	Kun He, Ph.D., Acting Team Leader
	Rajeshwari Sridhara, , Ph.D., Deputy Director
Medical Division:	Oncology Drug Products (HFD 150)
Clinical Team:	Michael Brave, M.D.
	Robert Justice, M.D. Director
Project Manager:	Susan Jenney

Keywords: Chi-square test

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results from the two studies submitted showed statistically significant results that plerixafor reduced the number of aphereses sessions required to collect transplantable cell dose and increased the percentage of patients able to undergo autologous HSC transplantations. There were significant amount of protocol violations in both studies. However, the violations are evenly distributed among the two study arms, and the results from both studies are robust after removing the patients with major protocol violations.

Based on the data submitted, the study results support the claims in the primary endpoints and key secondary endpoints. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

1.2 Brief Overview of Clinical Studies

Patients with malignant disease such as non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), Hodgkin's disease (HD), and other cancers including neuroblastoma, may be treated with high-dose chemotherapy and requires reinfusion of haematopoietic stem cell (HSCs) to repopulate the bone marrow and regenerate trilineage blood cells.

The HSCs can be autologous (from the patient) and allogeneic (from a donor). Overall, 5-year-treatment-related mortality is around 5 to 8% for unpurged autologous transplantation and 25 to 30% for allogeneic transplantation in adults. In the case of autologous transplantation, the mortality is mainly related to the side effects of high-dose chemotherapy. In the case of autologous transplantation, the use of peripheral blood as a HSC source is preferred to bone marrow due to the ease of harvesting and less likelihood of tumor cell contamination. In addition, transplantation with peripheral blood HSCs leads to faster engraftment and reconstitution than with marrow infusion.

Plerixafor has primarily been investigated in conjunction with G-CSF as a first-line mobilization therapy regimen, but has also been studied in poor mobilizer patients. The proposed target population for plerixafor is adult patients with lymphoma or multiple myeloma.

The applicant submitted results from 2 randomized, double-blind, placebo-controlled, parallel-group, multicentre Phase III studies (3101 and 3102) in patients with lymphoma and multiple myeloma.

Study 3101 compared G-CSF (10 μg/kg) plus plerixafor (240 μg/kg) versus G-CSF (10 μg/kg) plus placebo to mobilize and collect $\geq 5 \times 10^6$ CD34+ cells/kg in Non-Hodgkin's Lymphoma patients for autologous transplantation. Total of 298 patients were randomized to two treatment arms (150 to G-CSF+ plerixafor and 148 to G-CSF+

placebo). Eligible patients were randomized in a 1:1 ratio, stratified by study center. The fist patient was enrolled (randomized) on January 18, 2005, and the last patient's last 100-day visit was April 3, 2007. The study is still ongoing. The original submission includes data reported through the cut-off date of April 6, 2007. As of the cut-off date, 184 patients have had their 6 month visit and 104 patients have had their 12 month visit. Additional follow-up data on engraftment were submitted in August 2008.

Study 3102 compared G-CSF (10 μg/kg) plus plerixafor (240 μg/kg) versus G-CSF (10 μg/kg) plus placebo to mobilize and collect ≥ 6 x 10^6 CD34+ cells/kg in Multiple Myeloma patients for autologous transplantation. Total of 302 patients were randomized to two treatment arms (148 to G-CSF+ plerixafor and 154 to G-CSF+ placebo). Eligible patients were randomized in a 1:1 ratio, stratified by study centre, platelet count (< 0.2 x 106/dL versus ≥ 0.2 x 106/dL), and type of transplant planned (single or tandem). The fist patient was enrolled (randomized) on February 4, 2005, and the last patient's last 100-day visit was February 15, 2007. The study is still ongoing. The original submission includes data reported through the cut-off date of April 6, 2007. As of the cut-off date, 245 patients have had their 6 month visit and 130 patients have had their 12 month visit. Additional follow-up data on engraftment were submitted in August 2008.

1.3 Statistical Issues and Findings

This submission is to support the efficacy and safety claims of plerixafor to patients with lymphoma and multiple myeloma to enhance the mobilization of hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation. The determination of the efficacy is based on results from two Phase III studies 3101 and 3102.

Both studies are randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase III studies. Patients are randomized in a 1:1 ratio to the treatment arm or the control arm.

Study 3101 is designed to investigate the outcome of NHL patients, with the primary endpoint being difference of proportion of patients achieving ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis. Secondary endpoints include: 1) difference of proportion of patients achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis; 2) Number of apheresis days required to achieve ≥ 5 x 10^6 CD34+ cells/kg; 3) Time to neutrophil engraftment; 4) Time to platelet engraftment; and 5) engraftment at 100 days, 6 months, and 12 months.

Study 3102 is designed to investigate the outcome of multiple lymphoma patients, with the primary endpoint being difference of proportion of patients achieving ≥ 6 x 10^6 CD34+ cells/kg in 2 or fewer days of apheresis. Secondary endpoints include: 1) difference of proportion of patients achieving ≥ 6 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis; 2) difference of proportion of patients achieving ≥ 2 x 10^6 CD34+

cells/kg in 4 or fewer days of apheresis 3) Number of apheresis days required to achieve ≥ 6 x 10^6 CD34+ cells/kg; 4) Time to neutrophil engraftment; 5) Time to platelet engraftment; and 6) engraftment at 100 days, 6 months, and 12 months.

Statistical Issues:

There were significant amount of protocol violations in both the studies. However, the violations are evenly distributed among the two study arms, and the results from both studies are robust after removing the patients with major protocol violations.

Statistical Findings:

In study 3101, total of 298 primary ITT patients were randomized in 32 centers in the United States. Among them, 89 (59%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of ≥ 5 × 10^6 CD34+ cells/kg within 4 apheresis days, compared to 29 (20%) patients randomized to G-CSF/placebo ($p < 0.001$). Results for the secondary endpoints also showed statistically significant outcomes in favor of the treatment arm. Details of the results for secondary outcomes can be found in Section 3.1.

Table 1. Study 3101 Primary Endpoint
Mobilization of ≥ 5 x 106 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 150)**	**G-CSF/placebo (n = 148)**
≥ 5 x 10^6/kg	89 (59%)	29 (20%)
< 5 x 10^6/kg	61 (41%)	119 (80%)
Difference (95% CI)	39.7% (29.6, 49.9)	
Pearson's chi-square *P*	< 0.001	

In study 3102, total of 302 primary ITT patients were randomized to 40 centers in the United States, Canada and Germany. Among them, 106 (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of ≥ 6 × 10^6 CD34+ cells/kg within 2 apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($p < 0.001$). Results for the secondary endpoints also showed statistically significant outcomes in favor of the treatment arm. Details of the results for secondary outcomes can be found in Section 3.1.

Table 2. Study 3102 Primary Endpoint
Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 148)**	**G-CSF/placebo (n = 154)**
≥ 6 x 10^6/kg	106 (72%)	53 (34%)
< 6 x 10^6/kg	42 (28%)	101 (66%)
Estimated treatment effect (95% CI)	37.2% (26.7, 47.7)	
Pearson's chi-square *P*	< 0.001	

2. INTRODUCTION

2.1 Overview

Since the 1980s, autologous transplantation of peripheral blood (PB) HSCT has became a widely used strategy for haematologic and immunologic recovery following high-dose chemotherapy for haematologic malignancies such as MM, NHL, HD, and other cancers, including neuroblastom. Approximately 80% of autologous transplants are for the indications of MM (34%), NHL (33%), and HD (12%).

2.1.1 Indication

The indication statement for which marketing approval is being sought is: "Mozobil™ (plerixafor injection) is indicated to enhance mobilization of haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM)."

2.1.2 History of Drug Development

Plerixafor is a small molecule inhibitor of the chemokine receptor CXCR4. It was originally studied as an agent for the treatment of patients infected with human immunodeficiency virus (HIV) since some strains of HIV require CXCR4 as a co-receptor for cell entry. Rapid and reversible leukocytosis was noted in human volunteers and in HIV patients treated with plerixafor in initial clinical trials. Rapid leukocytosis was confirmed and associated with an increase of peripheral blood CD34+ cells in healthy volunteers participating in a subsequent clinical trial.

