# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-311**

# MEDICAL REVIEW(S)

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** December 2, 2008

**TO:** NDA 22-311/SN-0008

**FROM:** Michael Brave, M.D.
Medial Officer CDER/OND/DDOP

**SUBJECT:** Plerixafor-associated vasovagal reactions

## Introduction

On November 7, 2008, Genzyme submitted an information amendment to NDA 22-311 (SN 0008) regarding an observed association between plerixafor (Mozobil) and vasovagal reactions. The Sponsor noted this association in the 4-month safety update of the New Drug Application 22-311. The PDUFA goal date of that application is December 16, 2008, and the Applicant believes that this information should be included in the label if their product is approved.

## Relevant Data

The Sponsor identified a total of eight reports of syncope – six in healthy subjects, one in a patient with HIV, one in an oncology patient, and one in an allogeneic donor (Table 1). Five of the six healthy subjects had been enrolled in a recently completed thorough QT/QTc study (MOZO0707).

Syncope was typically preceded by gastrointestinal symptoms which began between approximately one and two hour hours following plerixafor administration. The duration of syncope, when reported, was 30 to 60 seconds.

**Reviewer's Table 1. Syncopal episodes in patients treated with plerixafor**

| Patient/subject | Dose | Associated symptoms | Investigator's attribution | Re-challenge? |
|---|---|---|---|---|
| Healthy volunteer MOZO0707-001-105 | 0.40 mg/kg | Abdominal cramps, diarrhea, emesis, bradycardia, hypotension | Probably related | No |
| Healthy volunteer MOZO0707-001-110 | 0.40 mg/kg | Abdominal cramps, lightheadedness, paresthesias | Possibly related | Yes (negative following dose of 0.24 mg/kg) |
| Healthy volunteer MOZO0707-001-209 | 0.24 mg/kg | Bradycardia, hypotension | Unrelated | Yes (negative following dose of 0.40 mg/kg) |
| Healthy volunteer MOZO0707-001-213 | 0.40 mg/kg | Diarrhea, emesis, hiccups, light-headedness, nausea | | No |

| | | | | |
|---|---|---|---|---|
| Healthy volunteer MOZO0707-001-221 | 0.40 mg/kg | Bradycardia, diarrhea | Unrelated | No |
| Healthy volunteer AMD3100-1002-01-102 | 0.40 mg/kg | Lightheadedness, nausea | Unrelated | No |
| Oncology patient 3101-017-001 | 0.24 mg/kg | Nausea, diaphoresis | Probably related | No |
| Allogeneic donor | 0.32 mg/kg | Abdominal cramps, diarrhea, dizziness, paresthesia, diaphoresis | Possibly related | No |

This reviewer found a total of eight reports of syncope or vasovagal reaction in the safety database of NDA 22-311. All eight of those reports occurred among patients receiving G-CSF/plerixafor (as opposed to plerixafor alone G-CSF/placebo), and in each case the dose of plerixafor administered was 0.24 mg/kg. Five of these eight events occurred during hematopoietic stem cell mobilization, whereas the other three occurred during myeloablative chemotherapy or later. All eight were assessed by investigators as being unrelated to study drug (Table 2).

**Reviewer's Table 2. Reports of syncope or vasovagal reaction in the NDA 22-311 safety database**

| Patient | Study | Cancer | Dose | Other AEs within one day | Study day | Investigator attribution |
|---|---|---|---|---|---|---|
| 01-404 | 2102 | MM | 0.24 mg/kg | Exertional dyspnea, hemorrhoids, orthostatic hypotension, thromboctopenia | 6 | Unrelated |
| 05-154 | 2104 | MM | 0.24 mg/kg | Dizziness | 12 | Unrelated |
| 01-114 | 2106 | HD | 0.24 mg/kg | Diarrhea, pyrexia | 112 | Unrelated |
| 02-113 | 2112 | NHL | 0.24 mg/kg | Oral mucosal disorder | 26 | Unrelated |
| 03-030 | 3101 | NHL | 0.24 mg/kg | Back pain, skin laceration, subcutaneous hematoma | 4 | Unrelated |
| 05-003 | 3101 | NHL | 0.24 mg/kg | None reported | 37 | Unrelated |
| 14-005 | 3101 | NHL | 0.24 mg/kg | None reported | 1 | Unrelated |
| 22-004 | 3101 | NHL | 0.24 mg/kg | Bone pain, hypotension, oral paresthesia | 6 | Unrelated |

Source: DEMOEXT.xpt and AE1.xpt, variables PATID, STUDYID, AEPT, TRTGRPRC, CANCER, AVDSGRPC, RELATED, AEDAY, and AEREL

## Discussion

In summary, a total of 16 patients – eight from the safety database and eight reported separately by the Applicant of NDA 22-311 – experienced syncope or vasovagal reactions while enrolled in investigational studies of plerixafor. The administration of plerixafor therefore does appear to pose a risk of syncope; however, several features of these reports mitigate against the notion that this risk is serious.

- Five of the six healthy volunteers were receiving plerixafor doses above that to be recommended in the product label.
- Syncope in the five healthy volunteers occurred in the context of abdominal cramping, diarrhea, and emesis, suggesting it may have been a secondary event.
- Two of the five healthy volunteers were re-challenged without recurrent symptoms.

- The Applicant adjudicated all the syncopal episodes reported in the safety database as being unrelated to study drug.
- There is no reason to believe *a priori* that healthy volunteers should be more at risk for drug-induced syncope than patients with cancer, yet their incidence of syncope was higher than that of cancer patients.

**Recommendation**
Information regarding plerixafor-induced syncope should be included Section 6 (*Adverse Reactions*) of the product label. The risk does not rise to the level where an entry in Section 5 (*Warnings and Precautions*) is required. This reviewer recommends the following language:

*Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following subcutaneous injections. In Mozobil oncology and healthy volunteer clinical studies, less than 1% of subjects experienced vasovagal reactions following subcutaneous administration of Mozobil doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of Mozobil administration. Because of the potential for these reactions, appropriate precautions should be taken.*

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/s/
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Michael Brave
12/3/2008 11:13:11 AM
MEDICAL OFFICER

Ann Farrell
12/10/2008 03:41:19 PM
MEDICAL OFFICER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** December 12, 2008

**TO:** NDA #22-311

**FROM:** Michael Brave, M.D.
Medical Officer, CDER/OND/DDOP

**SUBJECT:** The potential for plerixafor to mobilize tumor cells

**Introduction**

Plerixafor, a new molecular entity, is a hematopoietic stem cell mobilizer for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). An important consideration whenever autologous hematopoietic stem cell transplantation (HSCT) is performed for a hematologic malignancy is whether the transplanted product is likely to be contaminated by tumor cells, and whether this could affect outcomes such as progression-free survival (PFS), and overall survival (OS). The Applicant of NDA #22-311 submitted a White Paper discussing this issue with respect to plerixafor.

Most[1,2,3] but not all[4] published retrospective studies of autologous HSCT in MM suggest that the presence of detectable tumor cells in the transplanted product is associated with reduced PFS, OS, or both. In randomized controlled trials, tumor cell purging reduced levels of contamination of the stem cell product but had no demonstrable impact on PFS or OS.[5,6] Similarly, published studies in NHL appear inconclusive regarding whether the presence of detectable tumor cells in the autologous harvest are associated with reduced PFS or OS, and if so, whether they are directly responsible for or merely a marker for poor outcome.[7,8,9]

**Applicant-generated data**

The Applicant examined the potential for plerixafor to mobilize myeloma and lymphoma cells in Studies 2101, 2102, 2103, EU21, and 2112, 3101, and the compassionate use program.

1. Studies 2101 and 3101

   The Applicant retrospectively examined the apheresis products of eleven patients with NHL – three from the single arm Study 2101 and eight from the randomized Study 3101 – by polymerase chain reaction for the t(14;18) translocation. This translocation is found in approximately 80% of patients with follicular NHL and a third of patients with diffuse large B-cell lymphoma (DLBCL).

Six of the eight patients from Study 3101 had follicular lymphoma and the remainder had DLBCL. All three patients from 2101 had follicular lymphoma. Three of the eight patients in 3101 received G-CSF/plerixafor, and the other five received G-CSF/placebo. Patients had between one and four days of apheresis and mobilized between 0.70 and 10.12 $CD34^+$ cells/kg. A total of 50 analyses of apheresis products were performed on these 11 patients.

No apheresis product from any of the six NHL patients mobilized with G-CSF/plerixafor contained a detectable quantity of the major breakpoint for t(14;18). However, one of five patients (03-023) treated with G-CSF alone had detectable levels.

2. Study 2102

   Twenty patients with MM who previously failed to collect 5 x $10^6$ $CD34^+$ cells/kg were enrolled on 2102 and received G-CSF/plerixafor. The Applicant retrospectively analyzed the apheresis products from 10 of those 20 patients by flow cytometry (b) (4) plasma cells.

   No apheresis product was found to contain (b) (4) .

3. Study 2103

   The Applicant retrospectively analyzed pre- and post-plerixafor apheresis products from 10 of the 13 patients enrolled on Study 2103 by polymerase chain reaction for the major breakpoint for t(14;18) translocation. Six of the ten patients had follicular lymphoma, three had DLBCL, and the histology of one was unknown.

   No apheresis product contained a detectable quantity of the major breakpoint for t(14;18). One patient had 0.08% positive cells at baseline and none detected post-plerixafor. All other samples were negative pre- and post-treatment.

4. The Applicant retrospectively analyzed apheresis products of seven patients with MM from EU21 by allele-specific polymerase chain reaction at screening, after G-CSF treatment, and following plerixafor treatment. This study found that the addition of plerixafor did not increase the relative or total number of tumor cells over the amount present following administration of G-CSF.

5. Compassionate Use Program

Two patients in the CUP were thought to have previously undiagnosed plasma cell leukemia. One patient had circulating blasts prior to plerixafor administration, and following plerixafor administration, the number of circulating blasts increased. The second patient had 15% plasma cells in the apheresis product. Case report forms for these two patients are not available.

**Conclusion and recommendations**

Tumor cell mobilization by plerixafor has not been well studied. The available information is limited by imperfect methods of detecting circulating tumor cells and by short clinical follow-up. The possibility that plerixafor could mobilize tumor cells and that subsequent reinfusion of those tumor cells could contribute in some cases to disease relapse can not be ruled out. Because this represents a serious safety concern, the Applicant should study this area further.

My recommendation includes a review of the Sponsor's white paper which included a discussion of the fact that the risk of disease relapse due to re-infused plerixafor-mobilized tumor cells is relatively low. Three lines of evidence provide some reassurance of the safety of plerixafor-mobilized stem cells. First, patients in the G-CSF/plerixafor treatment arms of Studies 3101 and 3102 followed for up to 12 months following autologous HSCT showed no evidence of an increased risk of disease relapse compared to the G-CSF/placebo treatment arms. Second, the correlative data summarized above from Studies 2101, 2103, 3101, and EU21 show no evidence that plerixafor mobilizes MM or NHL cells. Third, published literature is unclear whether detectable tumor cells in the apheresis product directly contribute to relapse or are merely a marker of increased risk of relapse. The Applicant has fully agreed to comply with this Post-Marketing Requirement.

This reviewer recommends that the following language be incorporated into the approval letter:

1. *To* (b) (4) *follow* (b) (4) *3101 and 3102* (b) (4) *five years* (b) (4) .

[1] Gertz MA, Witzig TE, Pineda AA, et al. Monoclonal plasma cells in the blood stem cell harvest from patients with multiple myeloma are associated with shortened relapse-free survival after transplantation. Bone Marrow Transplant 1997;19:337-42.

[2] Kopp HG, Yildirim S, Weisel KC, et al. Contamination of autologous peripheral blood progenitor cell grafts predicts overall survival after high-dose chemotherapy in multiple myeloma. J Cancer Res Clin Oncol 2008 Oct 22 [e-pub ahead of print].

[3] Mitterer M, Oduncu F, Lanthaler AJ, et al. The relationship between monoclonal myeloma precursor B cells in the peripheral blood stem cell harvests and the clinical response of multiple myeloma patients. Br J Haematol 1999;106:737-43.

[4] Ho J, Yang L, Banihashemi B, et al. Contaminating tumour cells in autologous PBSC grafts do not influence survival or relapse following transplant for multiple myeloma or B-cell non-Hodgkin's lymphoma. Bone Marrow Transplant. 2008 Sept [e-pub ahead of print].

[5] Stewart AK, Vescio R, Schiller G, et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. J Clin Oncol 2001;19:3771-79.