Following these findings, Phase 1 studies were conducted in healthy volunteers and oncology patients, which confirmed that administration of plerixafor resulted in significant increases of circulating CD34+ cells. Furthermore, the results of Study AMD3100-2101, the proof-of-principle, Phase 2, cross-over study in patients with MM or NHL demonstrated that the combination of plerixafor and G-CSF was a superior mobilizing regimen compared with G-CSF alone.

The applicant has submitted 2 studies in this application to support the claimed indication. Both studies are randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase III studies. Patients are randomized in a 1:1 ratio to the treatment arm or the control arm.

Study 3101 is designed to investigate the outcome of NHL patients, with the primary endpoint being difference of proportion of patients achieving $\geq 5 \times 10^6$ CD34+ cells/kg in 4 or fewer days of apheresis. Secondary endpoints include: 1) difference of proportion of patients achieving $\geq 2 \times 10^6$ CD34+ cells/kg in 4 or fewer days of apheresis; 2) Number

of apheresis days required to achieve ≥ 5 x 10^6 CD34+ cells/kg; 3) Time to neutrophil engraftment; 4) Time to platelet engraftment; and 5) engraftment at 100 days, 6 months, and 12 months.

Study 3102 is designed to investigate the outcome of multiple lymphoma patients, with the primary endpoint being difference of proportion of patients achieving ≥ 6 x 10^6 CD34+ cells/kg in 2 or fewer days of apheresis. Secondary endpoints include: 1) difference of proportion of patients achieving ≥ 6 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis; 2) difference of proportion of patients achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis 3) Number of apheresis days required to achieve ≥ 6 x 10^6 CD34+ cells/kg; 4) Time to neutrophil engraftment; 5) Time to platelet engraftment; and 6) engraftment at 100 days, 6 months, and 12 months.

2.1.3 Major Statistical Issues

There were significant amount of protocol violations in both the studies. However, the violations are evenly distributed among the two study arms, and the results from both studies are robust after removing the patients with major protocol violations.

2.2 Data Sources

Data used for review is from the electronic submission received on 6/15/2008. The network path is \\CDSESUB1\EVSPROD\NDA022311\022311.enx. Specifically, datasets from Studies 3101 and 3102 were reviewed.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The applicant submitted results from two randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase III studies to support the administration of plerixafor and G-CSF combination in patients with NHL or MM to mobilize CD34+ cells for autologous HSC transplantations. The main focus of this review will be on the results from the analyses, particularly on the efficacy aspect of these two studies.

3.1.1 Study 3101

3.1.1.1 Study Design

This was a Phase III, multicenter, randomized, double-blind, placebo-controlled, comparative study in patients with NHL eligible for autologous hematopoietic stem cell transplant. The aim of the study was to claim that more patients with NHL who received

plerixafor plus G-CSF would achieve a target of ≥ 5 x 106 CD34+ cells/kg in 4 or fewer days of apheresis compared with patients who received G-CSF+ placebo.

Patients were randomized in a 1:1 ratio into one of the treatment arms, stratified by study center (no other stratification was applied). Randomized patients underwent mobilization with G-CSF 10 μg/kg/day for 4 days, administered by subcutaneous (SC) injection. On the evening of Day 4, patients received a dose of their assigned study treatment, i.e., plerixafor 240 μg/kg or placebo, administered by SC injection. On Day 5, patients returned to the clinic and received a morning dose of G-CSF 10 μg/kg and underwent apheresis approximately 10 to 11 hours after the dose of study treatment (within 60 minutes after administration of G-CSF). Patients continued to receive an evening dose of study treatment followed the next day by a morning dose of G-CSF and apheresis for up to a maximum of 4 aphereses or until ≥ 5 x 10^6 CD34+ cells/kg were collected.

Patients who failed to collect ≥ 0.8 x 10^6 CD34+ cells/kg after 2 days of apheresis or at least 2 x 10^6 CD34+cells/kg in 4 or fewer days of apheresis had the option of entering an open-label rescue procedure. After a minimum 7-day rest period, they received another 4-day course of G-CSF mobilization and a course of G-CSF+ plerixafor 240 μg/kg, after which cells were collected. (Study staff and patients remained blinded to the study treatment received before entering the rescue procedure.)

Graft durability was assessed at 100 days (±1 week), 6 months (±1 week), and 12 months (±1 week) post-transplantation. Graft failures occurring within 12 months post transplantation were recorded as serious adverse events (SAEs).

3.1.1.2 Study Objective

The primary objective was to determine if non-Hodgkin's lymphoma (NHL) patients mobilized with granulocyte-colony stimulating factor (G-CSF) plus 240 μg/kg plerixafor injection were more likely to achieve a target number of ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis than NHL patients mobilized with G-CSF plus placebo (G-CSF+ placebo).

The secondary objectives were:

- To evaluate the safety of G-CSF plus plerixafor 240 μg/kg (G-CSF+ plerixafor)compared to G-CSF+ placebo in patients with NHL
- To compare the 2 treatment arms with respect to the number of patients who achieved a minimum of 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis
- To compare the 2 treatment arms with respect to the number of days of apheresis required to reach the target of ≥ 5 x 10^6 CD34+ cells/kg
- To compare the 2 treatment arms with respect to PMN and PLT engraftment times
- To compare the 2 treatment arms for graft durability at 100 days, 6 months, and 12 months post-stem cell transplant.

3.1.1.3 Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients able to mobilize at least 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis.

The secondary efficacy endpoints were:

- The proportion of patients achieving a minimum transplantable number of CD34+ cells (2 x 10^6 CD34+ cells/kg) in 4 or fewer days of apheresis.
- The number of days of apheresis required to reach ≥ 5 x 10^6 CD34+ cells/kg.
- The number of days to PMN engraftment and to PLT engraftment.
- The proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post hematopoietic stem cell transplant. Graft durability was defined as maintenance of normal blood counts according to at least 2 of the 3 following criteria:
    i. PLT count > 50,000/μL (50 x 109/L) without transfusion for at least 2 weeks prior to the follow-up visit
    ii. Hemoglobin level ≥ 10 g/dL with no erythropoietin (EPO) or transfusions for at least 1 month prior to the follow-up visit
    iii. ANC > 1,000/μL (1 x 109/L) with no G-CSF for at least 1 week prior to the follow-up visit

3.1.1.4 Sample Size Consideration

The sample size was calculated based on satisfying assumptions for the primary efficacy variable, the number of patients mobilizing ≥ 5 x 10^6 CD34+ cells/kg within 4 days of apheresis with the following assumptions:

- Two-sided statistical test sized at $\alpha = 0.05$ and powered at 80% (i.e., $\beta = 0.20$)
- Placebo group response rate = 0.30
- Minimum difference in proportions to detect between 2 independent treatment arms = 0.20.

It was estimated that a sample size of 93 patients is needed per treatment group. This estimate was made for a PP population, and an additional estimate was needed to account for a lowered effect size under the alternative hypothesis when considering an ITT population. Assuming that 20% of the accrued patients would be excluded equally from both treatment arms for a PP analysis, and that none of these patients would achieve the primary endpoint, the target treatment effect for the ITT patients was 0.16. The sample size estimate was 150 patients per group or 300 total patients.

In order to better understand the safety and efficacy of plerixafor when given with Rituxan and G-CSF, up to an additional 40 patients (20 per treatment group) treated with Rituxan were permitted to be enrolled at selected centers, providing for up to a total of 340 enrolled patients. (During the study, only 1 center actually used Rituxan.)

3.1.1.5 Efficacy Analysis Methods

The ITT analyses were used to establish efficacy; the Per-Protocol (PP) analyses were considered supportive. The ITT population consisted of all randomized patients (with the exceptions noted below). The PP population consisted of all ITT patients who received any fraction of study treatment (plerixafor or placebo), completed the apheresis period, and did not have any major protocol deviations that significantly impacted the assessment of efficacy. Analyses for the ITT population were based on the actual randomization assignment, even if the patient received the other treatment. Data in the PP population were analyzed to reflect how the patients were actually treated.

For the primary efficacy endpoint (treatment success), each patient's value for CD34+ cells was calculated as the sum of all daily values collected over the 4 apheresis days. Efficacy endpoints were calculated using the percentage of CD34+ cells determined by the central laboratory applied to the WBC count from the local laboratory. When the central laboratory value was missing, the corresponding local laboratory value was used; 6 patients in the G-CSF+ plerixafor and 15 patients in the G-CSF+ placebo group each had 1 missing central laboratory CD34+ value during the study. The difference between the treatment arms in the proportion of patients meeting the target and the proportion not meeting the target was analyzed using Pearson's chi-square test (unstratified), uncorrected for continuity.