[6] Bourhis JH, Bouko Y, Koscielny S, et al. Relapse risk after autologous transplantation in patients with newly diagnosed myeloma is not related with infused tumor cell load and the outcome is not improved by CD34+ cell selection: long term follow-up of an EBMT phase III randomized study. Haematologica 2007;92:1083-90.
[7] Sharp JG, Kessinger A, Mann S, et al. Outcome of high-dose therapy and autologous transplantation in non-Hodgkin's lymphoma based on the presence of tumor in the marrow or infused hematopoietic harvest. J Clin Oncol 1996;14:214-19.
[8] Williams CD, Goldstone AH, Pearce RM, et al. Purging of bone marrow in autologous bone marrow transplantation for non-Hodgkin's lymphoma: a case-matched comparison with unpurged cases by the European Blood and Marrow Transplant Lymphoma Registry J Clin Oncol 1996;14:2454-64.
[9] Blystad AK, Delabie J, Kvaløy S, et al. Infused CD34 cell dose, but not tumour cell content of peripheral blood progenitor cell grafts, predicts clinical outcome in patients with diffuse large B-cell lymphoma and follicular lymphoma grade 3 treated with high-dose therapy. Br J Haematol 2004;125:605-12.

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/s/
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Michael Brave
12/12/2008 03:50:34 PM
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Ann Farrell
12/12/2008 05:19:26 PM
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# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 22-311/SN-000 |
| Priority or Standard | Priority |
| Submit Date | June 16, 2008 |
| Received Date | June 16, 2008 |
| PDUFA Goal Date | December 16, 2009 |
| Reviewer Name | Michael Brave, M.D. |
| Review Completion Date | November 21, 2008 |
| Established Name | Plerixafor |
| (Proposed) Trade Name | Mozobil™ |
| Therapeutic Class | CXCR inhibitor |
| Applicant | Genzyme Corporation |
| Formulation | Injectable solution |
| Dosing Regimen | In combination with granulocyte-colony stimulating factor |
| Indication | To enhance the mobilization of hematopoietic stem cells for collection and subsequent transplantation |
| Intended Population | Adults with non-Hodgkin's lymphoma or multiple myeloma |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The clinical review team recommends regular approval of plerixafor in combination with granulocyte-colony stimulating factor (G-CSF/plerixafor) to mobilize hematopoietic stem cells (HSC) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

## 1.2 Risk Benefit Assessment

The efficacy database for this application consisted of primary data from two randomized, placebo-controlled trials in patients with NHL (Study 3101) and MM (Study 3102) plus corroborative support from phase 2 studies in patients with NHL and MM (Study 2101) and Hodgkin's disease (HD; Study 2106). The safety database was composed of patients from those four studies plus eight single-arm, open-label studies of multiple doses of plerixafor with or without G-CSF in patients with NHL, HD, and/or MM (2101, 2102, 2103, 2105, 2106, 2108, 2109, C201, and EU21), one single-arm open-label study of G-CSF/plerixafor in poor mobilizers with malignancies (2112), two studies of patients with malignancies undergoing mobilization with G-CSF/plerixafor plus chemotherapy (2104) or rituximab (2113), one study in renally impaired patients (1101), and one study in patients with the human immunodeficiency virus (HIV; 2001).

Study 2101 enrolled 25 patients age 18 to 75 years with NHL or MM in first or second complete or partial remission who were eligible for autologous HSCT. It had a crossover design with the primary objective to evaluate the difference in the number of $CD34^+$ cells/kg collected with G-CSF/plerixafor compared to G-CSF alone. Patients with NHL had a mean average daily $CD34^+$ collection of $2.9 \times 10^6$ cells/kg with G-CSF/plerixafor, compared to $1.0 \times 10^6$ cells/kg with G-CSF alone ($p < 0.001$, paired t-test). Patients with MM collected a daily average of $6.6 \times 10^6$ $CD34^+$ cells/kg with G-CSF/plerixafor, compared to $2.5 \times 10^6$ cells/kg with G-CSF alone ($p = 0.025$, paired t-test).

Study 2106 was designed to determine the proportion of patients with HD who collected ≥ $5 \times 10^6$ $CD34^+$ cells/kg with G-CSF/plerixafor. The median number of $CD34^+$ cells collected was $6.9 \times 10^6$/kg. Fifteen of 22 patients (68%) succeeded in meeting the primary efficacy endpoint of collecting a total of ≥ $5 \times 10^6$ $CD34^+$ cells/kg.

Study 3101 randomized 298 patients with NHL who were planning to undergo autologous hematopoietic stem cell transplantation (HSCT) to G-CSF/plerixafor versus G-CSF plus placebo (G-CSF/placebo). The primary endpoint was the collection of $\geq 5 \times 10^6$ $CD34^+$ cells/kg within 4

apheresis days. Secondary endpoints were the percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the number of apheresis days required to reach $\geq 5 \times 10^6$ $CD34^+$ cells/kg, time to neutrophil and platelet engraftment, and the percentage of patients with durable engraftment at post-transplant Day 100, 6 months, and 12 months.

The combination arm showed statistically significant improvement in the primary endpoint and all secondary endpoints. Eighty nine (59%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $\geq 5 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 29 (20%) patients randomized to G-CSF/placebo ($P < 0.001$).

Study 3102 randomized 302 patients with MM who were planning to undergo autologous HSCT to G-CSF/plerixafor versus G-CSF/placebo. The primary efficacy endpoint was the collection of a total of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days. Secondary endpoints were the percentages of patients collecting $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days and $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the number of apheresis days required to reach $\geq 6 \times 10^6$ $CD34^+$ cells/kg, time to neutrophil and to platelet engraftment, and the percentage of patients with graft durability at 100 days, 6 months, and 12 months.

The combination arm showed statistically significant improvement in the primary endpoint and all secondary endpoints. One hundred and six (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($P < 0.001$).

The results of Studies 3101 and 3102 show that G-CSF/plerixafor provides an improvement over G-CSF alone in the mobilization of $CD34^+$ cells for autologous HSCT, a potentially life-saving procedure for patients with NHL and MM. The addition of plerixafor increased the proportion of patients who were able to collect a minimum transplantable cell dose (defined prospectively as $\geq 2 \times 10^6$ $CD34^+$ cells/kg) and an optimal cell dose for transplantation (defined prospectively as $\geq 5 \times 10^6$ $CD34^+$ cells/kg in $< 4$ apheresis days for NHL patients and $\geq 6 \times 10^6$ $CD34^+$ cells/kg in $< 2$ apheresis days of for MM patients). As a result, more patients treated with G-CSF/plerixafor underwent transplantation.

The addition of plerixafor reduced the median number of apheresis sessions required to collect an optimum transplantable cell dose compared to G-CSF/placebo. This reduction should theoretically allow more optimal use of apheresis machines and related resources, as well as reduce the morbidity associated with apheresis.

Approximately 99% of all transplanted patients achieved neutrophil and platelet engraftment. The number of days to neutrophil and platelet engraftment and graft durability rates through 12 months post-transplant were similar between the G-CSF/plerixafor and G-CSF/placebo groups. Among transplanted patients, the addition of plerixafor did not appear to affect the likelihood of graft durability at 100 days, at 6 months, or at one year.

The most common toxicities with G-CSF/plerixafor were gastrointestinal symptoms such as nausea, vomiting, and diarrhea. These symptoms were usually mild and rarely led to dose modification or study discontinuation.

The overall incidences and timing of AE and Grade 3 or 4 AEs were similar between treatment arms in the two randomized trials. The majority of SAEs occurred during and following the period when patients received ablative chemotherapy and were no longer receiving study drug. No deaths were attributed to plerixafor.

The most frequently reported (>10% in either treatment group) AEs during the administration of study drug were diarrhea, nausea, bone pain, fatigue, injection site erythema, headache, paresthesia, back pain, hypokalemia, arthralgia, catheter site pain and dizziness. Common AEs with an incidence ≥ 2% higher in the G-CSF/plerixafor group compared to G-CSF/placebo during Period 1 were diarrhea (38 vs. 17%), nausea (34 vs. 22%), vomiting (10 vs. 6%), flatulence (7 vs. 4%), injection site erythema (26 vs. 5%), injection-site pruritus (6 vs. 1%), and dizziness (10 vs. 6%). Common AEs with an incidence ≥ 2% higher in the G-CSF/placebo group compared to G-CSF/plerixafor during Period 1 were catheter site pain (14 vs. 11%), bone pain (36 vs. 32%), back pain (22 vs. 18%), extremity pain (7 vs. 5%).

There was no evidence that the risk of any toxicity was significantly higher in patients of any particular age group, gender, or race. Although no racial or ethnic groups were excluded from the randomized studies, most patients (87%) were Caucasian. The safety and efficacy of plerixafor in persons under age 18 and in pregnant or breast feeding women has not been established. Because of preclinical teratogenicity findings, plerixafor will be characterized pregnancy Category D.

## 1.3 Recommendations for Postmarketing Risk Management Activities

None

## 1.4 Recommendations for Postmarketing Studies or Trials

1. In accordance with ICH E14, a thorough QT study is ongoing (Protocol MOZ00707) to evaluate the effect of single therapeutic and supratherapeutic doses of plerixafor (0.24 and 0.4 μg/kg, respectively) on cardiac repolarization in healthy volunteers. The final study report should be submitted upon its completion.

2. Plerixafor has not been screened *in vitro* to assess whether it is a substrate or inhibitor of P-glycoprotein. The Applicant should perform such *in vitro* screen. Depending on the results, an *in vivo* drug-drug interaction study may be needed.

3. The currently proposed body weight adjusted dosing of plerixafor resulted in lower exposure to plerixafor in patients with low body weight compared to patients with higher

body weights. This decreased exposure was associated with decreased efficacy in patients with low body weight. In a logistic regression analysis, both low body weight and low $CD34^+$ baseline cell counts were predictors of poor $CD34^+$ cell mobilization with G-CSF/plerixafor. The applicant should design, conduct and submit a clinical study to optimize dosing in NHL patients with low exposure and low baseline $CD34^+$ count. The applicant should compare the results to the currently proposed dose and dosing schedule. Consideration should be given baseline $CD34^+$ count, and flat dosing regimens. The applicant should conduct sparse PK sampling and measure $CD34^+$ counts at time points similar to those in Study 3101. This protocol should be submitted to the division for review by February 1, 2009. The protocol should be initiated by July 2009, and the study should be completed by July 2010 and submitted to the Agency by October 2010.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Plerixafor is a small molecule (molecular weight = 503) bicyclam derivative that selectively and reversibly binds the CXCR4 chemokine receptor, blocking its cognate ligand, stromal cell derived factor 1α (SDF-1, also known as CXCL12). SDF-1 is a lymphocyte and monocyte chemoattractant expressed constitutively on several tissues such as brain, nerve, thymus, heart, lung, liver, pancreas, kidney, spleen, and gastrointestinal tract. In the bone marrow, SDF-1 is produced primarily by osteoblasts and its concentration gradient is important for HSC homing and anchoring in the bone marrow. The CXCR4 receptor is a 7-transmembrane G-protein expressed on the surface of most hematopoietic stem cells (HSCs), hematopoietic progenitor cells (HPCs), endothelial progenitor cells, several types of cancer cells, most T-lymphocyte subsets, all B cells and monocytes, and weakly on natural killer cells. The pro-inflammatory cytokine IL-4 up regulates CXCR4 expression, whereas the anti-inflammatory cytokine IL-10 down regulates CXCR4.

HSCs are defined as uncommitted cells capable of self-renewal, differentiation into specialized cells, and reconstitution of bone marrow when administered to patients following myeloablative therapy. HSC are characterized by expression of the CD34 antigen.

An early step in hematopoiesis is the differentiation of a HSC to a HPC further down a particular haematopoietic lineage pathway. HPC can be isolated and characterized *in vitro* by colony forming assays as colony forming units-granulocyte macrophage (CFU-GM), burst forming units-erythroid (BFU-E), and colony forming units-granulocyte, erythroid, megakaryocyte, macrophage (CFU-GEMM).

Plerixafor reversibly inhibits the binding of SDF-1 to CXCR4. This results in the release of HSC, HPCs and mature leukocytes from the marrow to the peripheral blood where they can be

collected for transplantation. Plerixafor primarily affects stem cell trafficking, and unlike hematopoietic growth factors, does not affect cell proliferation.

## 2.2 Currently Available Treatments for Proposed Indications

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) is an important therapeutic option for patients with MM and advanced or treatment-refractory NHL. The European Group for Blood and Marrow Transplantation reported that patients with NHL or MM accounted for 45% of the 310,455 autologous transplants performed between 2000 and 2007.[1]

Peripheral blood is the most commonly used source of hematopoietic progenitor cells for autologous transplantation.[2] Its advantages over bone marrow include not requiring general anesthesia, shorter duration of neutropenia and thrombocytopenia, more rapid immune reconstitution, and lower incidence of infectious complications and mortality.[3,4,5,6,7]

During steady-state homeostasis, less than 0.05% of peripheral blood leukocytes express the putative HSC marker CD34. HPCs must therefore be "mobilized" from the bone marrow, where they normally reside, to the peripheral blood in order to be collected for transplantation.