For the secondary efficacy endpoints, the proportion of patients achieving the minimum threshold of 2×10^6 CD34+ cells/kg in 4 or fewer apheresis days and the proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post-transplantation are analyzed in a manner similar to the analysis of the primary efficacy endpoint. The other secondary endpoints, number of apheresis days required to achieve the target of $\geq 5 \times 10^6$ CD34+ cells/kg and number of days to PMN engraftment and to PLT engraftment, were tested using an unstratified logrank statistic. A supportive analysis was conducted using Cox's PH regression model, parameterized to include fixed effect terms for treatment and study center. Kaplan-Meier curves were estimated per treatment group.

3.1.1.6 Applicant's Results and Statistical Reviewer's Findings / Comments

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Primary ITT population are summarized by treatment group in Table 3.1.1.1. The 2 treatment groups were similar to each other with respect to most demographics and baseline characteristics.

Table 3.1.1.1 Study 3101 Demographics

	G-CSF/plerixafor (n = 150)	G-CSF/placebo (n = 148)	Total (n = 298)
Median age (y)	56	59	58
Male/female (%)	67/33	69/31	68/32
Caucasian/non-Caucasian (%)	91/9	95/5	93/7
Stage I-II (%) Stage III-IV (%) Missing (%)	14 69 17	27 58 15	19 64 16
Time from Dx to RND (mo) Time from prog/rel to RND (mo)	12 4	13 4	13 4
Prior chemo/RT/surgery (%)	97/17/99	95/20/100	9618/99
1st CR 1st PR 2nd CR 2nd PR missing	34 17 20 29 0	30 13 20 36 1	32 15 20 33 1

Reviewer's comments:

There appears to be imbalance in the proportion of patients with baseline stage I/II disease. However, the imbalance favors the control arm.

Primary Efficacy Endpoint

Proportion of Patients Achieving ≥ 5 x 10^6 CD34+ cells/kg in 4 or Fewer Days of Apheresis

The proportion of patients achieving treatment success (i.e., mobilization of ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis) was the primary efficacy endpoint. The results for the Primary ITT population are summarized in Table 3.1.1.2. In the G-CSF+ plerixafor group, 89/150 (59.3%) of the patients achieved treatment success compared with 29/148 (19.6%) of the patients in the G-CSF+ placebo group. The estimated treatment effect (i.e., the difference in proportions between the treatment arms) was 39.7% (95% CI: 29.6% to 49.9%, $p < 0.001$).

Table 3.1.1.2 Study 3101 Primary Endpoint
Mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 150)**	**G-CSF/placebo (n = 148)**
≥ 5 x 10^6/kg	89 (59%)	29 (20%)
< 5 x 10^6/kg	61 (41%)	119 (80%)
Estimated treatment effect (95% CI)	39.7% (29.6, 49.9)	
Pearson's chi-square *p*-value	< 0.001	

Reviewer's Comments:

These are the results after imputing the missing data. All of the 9 missing data points were imputed as 'failure'. Three of the 9 patients are in the G/plerixafor arm and 6 in the G/placebo arm. The change in the analysis results is minor if the imputed data were removed.

Secondary Efficay Endpoints

Proportion of Patients Achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or Fewer Days of Apheresis

The proportion of patients achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis was a secondary efficacy endpoint. The results for the Primary ITT population are summarized in Table 3.1.1.3. In the G-CSF+ plerixafor group, 130/150 (86.7%) of the patients achieved ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis compared with 70/148 (47.3%) of the patients in the G-CSF+ placebo group. The estimated treatment effect was 39.4% (95% CI: 29.7% to 49.1%, p < 0.001).

Table 3.1.1.3 Study 3101 Secondary Endpoint
Mobilization of ≥ 2 x 10^6 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 150)**	**G-CSF/placebo (n = 148)**
≥ 2 x 10^6/kg	130 (87%)	70 (47%)
< 2 x 10^6/kg	20 (13%)	78 (53%)
Estimated treatment effect (95% CI)	39.4% (29.7, 49.1)	
Pearson's chi-square p-value	< 0.001	

Reviewer's Comments:

These are the results after imputing the missing data. The change in the analysis results is minor if the imputed data were removed.

Number of Days of Apheresis Required to Achieve ≥ 5 x 10^6 CD34+ cells/kg

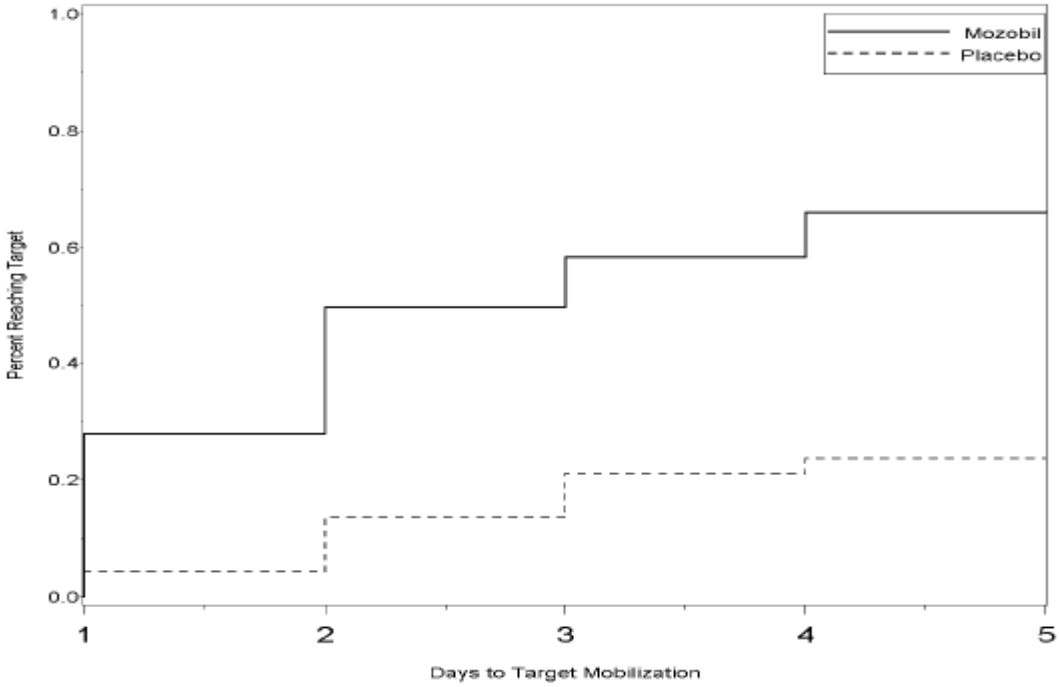
The number of apheresis days required to achieve the target of ≥ 5 x 10^6 CD34+ cells/kg was a secondary efficacy endpoint. Results for the Primary ITT population are depicted graphically in Figure 3.1. Based on Kaplan Meier estimates, the median time to reach the target CD34+ cell dose was 3.0 days in the G-CSF+ plerixafor group but was not estimable in the G-CSF+ placebo group since less than half of the patients in that group reached the target in 4 days of apheresis.

For the G-CSF+ plerixafor group versus the G-CSF+ placebo group, the estimated proportion of patients who achieved the target was:

- 27.9% versus 4.2% (first apheresis day),
- 49.1% versus 14.2% (second day),
- 57.7% versus 21.6% (third day), and
- 65.6% versus 24.2% (fourth day).

In a Cox PH model adjusted for treatment, patients in the G-CSF+ plerixafor group were 3.6 times more likely to achieve the target CD34+ cell count compared to the G-CSF+ placebo group (hazard ratio = 3.6, 95% CI = 2.4 to 5.5, $p < 0.001$).

Figure 3.1 Study 3101 Secondary Endpoint
Apheresis Days to Mobilize ≥ 5 x 10^6 CD34+ cells/kg



Engraftment Success and Time to Engraftment

In the Primary ITT population, 135/150 (90.0%) of the patients in the G-CSF+ plerixafor group underwent transplantation compared with 82/148 (55.4%) in the G-CSF+ placebo group.

The number of days to PMN engraftment was a secondary efficacy endpoint. Engraftment was defined as PMN counts ≥ 0.5 x 10^9/L for 3 consecutive days or ≥ 1.0 x 10^9/L for 1 day. The applicant reported that there were no statistically significant differences between the treatment groups. In each treatment group, all of the patients who underwent transplantation achieved successful PMN engraftment. The Kaplan Meier estimate of the median time to engraftment was 10.0 days in each treatment group.

The number of days to PLT engraftment was a secondary efficacy endpoint. Engraftment was defined as PLT counts ≥ 20 x 10^9/L for the first of 7 consecutive days without receiving a transfusion in the prior 7 days. The applicant reported that there were no statistically significant differences between the treatment groups. Among the patients who underwent transplantation, 132/135 (97.8%) in the G-CSF+ plerixafor group achieved successful PLT engraftment compared with 81/82 (98.8%) in the G-CSF+ placebo group. The median time to engraftment was 20.0 days in each treatment group.

The above results are summarized in Table 3.1.1.4.

Table 3.1.1.4 Study 3101 Secondary Endpoints Times to Neutrophil and Platelet Engraftment in the Subgroup of Patients who had Engratment

	G-CSF/plerixafor (n = 135)	G-CSF/placebo (n = 82)
Neutrophil engraftment		
Achieved (n)	135 (100%)	82 (100%)
Median time to achieve (days)	10	10
HR (95% CI)	1.1 (0.8, 1.5)	
Log-rank *P*	0.33	
Platelet engraftment		
Achieved (n)	132 (98%)	81 (99%)
Median time to achieve (days)	20	20
HR (95% CI)	1.1 (0.8, 1.4)	
Log-rank *P*	0.63	

Reviewer's Comments:

The above two endpoints of time to neutrophil and platelet engraftment was evaluated in a non-randomized subgroup of patients who had engraftment. Thus no formal hypotheses testing or statistical inference including interpretation of p-value can be considered.

Graft Durability

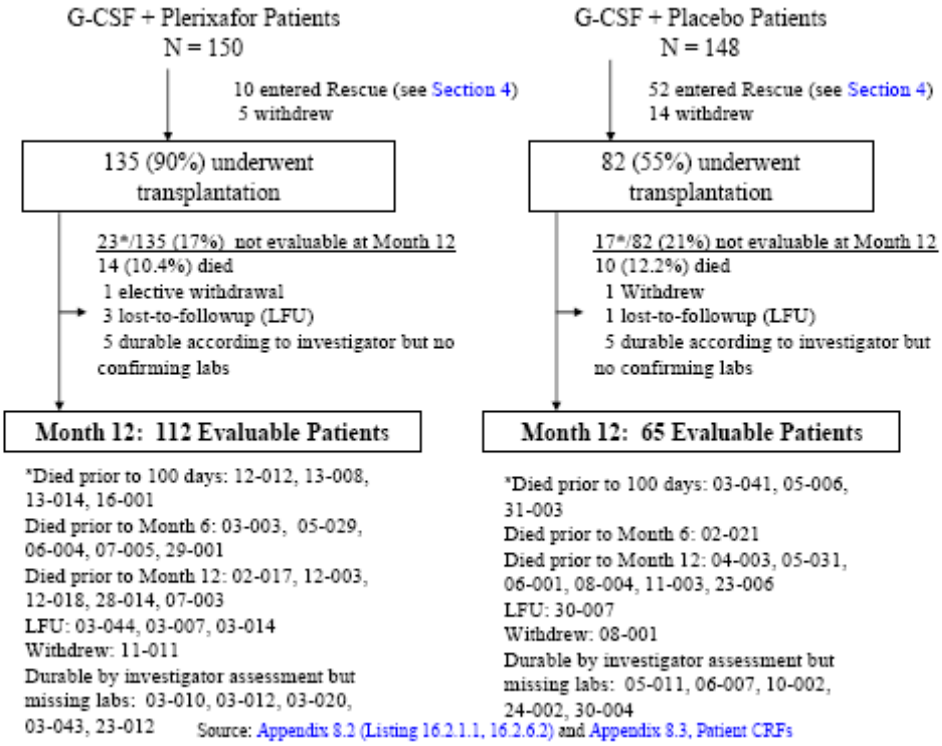
The proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post-transplantation was a secondary efficacy endpoint.

Updated information on graft durability was sent by the applicant on August 26, 2008 (data source **\\CDSESUB1\EVSPROD\NDA022311\0002**).

The Primary ITT population (N=298) comprised 150 patients in the G-CSF+ plerixafor group and 148 patients in the G-CSF+ placebo group. Of these, 135 patients in the G-CSF+ plerixafor group and 82 patients in the G-CSF+ placebo group underwent

autologous transplantation (N=217). The disposition of patients over the 12 months following transplantation is shown in Figure 3.2.

Figure 3.2 Study 3101 Disposition Over 12 Months Following Transplantation



The proportion of patients who underwent transplantation and maintained a durable graft, as defined by laboratory criteria, at 100 days, 6 months, and 12 months post-transplantation was a secondary efficacy endpoint in the study. The results are shown in Table 3.1.1.5.

A total of 62 patients from the Primary ITT population entered the rescue procedure after failing to meet minimal CD34+ cell collection criteria: 10/150 (6.7%) from the G-CSF+ plerixafor group and 52/148 (35.1%) from the G-CSF+ placebo group. (Table 3.1.1.6)

Table 3.1.1.5 Study 3101 Secondary Endpoint
Graft Durability (Evaluable Population)

	G-CSF/plerixafor (n = 135)	G-CSF/placebo (n = 82)
At 100 days		
N	128/135 (95%)	78/82 (95%)
Est. Treatment Effect	-0.3 (-6.3, 5.7)	
Pearson chi-square *P*	0.92	
At 6 months		
N	120/123 (98%)	77/78 (99%)
Est. Treatment Effect	-1.2 (-4.9, 2.5)	
Pearson chi-square *P*	0.57	
At 12 months		
N	110/112 (98%)	65/65 (100%)
Est. Treatment Effect	-1.8 (-4.2, 0.7)	
Pearson chi-square *P*	0.28	

Table 3.1.1.6 Study 3101 Secondary Endpoint
Graft Durability (Rescue Population)

	Total rescue patients n = 52, 6 from testing, 46 from control
At 100 days	
N	52(100%)
Yes	48 (92%)
No	4 (8%)
At 6 months	
N	46 (100%), 2 missing, 4 died
Yes	43 (94%)
No	3 (6%)
At 12 months	
N	44(100%), 1 missing, 7 died
Yes	40 (91%)
No	4 (9%)

Reviewer's Comments:

The above analyses were based on the evaluable population, a subgroup of patients who had engraftment, and the rescue population, instead of the Primary ITT population. No statistical inference or interpretation of p-value can be considered for these two endpoints.

Protocol Violations

About one third of the patients in Study 3101 have major protocol violations. They are summarized in Table 3.1.1.7.

Table 3.1.1.7 Major Protocol Violations

	G-CSF/ plerixafor (n = 150)	**G-CSF/ Placebo (n = 148)**
Eligibility	13 (9%)	14 (9%)
Apheresis	14 (9%)	8 (5%)
Missing/unknown	11 (7%)	12 (8%)
G-CSF dosing	6 (4%)	6 (4%)
Treatment dosing	1 (1%)	4 (3%)
Timing	3 (2%)	3 (2%)
Concurrent Tx	2 (1%)	1 (1%)
Total	**50 (33%)**	**48 (32%)**

Reviewer's Comments:

There are large proportions of patients had major protocol violations. The violations appear to be evenly distributed between the two treatment arms. The efficacy analysis was performed again by excluding the patients with major violations. Total of 217 patients were included in the analysis. The results showed statistically significant results between the two treatment arms. The percent difference between the two treatment arms was 42.03% with 95% confidence interval (30.16%, 53.91%).

Exploratory Subgroup Analysis of Weight and the Number of CD34 Cells

The primary efficacy analysis was also applied to the subgroups defined by patient weight and the number of CD34 cells obtained following the first dose of treatment. The results are summarized in Table 3.1.1.8 and 3.1.1.9.