Time to post-transplant engraftment and the long-term success of transplantation correlate with the number of $CD34^+$ cells infused over the range of 2 to 5 x $10^6$/kg.[8,9,10,11] Current mobilization protocols allow approximately 80% of patients with NHL to mobilize a total number of $CD34^+$ cells in that target range within three apheresis sessions. The remainder require multiple mobilizations or may be unable to undergo autologous HSCT altogether.

The term "poor mobilizer" is sometimes used to denote patients who are unable to collect 1-2 x $10^6$ $CD34^+$ cell/kg within two consecutive large-volume aphereses. Such patients tend to be older, more heavily pre-treated and have more extensive disease. Poor mobilization is an independent predictor of shorter progression-free survival (PFS) and overall survival (OS) following transplantation.[12,13,14] At the other end of the spectrum, the ability to collect ≥ 8 x $10^6$ $CD34^+$ cells/kg ("super mobilization") predicts superior OS.[15]

### 2.2.1 Myelosuppressive chemotherapy

During the recovery phase after cytotoxic chemotherapy, circulating HSC numbers increase in proportion to the severity and duration of myelosuppression. Chemotherapeutic agents such as cyclophosphamide were the first clinically useful means of hematopoietic progenitor cell mobilization.[16] The main limitations are complications from neutropenia and thrombocytopenia and the unpredictability of the timing of apheresis. With the advent of hematopoietic growth factors it is no longer necessary to use chemotherapy alone for mobilization.

### 2.2.2 Hematopoietic growth factors

G-CSF and granulocyte-macrophage colony stimulating factor (GM-CSF) are the only drugs currently approved for autologous stem cell mobilization. In practice, G-CSF is almost always used,[17] and there is little benefit to adding GM-CSF.[18] Three forms of G-CSF are available: filgrastim (non-glycosylated *E. coli*-derived), lenograstim (glycosylated, from Chinese hamster ovary cells), and pegfilgrastim. Progenitor cell mobilization peaks in approximately five days at five- to ten-fold above baseline and is dose-dependent over G-CSF doses of 3 to 10 μg/kg/day.[19] The use of hematopoietic growth factors for HSC mobilization has shortened post-transplant neutrophil and platelet recovery times and reduced associated morbidity.[20]

### 2.2.3 Myelosuppressive chemotherapy plus hematopoietic growth factors

The combination of myelosuppressive chemotherapy with a hematopoietic growth factor results in higher $CD34^+$ cell yields compared to mobilization using either component alone and may further shorten post-transplant hematopoietic recovery.[21,22,23,24,25] However, the addition of myelosuppressive chemotherapy prolongs the mobilization procedure and entails risks.

## 2.3 Availability of Proposed Active Ingredient in the United States

Plerixafor is available for patients who have previously failed other mobilization regimens through a Single Patient INDs and a Compassionate Use Protocol.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Plerixafor is the first CXCR4 inhibitor, so there are no other approved drugs in this class.

G-CSF and GM-CSF are approved for this indication. Frequent adverse effects of G-CSF and GM-CSF are bone pain, fatigue, and headache. G-CSF causes transient spleen enlargement,[26,27] and spontaneous splenic rupture has been reported.[28,29] Rare complications include thrombosis, flare of autoimmune disease, and precipitation of sickle-cell crisis. Transient neutropenia and thrombocytopenia usually follow apheresis.[30]

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

April 1, 2002 — IND # 55,851 was transferred within the FDA from the Division of Antiviral Drugs to the Division of Drug Oncology Products.

April 7, 2004 — The Applicant and the FDA held an End-of-Phase 1 meeting. Discussion included the following:

- The optimal dose of AMD3100 to be used with G-CSF should be determined from the Phase 1 study AMD3100-1004 in cancer patients.

- The Agency recommends two randomized controlled studies for approval.
- The Applicant will submit concept sheets for each proposed phase 3 protocol.

May 25, 2004 The Applicant submitted concept sheets for phase 3 protocols in patients with NHL and in patients with MM.

Sept. 10, 2004 The Applicant and the FDA held an End-of-Phase 2 meeting. Discussion included the following:

- Safety data from phase 1 and phase 2 studies conducted to date and from the Compassionate Use Program were sufficient to proceed to phase 3 studies.
- Studies 3101 and 3102 could potentially support an NDA.
  - Reporting toxicity using WHO criteria is acceptable.
  - Patients for whom selection or purging of the apheresis product is planned or who have received radio-immunotherapy should be ineligible.
  - A central laboratory should be used for the CD34 assay.
  - The NDA may be filed with 100 day graft durability data. Six month data should be provided at the 120 day safety update. One year data should be provided for all patients at the completion of the trial.
- Since patients with MM on dialysis are eligible for transplantation, it would be useful to know how to dose plerixafor in that population.
- Plerixafor should be studied in children.

Sept. 20, 2004 The FDA received a request for Special Protocol Assessments (SPA) of Studies 3101 and 3102.

Oct. 26, 2004 The FDA received the Oncology Drug Advisory Committee consultant's review of the SPAs.

Nov. 29, 2004 The FDA issued responses to the SPAs for Studies 3101 and 3102. Comments included the following:

- The proposed primary endpoints were acceptable.
- The primary analysis should be performed on the intent-to-treat (ITT) population, where a 20% improvement in the primary endpoint would be an appropriate goal.
- The proposed sample sizes appeared appropriate.
- The safety reporting plan appeared acceptable pending review of the DSMB charter. The Applicant should consider following NIH DSMB guidelines.
- The exact indication would be a review issue.
- Reasons why patients were discontinued or excluded from per-protocol analyses should be well-documented. Excluded patients should be

identified prior to unblinding.

- The protocol did not specify a $CD34^+$ cell dose for transplantation, and indicated that some harvested cells may be cryopreserved for later use. Comparisons of hematopoietic recovery between arms should be corrected for the dose of cells administered.
- Unstratified analyses are preferred for all efficacy endpoints because the number of study centers (up to 30) is relatively large.
- The log-rank test is preferred for analysis of secondary time-to-event endpoints.

Mar. 10, 2005 The Applicant submitted a Proposed Pediatric Written Request.

June 29, 2005 The FDA issued the Applicant a Written Request that two studies be conducted to establish the efficacy and safety of plerixafor in pediatric cancer patients. See Section 7.6.3 of this review for details.

July 13, 2005 DMETS and DDMAC found the proprietary name Mozobil acceptable from a promotional perspective.

Dec. 21, 2005 The FDA and the Applicant held a teleconference to negotiate details of the Pediatric Written Request.

April 19, 2006 The Applicant notified the FDA that sponsorship of IND #55,851 was to be changed from AnorMED to AnorMED of Genzyme.