Table 3.1.1.8 Exploratory Analyses of Mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by Baseline Weight

CD34+ cells mobilized	Weight < 85 kg		Weight ≥ 85 kg	
	G-CSF /plerixafor	G-CSF /placebo	G-CSF /plerixafor	G-CSF /placebo
	(n = 71)	(n = 67)	(n = 76)	(n = 75)
≥ 5 x 10^6/kg	33 (46%)	12 (18%)	56 (74%)	17 (23%)
< 5 x 10^6/kg	38 (54%)	55 (82%)	20 (26%)	58 (77%)
Estimated treatment effect (95% CI)	28.6% (13.4%, 43.7%)		51.0% (37.1%, 67.9%)	

Reviewer's comments:

The cut-off line for weight was chosen at 85kg, which was about the mean and median of the weight distribution of the patients. Nine patients were excluded from the analysis due to missing data of weight and study outcome. There is a strong trend that the treatment effect is smaller in the lower weight patients than those with higher weight. However, these analyses can only be considered as exploratory as these were not as randomized groups and may include confounding factors.

Table 3.1.1.9 Exploratory Analyses of Mobilization of ≥ 5 x 10^6 $CD34^+$ cells/kg within 4 days by CD34 count on Day 5* by Baseline CD34+ Cells

CD34+ cells mobilized	CD34 < 0.93		CD34 ≥ 0.93	
	G-CSF /plerixafor	G-CSF /placebo	G-CSF /plerixafor	G-CSF /placebo
	(n = 31)	(n = 82)	(n = 116)	(n = 60)
≥ 5 x 10^6/kg	3 (9.7%)	1 (1.2%)	86 (74.1%)	28 (46.7%)
< 5 x 10^6/kg	28 (90.3%)	81 (98.8%)	30 (25.9%)	32 (53.3%)
Estimated treatment effect (95% CI)	8.5% (0.8%, 16.1%)		27.5% (13.0%, 42.0%)	

Reviewer's comments:

The cut-off line for CD34+ was chosen at 0.93 x 10^6/kg per request of the clinical pharmacology reviewer. Nine patients were excluded from the analysis due to missing data. When the CD 34+ is low after the first day of treatment, most of the patients in this group responded to the treatment after all. Also there is a strong trend that the treatment effect is smaller among patients with lower CD 34+ counts than those with higher counts. However, these analyses can only be considered as exploratory as these were not as randomized groups and may include confounding factors.

3.1.2 Study 3102

3.1.2.1 Study Design

This was a Phase III, multicenter, randomized, double-blind, placebo-controlled, comparative study in patients with MM eligible for autologous hematopoietic stem cell transplant. The aim of the study was to claim that more patients with MM would achieve a target of ≥ 6 x 10^6 CD34+ cells/kg in 2 or less apheresis days with G-CSF plus plerixafor (G-CSF+ plerixafor) than with G-CSF plus placebo (G-CSF+ placebo).

Eligible patients were randomized 1:1 ratio into one of the two groups: G-CSF+ placebo or G-CSF+ plerixafor, stratified by study center, PLT count (< 200,000/dL versus ≥ 200,000/dL, because premobilization PLT count of 200,000/dL has been suggested to distinguish populations of good versus poorer mobilizers; and type of transplant planned (single or tandem). Randomized patients underwent mobilization with G-CSF 10 μg/kg/day for 4 days, administered by subcutaneous (SC) injection. On the evening of Day 4, patients received a dose of their assigned study treatment, i.e. plerixafor 240 μg/kg or placebo, administered by SC injection. On Day 5, patients returned to the clinic and received a morning dose of G-CSF 10 μg/kg and underwent apheresis approximately 10 to 11 hours after the dose of study treatment and within 60 minutes after administration of G-CSF.. Patients continued to receive an evening dose of study treatment followed the next day by a morning dose of G-CSF and apheresis for up to a maximum of 4 aphereses or until ≥ 6 x 10^6 CD34+ cells/kg were collected. At the Investigator's discretion ≥ 6 x 10^6 CD34+ cells/kg could be collected for patients who had planned tandem transplants if this was done within 4 apheresis days.

Patients who failed to collect ≥ 0.8 x 10^6 CD34+ cells/kg after 2 days of apheresis or ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis, or patients who were planned for tandem transplant and did not collect at least 4 x 10^6 CD34+ cells/kg in 4 or fewer apheresis days had the option of entering an open-label rescue procedure. After a minimum 7-day rest period, they received another 4-day course G-CSF mobilization and a course of G-CSF+ plerixafor 240 μg/kg, after which cells were collected. (Study staff and patients remained blinded to thestudy treatment received before entering the rescue

procedure.) Graft durability was assessed at 100 days (±1 week), 6 months (±1 week), and 12 months (±1 week) post-transplantation. Graft failures occurring within 12 months post transplantation were recorded as serious adverse events (SAEs).

3.1.2.2 Study Objective

The primary objective was to determine if multiple myeloma (MM) patients who were mobilized with granulocyte colony-stimulating factor (G-CSF) plus 240 μg/kg AMD3100 (plerixafor injection, referred to as plerixafor) were more likely to achieve a target number of $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer days of apheresis than MM patients mobilized with G-CSF plus placebo (G-CSF+ placebo).

The secondary objectives were:

- To evaluate the safety of G-CSF plus plerixafor (G-CSF+ plerixafor) 240 μg/kg compared to G-CSF+ placebo in patients with MM.
- To determine if MM patients who were mobilized with G-CSF+ plerixafor (240 μg/kg) were more likely to achieve a target number of $\geq 6 \times 10^6$ CD34+ cells/kg in 4 or fewer apheresis days than MM patients who were mobilized with G-CSF+ placebo.
- To compare MM patients mobilized with G-CSF plus 240 μg/kg plerixafor versus patients mobilized with G-CSF+ placebo with respect to the number of patients who achieved a minimum of 2×10^6 CD34+ cells/kg in 4 apheresis days.
- To compare the 2 treatment arms with respect to the number of days of apheresis required to reach the target of ≥ 6 x 106 CD34+ cells/kg.
- To compare the 2 treatment arms with respect to PMN and PLT engraftment times.
- To compare the 2 treatment arms for graft durability at 100 days, 6 months, and 12 months post stem cell transplant.

3.1.2.3 Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients achieving ≥ 6 x 106 CD34+ cells/kg in 2 or fewer days of apheresis.

Secondary endpoints were:

- The proportion of patients achieving $\geq 6 \times 10^6$ CD34+ cells/kg in 4 or fewer apheresis days.
- The proportion of patients achieving a minimum transplantable number of CD34+ cells (2×10^6 CD34+ cells/kg) in 4 or fewer days of apheresis.
- The number of days of apheresis required to reach the target of $\geq 6 \times 10^6$ CD34+ cells/kg.
- The number of days to PMN engraftment and to PLT engraftment.

- The proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post hematopoietic stem cell transplant. Graft durability was defined as maintenance of normal blood counts according to at least 2 of the 3 following criteria:
    i. PLT count > 50,000/μL (50 × 109/L) without transfusion for at least 2 weeks prior to the follow-up visit
    ii. Hemoglobin level ≥ 10 g/dL with no erythropoietin (EPO) or transfusions for at least 1 month prior to the follow-up visit
    iii. Absolute neutrophil count > 1,000/μL (1 x 109/L) with no G-CSF for at least 1 week prior to the follow-up visit

Further analysis was done to determine true failures. Patients who were unable to maintain normal blood counts due to other causes, such as recurrent progressive disease, renal failure, chronic bleeding, severe infection, drug-induced cytopenias, or development of new hematologic problems (nutritional or otherwise) were considered to have durable grafts.

3.1.2.4 Sample Size Consideration

The sample size was calculated based on satisfying design assumptions for the primary efficacy variable, the number of patients mobilizing ≥ 6 x 10^6 CD34+ cells/kg within 2 days of apheresis with the following assumptions:

- Two-sided statistical test sized at $\alpha = 0.05$ and powered at 80% (i.e., $\beta = 0.20$)
- Placebo group response rate = 0.30
- Minimum difference in proportions to detect between 2 independent treatment groups = 0.20.

It was estimated that a sample size of 93 patients is needed per treatment group. Since this estimate was made for a PP population, an additional estimate was needed to account for a lowered effect size under the alternative hypothesis when considering an ITT population. Assuming that 20% of the accrued patients would be excluded equally from both treatment groups for a PP analysis and that none of these patients achieved the primary endpoint, the target treatment effect for the ITT patients was 0.16. The sample size estimate was 150 patients per group or 300 total patients.

Up to an additional 30 patients (15 per treatment group) may have been enrolled and permitted to receive cyto-reductive chemotherapy following stem cell transplant (SCT). To allow for these extra patients, the maximum sample size was 330 patients. (During the study, only 1 patient enrolled under these criteria.)

3.1.2.5 Efficacy Analysis Methods

The ITT analyses were used to establish efficacy; the Per-Protocol (PP) analyses were considered supportive. The ITT population consisted of all randomized patients (with the exceptions noted below). The PP population consisted of all ITT patients who received

any fraction of study treatment (plerixafor or placebo), completed the apheresis period, and did not have any major protocol deviations that significantly impacted the assessment of efficacy. Analyses for the ITT population were based on the actual randomization assignment, even if the patient received the other treatment. Data in the PP population were analyzed to reflect how the patients were actually treated.

For the primary efficacy endpoint (treatment success), each patient's value for CD34+ cells was calculated as the sum of all daily values collected over the 2 apheresis days. Efficacy endpoints were calculated using the percentage of CD34+ cells determined by the central laboratory applied to the WBC count from the local laboratory. When the central laboratory value was missing, the corresponding local laboratory value was used; 12 patients in the G-CSF+ plerixafor and 13 patients in the G-CSF+ placebo group each had 1 missing central laboratory CD34+ value during the study. The difference between the treatment arms in the proportion of patients meeting the target and the proportion not meeting the target was analyzed using Pearson's chi-square test (unstratified), uncorrected for continuity.

For the secondary efficacy endpoints, the proportion of patients achieving the minimum threshold of 6 x 10^6 CD34+ cells/kg in 4 or fewer apheresis days, the proportion of patients achieving the minimum threshold of 2 x 10^6 CD34+ cells/kg in 4 or fewer apheresis days and the proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post-transplantation are analyzed in a manner similar to the analysis of the primary efficacy endpoint. The other secondary endpoints, number of apheresis days required to achieve the target of $\geq$ 6 x 10^6 CD34+ cells/kg and number of days to PMN engraftment and to PLT engraftment, were tested using an unstratified logrank statistic. A supportive analysis was conducted using Cox's PH regression model, parameterized to include fixed effect terms for treatment and study center. Kaplan-Meier curves were estimated per treatment group.

3.1.2.6 Applicant's Results and Statistical Reviewer's Findings/ Comments

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Primary ITT population are summarized by treatment group in Table 3.1.2.1. The 2 treatment groups were similar to each other with respect to most demographics and baseline characteristics.

Table 3.1.2.1 Study 3102 Demographics

	G-CSF/plerixafor (n = 148)	G-CSF/placebo (n = 154)	Total (n = 302)
Median age (y)	58	59	59
Male/female (%)	66/32	69/31	68/32
Caucasian/non-Caucasian (%)	79/21	83/17	81/19
Stage I-II (%) Stage III (%) Missing (%)	29 61 0	41 58 1	40 60 1
Time from Dx to RND (mo)	7	7	7
Prior chemo/RT/surgery (%)	97/27/99	96/31/99	9729/99
1st CR 1st PR 2nd PR	7 87 5	12 82 6	10 84 6

Reviewer's comments:

There appears to be imbalance in the proportion of patients with baseline stage I/II disease and patients with 1st CR. However, these imbalances favor the control arm.

Primary Efficacy Endpoint

Proportion of Patients Achieving ≥ 6 x 10^6 CD34+ Cells/kg in 2 or Fewer Days of Apheresis

The number of patients achieving treatment success (i.e. collection of ≥ 6 x 10^6 CD34+ cells/kg in 2 or fewer days of apheresis) was the primary efficacy endpoint. As low PLT count has been suggested to be a predictor of poor mobilization, patients were stratified by platelet count at randomization (baseline platelet count < 200,000 cells/dL and baseline platelet count ≥ 200,000 cells/dL). The results for the Primary ITT population are summarized in Table 3.1.2.2. In the G-CSF+ plerixafor group, 106/148 (71.6%) of the patients achieved treatment success compared with 53/154 (34.4%) of the patients in the G-CSF+ placebo group. The estimated treatment effect (i.e. the difference in proportions between the treatment groups) was 37.2% (95% CI: 26.8% to 47.6%; $p < 0.001$).

Table 3.1.2.1 Study 3102 Primary Endpoint
Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 148)**	**G-CSF/placebo (n = 154)**
≥ 6 x 10^6/kg	106 (72%)	53 (34%)
< 6 x 10^6/kg	42 (28%)	101 (66%)
Estimated treatment effect (95% CI)	37.2% (26.7, 47.7)	
Pearson's chi-square *p*-value	< 0.001	

Reviewer's Comments:

These are the results after imputing the missing data. All of the 8 missing data points were imputed as 'failure'. Four of the 8 patients are in the G-CSF/plerixafor arm and 4 in the G-CSF/placebo arm. The change in the analysis results is minor if the imputed data were removed.

Secondary Efficacy Endpoints

Proportion of Patients Achieving ≥ 6 x 10^6 CD34+ Cells/kg in 4 or Fewer Days of Apheresis

The proportion of patients achieving ≥ 6 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis was a secondary efficacy endpoint. The results for the Primary ITT population are shown in Table 3.1.2.3. In the G-CSF+ plerixafor group, 112/148 (75.7%) of the patients achieved treatment success compared with 79/154 (51.3%) of the patients in the G-CSF+ placebo group. The estimated treatment effect was 24.4% (95% CI: 13.9% to 34.9%; $p < 0.001$).

Table 3.1.2.3 Study 3102 Secondary Endpoint
Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 148)**	**G-CSF/placebo (n = 154)**
≥ 6 x 10^6/kg	112 (76%)	79 (51%)
< 6 x 10^6/kg	36 (24%)	75 (49%)
Estimated treatment effect (95% CI)	24.4% (13.9, 34.9)	
Pearson's chi-square *P*	< 0.001	

Proportion of Patients Achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or Fewer Days of Apheresis

The proportion of patients achieving ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis was a secondary efficacy endpoint. The results for the Primary ITT population are shown in Table 3.1.2.4. In the G-CSF+ plerixafor group, 141/148 (95.3%) of the patients achieved treatment success compared with 136/154 (88.3%) of the patients in the G-CSF+ placebo group. The estimated treatment effect was 7.0% (95% CI: 0.8% to 13.1%; p = 0.031).

Table 3.1.2.4 Study 3102 Secondary Endpoint
Mobilization of ≥ 2 x 10^6 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF /plerixafor (n = 148)**	**G-CSF /placebo (n = 154)**
≥ 6 x 10^6/kg	141 (95.3%)	136 (88.3%)
< 6 x 10^6/kg	7 (4.8%)	18 (11.7%)
Estimated treatment effect (95% CI)	7.0% (0.8%, 13.1%)	
Pearson's chi-square *P*	0.031	

Reviewer's Comments:

These are the results after imputing the missing data. The change in the analysis results is minor if the imputed data were removed.

Number of Days of Apheresis Required to Reach ≥ 6 x 10^6 CD34+ cells/kg

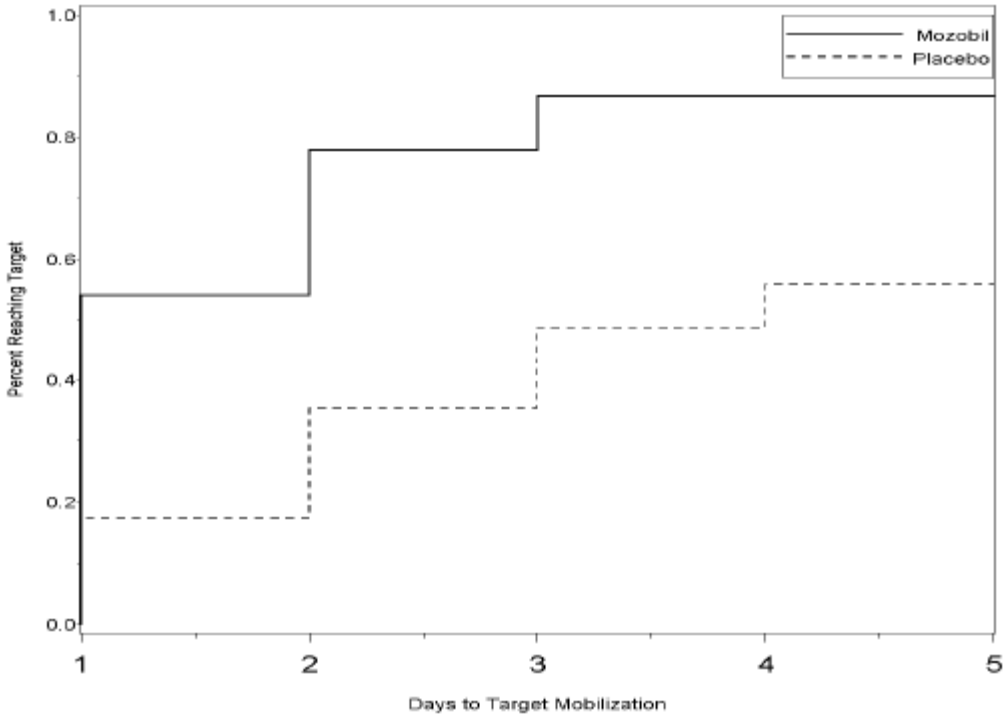
The number of apheresis days required to reach the target of ≥ 6 x 10^6 CD34+ cells/kg was a secondary efficacy endpoint. Results for the Primary ITT population are depicted graphically in Figure 3.3. Based on Kaplan-Meier estimates, the median time to reach the target CD34+ cell dose was 1.0 day in the G-CSF+ plerixafor group and 4.0 days in the G-CSF+ placebo group.