July 25, 2006 The Applicant and the FDA held a CMC meeting. Please the CMC review of this application for details.

Mar. 22, 2007 The Applicant proposed that safety data from the Compassionate Use Program be incorporated into the NDA. The FDA agreed.

June 6, 2007 The Applicant and the FDA held a CMC meeting. Please the CMC review of this application for details.

Oct. 1, 2007 The Applicant and the FDA held a pre-NDA meeting. Discussion included the following:

- Due to the different study designs and patient populations investigated in the studies supporting efficacy (3101, 3102, 2101, and 2106), efficacy data should be presented separately instead of pooled.
- All data sets used to support PK claims should be included (studies 1002, C201, 2106 and 1101).
- The NDA may be filed with 100 day graft durability data from the Phase III studies. Six month data should be provided with or prior to the 120 day safety update, and one year data at the completion of the trial.

Jan. 8, 2008 The FDA provided feedback regarding proposed protocol MOZ00707 entitled *A phase 1, Randomized, Placebo- and Positive-Controlled, Crossover Study to Determine if Plerixafor Delays Cardiac Repolarization as Determined by the Measurement of QT/QTc Interval in Healthy Normal Subject*s". See Clinical Pharmacology review of this application for details.

Feb. 20, 2008 The FDA received a proposed Treatment Protocol entitled, *Expanded Access Study of Plerixafor and G-CSF for the Mobilization and Collection of Peripheral Blood Stem Cells for Autologous Stem Cell Transplantation in Patients with Non-Hodgkin's Lymphoma, Hodgkin's Disease or Multiple Myeloma* (SN-0546).

April 24, 2008 The FDA granted the Applicant permission to proceed with the proposed Treatment Protocol in accordance with the United States Code of Federal Regulations (CFR) 21 §312.34 and 312.35.

## 2.6 Other Relevant Background Information

### 2.6.1 Non-Hodgkin's lymphoma

NHL is a heterogeneous group of lymphoproliferative malignancies which will be diagnosed in an estimated 66,120 new patients and cause 19,160 deaths in the United States in 2008.[31] Like Hodgkin's disease (HD), NHL usually originates in lymphoid tissues; however, its clinical course is more variable than that of HD, including a greater predilection to disseminate to noncontiguous and extranodal sites.

NHL can be divided into indolent and aggressive histologic subtypes. Indolent subtypes have a relatively good prognosis with a median survival as long as 10 years, but usually are not curable in advanced clinical stages. Aggressive types have a shorter natural history but often can be cured with intensive combination chemotherapy regimens.

Autologous HSCT has been investigated as consolidation therapy for patients with NHL in several clinical settings. This modality is most frequently considered for patients with primary refractory[32] forms of aggressive NHL and for patients with indolent NHL in second or subsequent remission.[33,34,35]

### 2.6.2 Multiple myeloma

MM is the prototypic tumor of terminally differentiated plasma cells. With a yearly incidence of nearly 20,000 patients in the United States, MM accounts for about 10% of hematologic malignancies, and is the second most frequent hematologic malignancy among older

individuals.[36] Prognostic factors include disease stage, renal and hematopoietic function, serum $\beta_2$-microglobulin and albumin levels, and cytogenetics.[37,38]

The malignant plasma cells in MM produce a patient-specific monoclonal immunoglobulin heavy and/or light chain (paraprotein) that is detectable by serum and/or urine electrophoresis in all patients except 1-2% with non-secretory disease. Clinical and laboratory features include bone pain, anemia, renal insufficiency, hypercalcemia, increased susceptibility to infection, and constitutional symptoms. Less common complications include spinal cord compression by extramedullary plasmacytomas or vertebral collapse, peripheral neuropathy, amyloidosis and hyperviscosity syndrome.

Median OS is approximately five years with contemporary therapeutic approaches. First-line chemotherapeutic options include melphalan and prednisone;[39] and dexamethasone, either alone or in combination with vincristine and doxorubicin,[40] thalidomide,[41] lenalidomide;[42] and bortezomib.[43]

The failure of conventional therapy to cure MM has led to the investigation of high dose chemotherapy followed by autologous HSCT. Investigators of select trials have reported improved PFS and/or OS following single and tandem autologous HSCT compared to either conventional-dose chemotherapy or allogeneic HSCT.[44,45,46,47]

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

All clinical study endpoints were predefined in data analysis plans. Data were double-entered into the database and verified against source documents so that any data entry errors could be detected and corrected.

Datasets in general corresponded to submitted CRFs. Safety and efficacy appeared reasonably uniform with respect to site of patient enrollment. No one site or group of sites appeared to drive the overall results.

The Applicant submitted all efficacy and safety data in raw form. As a result, the FDA was able to verify the claimed efficacy and safety findings.

## 3.2 Compliance with Good Clinical Practices

The Applicant provided the following assurances regarding clinical study conduct:

- Investigators were responsible for ensuring that the registration studies were conducted in conformance with CFR 21 regarding human research (including parts 50 and 56 concerning informed consent and IRB regulations), ICH Harmonized Tripartite Guidelines for Good Clinical Practices 1996, and the Declaration of Helsinki 2000.

- An independent Data Safety Monitoring Board (DSMB) oversaw each registration study. Each DSMB was composed of 3 physicians with training in hematology and medical oncology and experience in the conduct and assessment of clinical trials. Their primary role was to evaluate any safety issues arising from the study and to arbitrate continuation or stopping of the trial, or any changes to the conduct of the study, for the protection of the patients.

- Prior to initiation at individual sites, all clinical protocols, subsequent amendments, and informed consent documents were reviewed and approved by a local Institutional Review Board, per CFR 21 Part 56.

- Investigators explained to patients the nature of each proposed study, its purpose, the procedures involved, expected duration, and potential risks and benefits. Patients were informed that study participation was voluntary and that they could withdraw consent at any time without affecting their subsequent medical treatment or relationships with the treating physician. Informed consent was given via a standard written statement in non-technical language.

***Reviewer's comments:***

1. *The informed consent documents adequately explained the voluntary nature of the trials and their risks and benefits.*
2. *Protocol violations appeared well balanced between treatment arms.*
3. *No clustering of efficacy or AE findings seemed to be site-specific.*
4. *The clinical trials were conducted in accordance with accepted ethical standards.*

The Clinical Review Team consulted the FDA Division of Scientific Investigation (DSI) and suggested inspection of three clinical study sites based on numbers of patients enrolled and numbers of major protocol violations. The DSI found in general that the study records appeared in order without underreporting of AEs and that the data were acceptable in support of the application. See the DSI report for additional detail.