For the G-CSF+ plerixafor group versus the G-CSF+ placebo group, respectively, the estimated proportion of patients who achieved the target was:

- 54.2% versus 17.3% (first apheresis day),
- 77.9% versus 35.3% (second day),
- 86.8% versus 48.9% (third day),
- and 86.8% versus 55.9% (fourth day).

In a Cox PH model adjusted for treatment, patients in the G-CSF+ plerixafor group were 2.5 times more likely to achieve the target CD34+ cell count compared to patients in the G-CSF+ placebo group (hazard ratio = 2.539, 95% CI: 1.878 to 3.441, p < 0.001).

Figure 3.3 Study 3102 Secondary Endpoint
Apheresis Days to Mobilize ≥ 6 x 10^6 CD34+ cells/kg



Engraftment Success and Time to Engraftment

In the Primary ITT population, 142/148 (95.9%) patients in the G-CSF+ plerixafor group underwent transplantation, and in the G-CSF+ placebo group, 136/154 (88.3%) underwent transplantation.

The number of days to PMN engraftment was a secondary efficacy endpoint. Engraftment was defined as PMN counts > 0.5 x 10^9/L for 3 consecutive days or > 1.0 x 10^9/L for 1 day. The applicant has reported that there was no statistically significant difference between the treatment groups in PMN engraftment. In the Primary ITT G-CSF+ plerixafor group, 141/142 (99.3%) of the patients who underwent transplantation achieved successful PMN engraftment, and in the G-CSF+ placebo group, 136/136 (100%) of the patients who underwent transplant achieved successful PMN engraftment. The Kaplan Meier estimate of the median time to PMN engraftment was 11.0 days in each treatment group.

The number of days to PLT engraftment was a secondary efficacy endpoint. Engraftment was defined as PLT counts > 20 x 10^9/L for the first of 7 consecutive days without receiving a transfusion in the prior 7 days. The applicant has reported that there were no statistically significant differences between the treatment groups in PLT engraftment.

Among the patients who underwent transplantation, 141/142 (99.3%) in the G-CSF+ plerixafor group achieved successful PLT engraftment compared with 135/136 (99.3%) in the G-CSF+ placebo group. The median time to engraftment was 18.0 days in each treatment group.

The above results are summarized in Table 3.1.2.5.

Table 3.1.2.5 Study 3102 Secondary Endpoint Times to Neutrophil and Platelet Engraftment in the Subgroup of Patients who had Engratment

	G-CSF/plerixafor (n = 142)	**G-CSF/placebo (n = 136)**
Neutrophil engraftment		
Achieved (n)	141 (99%)	136 (100%)
Median time to achieve (days)	11	11
HR (95% CI)	1.0 (0.81, 1.31)	
Log-rank *P*	0.69	
Platelet engraftment		
Achieved (n)	141 (99%)	135 (99%)
Median time to achieve (days)	18	18
HR (95% CI)	0.9 (0.69, 1.11)	
Log-rank *P*	0.18	

Reviewer's Comments:

The above two endpoints of time to neutrophil and platelet engraftment was evaluated in a non-randomized subgroup of patients who had engraftment. Thus no formal hypotheses testing or statistical inference including interpretation of p-value can be considered.

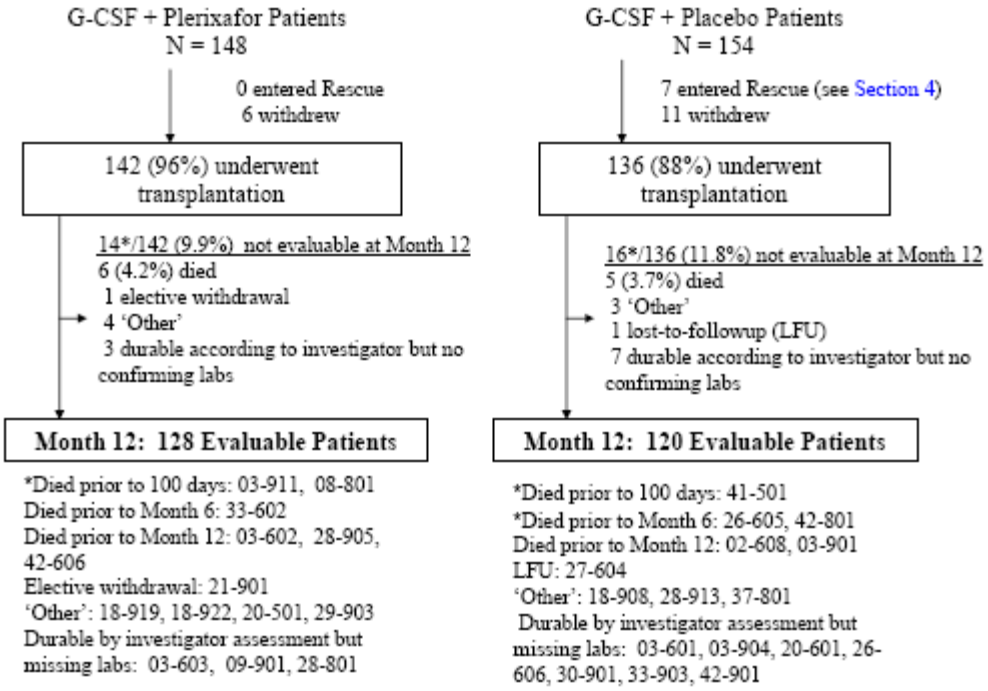
Graft Durability

The proportion of patients maintaining a durable graft at 100 days, 6 months, and 12 months post-transplantation was a secondary efficacy endpoint.

Updated information on graft durability was sent by the applicant on August 26, 2008 (data source **\\CDSESUB1\EVSPROD\NDA022311\0002**).

The Primary ITT population (N=302) comprised 148 patients in the G-CSF+ plerixafor group and 154 patients in the G-CSF+ placebo group. Of these, 142 patients in the G-CSF+ plerixafor group and 136 patients in the G-CSF+ placebo group underwent autologous transplantation (N=278). The disposition of patients over the 12 months following transplantation is shown in Figure 3.4.

Figure 3.4 Study 3102 Disposition Over 12 Months Following Transplantation



The proportion of patients who underwent transplantation and maintained a durable graft, as defined by laboratory criteria, at 100 days, 6 months, and 12 months post-transplantation was a secondary efficacy endpoint in the study. The results are shown in Table 3.1.2.6.

A total of 7 patients from the G-CSF+ placebo group (4.5%) of the Primary ITT population entered the rescue procedure after failing to meet minimal CD34+ cell collection criteria. No patients entered the rescue procedure from the G-CSF+ plerixafor group. All patients who underwent transplantation in the Rescue population (n=7) maintained a durable graft at 100 days, 6 months, and at 12 months.

Table 3.1.2.6 Study 3102 Secondary Endpoint
Graft Durability (Evaluable Population)

	G-CSF/plerixafor (n = 142)	G-CSF/placebo (n = 136)
At 100 days		
N	140/142 (99%)	133/136 (98%)
Est. treatment effect	0.8% (-2.3, 3.9)	
Pearson chi-square *P*	0.62	
At 6 months		
N	133/135 (98%)	127/125 (98%)
Est. treatment effect	0.1% (-2.9, 3.1)	
Pearson chi-square *P*	0.95	
At 12 months		
N	127/128 (99%)	119/120 (100%)
Est. treatment effect	0.1 (-2.2, 2.3)	
Pearson chi-square *P*	0.96	

Reviewer's Comments:

The analyses were based on the subgroup evaluable population who had engraftment and the rescue population, instead of the Primary ITT population. No statistical inference or interpretation of p-value can be considered for these two endpoints.

Protocol Violations

About half of the patients in Study 3102 had major protocol violations. They are summarized in Table 3.1.2.7.

Table 3.1.2.7 Major Protocol Violations

	G-CSF/ plerixafor (n = 148)	G-CSF/ placebo (n = 154)
Eligibility	21 (14%)	14 (9%)
Apheresis	19 (13%)	30 (19%)
Missing/unknown	22 (15%)	23 (15%)
G-CSF dosing	11 (7%)	9 (6%)
Treatment dosing	1 (1%)	4 (3%)
Timing	9 (6%)	7 (5%)
Concurrent Tx	0 (0%)	4 (3%)
Total	**83 (56%)**	**91 (59%)**

Reviewer's Comments:

There are large proportions of patients who had major protocol violations. The violations appear to be evenly distributed between the two treatment arms. The efficacy analysis was performed again by excluding patients with major violations. The percent difference between the two treatment arms was 39.26% with 95% confidence interval (25.45%, 53.08%).

3.2 Evaluation of Safety

Please refer to the Clinical Review of this application for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 4.1.1 presents the summary statistics of mobilization of $\geq 5 \times 10^6$ CD34+ cells/kg within 4 days by Gender.

Table 4.1.1 Mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by Gender

Study	Gender	Arm	Number of ≥ 5 x 10^6/kg	Difference (95% CI)
3101	Male	G-CSF /plerixafor	62/100 (62%)	44.4% (32.2%, 56.5%)
		G-CSF /placebo	18/102 (17.7%)	
	Female	G-CSF /plerixafor	27/50 (54%)	30.1% (11.0%, 49.2%)
		G-CSF /placebo	11/46 (23.9%)	

Table 4.1.2 presents the summary statistics of mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by Gender in Study 3102.

Table 4.1.2 Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by Gender

Study	Gender	Arm	Number of ≥ 6 x 10^6/kg	Difference (95% CI)
3102	Male	G-CSF /plerixafor	74/100 (74%)	39.4% (26.8%, 52.0%)
		G-CSF /placebo	37/107 (34.6%)	
	Female	G-CSF /plerixafor	32/48 (66.7%)	32.6% (13.2%, 52.1%)
		G-CSF /placebo	16/47 (34.0%)	

Table 4.1.3 presents the summary statistics of mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by age in Study 3101.

Table 4.1.3 Mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by Age

Study	Age	Arm	Number of ≥ 5 x 10^6/kg	Difference (95% CI)
3101	< 65 yrs	G-CSF /plerixafor	72/117 (61.5%)	40.8% (29.1%, 52.6%)
		G-CSF /placebo	23/111 (20.7%)	
	≥ 65 yrs	G-CSF /plerixafor	17/33 (51.5%)	35.3% (14.2%, 56.4%)
		G-CSF /placebo	6/37 (16.2%)	

Table 4.1.4 presents the summary statistics of mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by age in Study 3102.

Table 4.1.4 Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by Age

Study	Age	Arm	Number of ≥ 6 x 10^6/kg	Difference (95% CI)
3102	< 65 yrs	G-CSF /plerixafor	83/115 (72.2%)	32.5% (20.3%, 44.7%)
		G-CSF /placebo	46/116 (39.7%)	
	≥ 65 yrs	G-CSF /plerixafor	23/33 (69.7%)	51.3% (30.9%, 71.6%)
		G-CSF /placebo	7/38 (18.4%)	

Table 4.1.5 presents the summary statistics of mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by origin in Study 3101.

Table 4.1.5 Mobilization of ≥ 5 x 10^6 CD34+ cells/kg within 4 days by Origin

Study	Origin	Arm	Number of ≥ 5 x 10^6/kg	Difference (95% CI)
3101	Caucasians	G-CSF /plerixafor	82/136 (60.3%)	40.3% (29.7%, 50.9%)
		G-CSF /placebo	28/140 (20%)	
	Non-Caucasians	G-CSF /plerixafor	7/14 (50%)	37.5 % (-0.057%, 80.7%)
		G-CSF /placebo	1/8 (12.5%)	

Table 4.1.6 presents the summary statistics of mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by origin in Study 3102.

Table 4.1.6 Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days by Origin

Study	Origin	Arm	Number of ≥ 6 x 10^6/kg	Difference (95% CI)
3102	Caucasians	G-CSF /plerixafor	82/117 (70.1%)	37.3% (25.5%, 49.0%)
		G-CSF /placebo	42/128 (32.8%)	
	Non-Caucasians	G-CSF /plerixafor	24/31 (77.4%)	35.1% (10.5%, 59.8%)
		G-CSF /placebo	11/26 (42.3%)	

4.2 Other Special/Subgroup Populations

There is no other subgroup analysis performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In study 3101, total of 298 primary ITT patients were randomized to 32 centers in the United States. Among them, 89 (59%) patients randomized to G-CSF/plerixafor met the

primary efficacy endpoint of mobilization of ≥ 5 × 10^6 CD34+ cells/kg within 4 apheresis days, compared to 29 (20%) patients randomized to G-CSF/placebo ($p < 0.001$). Results for the secondary endpoints also showed supportive outcomes in favor of the treatment arm. Table 5.1 presents the primary analysis results.

Table 5.1 3101 Primary Endpoint
Mobilization of ≥ 5 x 106 CD34+ cells/kg within 4 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 150)**	**G-CSF/placebo (n = 148)**
≥ 5 x 10^6/kg	89 (59%)	29 (20%)
< 5 x 10^6/kg	61 (41%)	119 (80%)
Difference (95% CI)	39.7% (29.6, 49.9)	
Pearson's chi-square *P*	< 0.001	

In study 3102, total of 302 primary ITT patients were randomized to 40 centers in the United States, Canada and Germany. Among them, 106 (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of ≥ 6 × 10^6 CD34+ cells/kg within 2 apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($p < 0.001$). Results for the secondary endpoints also showed supportive outcomes in favor of the treatment arm. Table 5.2 presents the primary analysis results.

Table 5.2 3102 Primary Endpoint
Mobilization of ≥ 6 x 10^6 CD34+ cells/kg within 2 days

$CD34^+$ cells mobilized	**G-CSF/plerixafor (n = 148)**	**G-CSF/placebo (n = 154)**
≥ 6 x 10^6/kg	106 (72%)	53 (34%)
< 6 x 10^6/kg	42 (28%)	101 (66%)
Estimated treatment effect (95% CI)	37.2% (26.7, 47.7)	
Pearson's chi-square *P*	< 0.001	

There were significant amount of protocol violations in both studies. However, the violations are evenly distributed among the two study arms, and the results from both studies are robust after removing the patients with major protocol violations.

5.2 Conclusions and Recommendations

The results from the two studies submitted showed statistically significant results that plerixafor reduced the number of aphereses sessions required to collect transplantable cell

dose and increased the percentage of patients able to undergo autologous HSC transplantations.

Based on the data submitted, the study results support the claims in the primary endpoints and key secondary endpoints. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Weishi Yuan
Date: 11/03/2008

Concurring Reviewers:
Kun He, Acting Statistical Team Leader
Rajeshwari Sridhara, Biometrics Deputy Division Director

cc:
HFD-150/ Susan Jenney
HFD-150/ Michael Brave
HFD-150/ Robert Justice
HFD-711/ Weishi Yuan
HFD-711/ Kun He
HFD-711/ Rajeshwari Sridhara
HFD-711/ Aloka Chakravarty
HFD-700/ Lillian Patricia

c:\NDA\statreview.doc

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

/s/

Weishi Yuan
11/12/2008 01:21:16 PM
UNKNOWN

Kun He
11/12/2008 01:22:26 PM
BIOMETRICS

Rajeshwari Sridhara
11/12/2008 02:34:03 PM
BIOMETRICS