## 3.3 Financial Disclosures

The Applicant submitted Form 3453 with the names of 63 Primary Investigators who, for at least one of the clinical registration studies, received no compensation that could have affected the study outcome and had no any proprietary interest in the product.

Eleven investigators submitted 3455 forms, per CFR Part 54, disclosing financial interests in one or more of the clinical registration studies. Seven (b) (6)

(b) (6) indicated having entered into a financial arrangement with the sponsor of one or more studies, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by its outcome. Nine (b) (6) indicated having received significant payments on or after February 2, 1999 from the Sponsor of one or more studies, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. One investigator (b) (6) indicated having a proprietary interest in the product being tested.

Despite due diligence, the Applicant could not obtain financial disclosure from seven Investigators and 72 Sub-investigators.

***Reviewer's comment:*** *The following features of the phase 3 studies minimized the potential for the financial arrangements disclosed to have biased the plerixafor development program:*

- *The studies were double-blinded and placebo-controlled.*
- *Patients were randomized centrally.*
- *The studies were conducted at multiple centers.*
- *Efficacy endpoints were assessed by a central laboratory.*
- *The statistical analyses were prospectively defined, and analyses of the primary endpoints were based on the ITT populations.*

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Plerixafor is a small-molecule bicyclam derivative. The commercial formulation is a sterile, preservative-free, clear to pale yellow, isotonic, 20 mg/mL solution for subcutaneous injection. Each single-use 2 ml glass vial is filled to deliver 1.2 ml of solution containing 24.0 mg of plerixafor and 5.9 mg of sodium chloride in water for injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required. Please see the CMC review for additional details.

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

The CXCR4 receptor is highly conserved across mammalian species, as demonstrated by CXCR4-related activity in receptor studies *in vitro* using mouse and dog cells and *in vivo* by plerixafor-induced transient leukocytosis observed in all animal species evaluated (mouse, rat, dog, and monkey).

Plerixafor octahydrochloride was the drug substance used in some earlier conducted preclinical studies. Because the free base form had an improved impurity profile, the free base was used for most preclinical and all clinical studies. With pH adjustment towards neutrality in aqueous solution, plerixafor free base and plerixafor octahydrochloride both become partially protonated to the pharmacologically active +4 state.

### 4.3.1 Safety Pharmacology studies

The Applicant conducted a series of *in vivo* safety pharmacology studies to evaluate the potential for plerixafor to elicit adverse cardiovascular, neurologic, and respiratory effects.

Plerixafor exhibited low to moderate affinity for calf $\alpha_1$ and $\alpha_2$ adrenergic and dopamine $D_2$ receptors ($pK_i$ 6.2, 5.9, and 5.5, respectively). An interaction with rat adrenergic receptors was also observed when plerixafor was tested at a single concentration (6 μM; 3 μg/ml), with 40 to and 41% inhibition of $\alpha_1$ and $\alpha_2$ receptor binding, respectively.

Potential effects of plerixafor on CNS function were evaluated in an Irwin test in rats. Between 30 minutes and two hours post-dose, rats administered plerixafor at 20 mg/kg (approximately 6.7 times the recommended human dose) displayed CNS depressant-like effects when not stimulated (e.g., passivity, decreased motor activity, apathy, decreased alertness) and CNS stimulant-like effects (e.g., fast respiration, fearfulness, aggression) when stimulated.

Potential effects of plerixafor on respiratory function were evaluated by plethysmography in conscious rats. The SC administration of plerixafor at 10 mg/kg caused a transient decrease in tidal volume at 30 minutes post-dose. A dose of 20 mg/kg (approximately 6.7 times the recommended human dose) caused a decrease in respiratory rate between 30 and 120 minutes and a decrease in tidal volume at 30 minutes.

Potential effects of plerixafor on cardiovascular function were evaluated by *in vitro* binding and inhibition studies for selected receptors and enzymes. The $IC_{50}$ for angiotensin converting enzyme was 2.5 μM (1.3 μg/ml). Plerixafor at 6 μM (3.0 μg/ml) produced an agonist response in neuropeptide $Y_2$ and $Y_3$ assays. Plerixafor at 2 and 20 μg/ml produced dose-dependent inhibition of angiotensin II-induced contractions in an aortic smooth muscle preparation, which were abolished by the addition of free $Ca^{+2}$ at 4 mM. No inhibition of the hERG $K^+$ channel was observed up to 50 μg/ml which is 50-fold greater than the $C_{max}$ in humans at the recommended clinical dose.

In a cardiovascular safety study, two conscious dogs received plerixafor as a continuous IV infusion for eight hours at rates targeted to deliver steady state plasma levels of 7.5 or 15 μg/ml. No changes in ECG, heart rate, blood pressure, or cardiovascular function were observed at the lower infusion rate (actual plasma concentration, 7.0 to 7.4 μg/ml). At the higher infusion rate (actual plasma concentrations, 10.9 to 14.3 μg/ml), increases in heart rate were noted soon after initiation of the infusion, and increased blood pressure was noted at approximately 3 hours with the onset of adverse clinical signs (hypoactivity, tremors, uncoordinated movement, recumbency, labored breathing). The more severely affected dog had clinical signs sufficiently severe to prematurely stop dosing and an elevated pulmonary wedge pressure for approximately 1.75 hours after cessation of dosing. Electrocardiography showed physiologic PR shortening and no change in QRS duration or QTc interval.

### 4.3.2 Toxicology studies

The Applicant conducted a series of animal toxicology studies summarized below. For additional detail, see the Pharmacology/Toxicology review of this application.

#### 4.3.2.1 Studies in rats

Single IV or SC injections induced a rapid onset (< 2 hour) of neuromuscular signs including hypoactivity, dyspnea, spasms, recumbency, abnormal posture, and uncoordinated movements, with complete recovery usually within four hours. The no-observed adverse effect level (NOAEL) was 2 mg/kg SC. The lowest SC doses producing deaths in mice and rats were 4.7 and 27 fold higher, respectively, than the equivalent recommended human dose.

The SC injection of a single 10 mg/kg dose produced a peak leukocytosis at 6 hours, due primarily to myeloid cells (neutrophils, monocytes, eosinophils, and basophils) with a trend for increased lymphocyte counts. The SC injection of single doses of 10 to 40 mg/kg did not significantly decrease plasma total or ionized calcium levels but affected parameters important in calcium homeostasis (e.g., blood pH, albumin levels, and inorganic phosphorus). Plasma magnesium levels were increased at 1 hour and decreased at 2 and 4 hours post dose. Once daily SC dosing at 9.49 mg/kg for seven days caused hypocalcemia, hypomagnesemia, and increased urinary excretion of $Ca^{2+}$, $Zn^{2+}$, and $Cu^{2+}$.

Daily dosing for four weeks produced a dose-dependent leukocytosis at 1.9 mg/kg/day. At 7.6 mg/kg/day, adverse clinical signs were observed between 15 minutes and one hour, including twitching, labored respiration, recumbency, and hyper-excitability. Also at 7.6 mg/kg/day hypomagnesemia and increased urinary excretion of calcium and magnesium were observed. At the MTD of 11.4 mg/kg/day, there was extramedullary hematopoiesis, thymic atrophy and decreased bone mineral density. Except for evidence of irritation at the injection site, there were no positive histopathology findings, and all adverse findings were reversible. Mortality during Weeks 1 to 4 occurred at the 15.2 mg/kg/day dose level.

Twice daily dosing for four weeks produced a dose-dependent leukocytosis at 2 mg/kg BID. At the MTD of 12 mg/kg BID, hypomagnesemia, increased urinary calcium excretion, and increased serum ALT levels were observed. Except for irritation at the injection site, there were no positive histopathology findings. Mortality was observed on Day 7 in one rat at 24 mg/kg BID.

4.3.2.2 Dog studies

Four-week daily dosing caused diarrhea, reduced food consumption, reduced body weight gain, and skin thickening at injection sites at 1.0 mg/kg/day. Mild tachycardia was noted for up to 4 hours post dose on Days 1 and 22, associated with a shortened QT interval in dogs at 4.0 mg/kg/day. Males at 4.0 mg/kg/day produced a higher volume of low specific gravity urine. All treatment-related changes returned to baseline during a two-week recovery period. No changes in water consumption, neurological examinations, ophthalmology, hematology, serum chemistry, organ weights, or histopathology were noted, and no deaths occurred.

Twice daily dosing for four weeks caused reduced food consumption, decreased body weight gain, hypomagnesemia, and increased urinary calcium excretion during the first week at 0.75 mg/kg/day, and leukocytosis at the end of treatment (primarily neutrophils). All changes returned to baseline during a two-week recovery period. No changes in water consumption, neurological exams, ophthalmology, electrocardiography, bone marrow, organ weights, or histopathology were noted. The MTD was determined to be 4 mg/kg BID. No mortality was observed in the study.

4.3.2.3 Reproductive Toxicity

A GLP embryo-fetal development study was conducted in rats administered plerixafor SC at doses of 0, 0.5, 3, or 15 mg/kg/day for 12 days from gestation day 6 to 17. At 15 mg/kg/day, there was reduced food consumption, and less body weight gain in dams, and an increased incidence of resorption, low fetal weight, retarded skeletal development, and fetal abnormalities. The NOAEL for embryo-fetal development was 3 mg/kg/day, which is approximately twice the recommended human dose. A NOAEL for maternal toxicity was not reported. Because of the positive findings in the rat embryo-fetal study, a rabbit study was not conducted.

***Reviewer's comment:*** *Based on these results, plerixafor administration during pregnancy is a potential risk to the fetus.*

The potential effects of plerixafor on male and female fertility or on post-natal development were not evaluated in specific nonclinical studies. However, distribution of plerixafor to the rat testis was low in tissue distribution studies, and no histopathological evidence of toxicity to male or female reproductive organs was observed in rats or dogs dosed with plerixafor daily or BID for 28 days.

***Reviewer's comment:*** *The effect of plerixafor on human fertility is unknown. The effect of plerixafor on male or female fertility was not studied in designated reproductive toxicology studies.*

4.3.2.4 Genotoxicity

Plerixafor was not genotoxic in a bacterial mutation assay using *Salmonella typhimurium,* a chromosomal aberration test using V79 CHO cells, and an *in vivo* rat micronucleus test.

4.3.2.5 Carcinogenicity

Carcinogenicity studies have not been conducted.

4.3.2.6 Additional Toxicology Studies

In a non-GLP intradermal irritation study in rabbits, plerixafor was a slight irritant at ≥ 3 mg/mL in a hydrochloride preparation and at ≥ 25 mg/mL in a citrate preparation. Local irritation was also observed in repeat-dose SC toxicity studies.

In a non-GLP splenic plaque-forming assay, no inhibition of primary IgM antibody to sheep red blood cells was observed in splenic cells collected from rats administered plerixafor at SC doses of 5.1 and 12.7 mg/kg/day for 4 days.

In a GLP study, plerixafor incubated *in vitro* in human whole blood at a final concentration of 0.2 μg/ml produced no significant hemolysis or flocculation.

4.3.3 Potential clinical toxicities of plerixafor predicted by preclinical models

4.3.3.1 Neuromuscular

The dose-limiting toxicity and presumed cause of death associated with SC administration of single and repeat daily doses of plerixafor in rats and dogs was the rapid onset (~30 to 60 min) of transient (~4 hours) clinical signs of apparent neuromuscular origin. These included apathy, ataxia, diarrhea, emesis, labored breathing, recumbency, decreased activity, and muscle twitches, and at higher doses progression to tremors and convulsions.

Because plerixafor does not significantly cross the blood brain barrier, this toxicity was more likely of peripheral than central origin. Although changes in plasma magnesium levels and biochemical parameters associated with calcium homeostasis (e.g., plasma albumin, total protein,

inorganic phosphorus, and pH) were observed in rats, there was no significant lowering of ionized plasma calcium levels.

The time course of this toxicity in single-dose studies suggested a relationship to plerixafor plasma $C_{max}$ rather than to total exposure. In contrast, in repeat daily dose studies, signs were typically not evident until after approximately 5 to 8 doses had been administered, and became dose-limiting around study day 8 or 10. No significant accumulation of plerixafor blood levels was observed. These findings suggest a lowering toxicity threshold with repeated daily dosing.

With 4-week daily dosing, neuromuscular signs in rats and dogs were first apparent at doses ~2 to 4 fold lower than their single administration MTD values of ~12 mg/kg (72 mg/m$^2$) in rats and 4 mg/kg (80 mg/m$^2$) in dogs. These MTD values are ~7.7 to 9 fold above the recommended human dose of 8.9 mg/m$^2$.

4.3.3.2 Gastrointestinal

Diarrhea and emesis was observed in repeat-dose toxicity studies in dogs following SC injection of plerixafor at doses of 1 to 4 mg/kg. Diarrhea occurred at doses approximately 2.2 fold above the equivalent recommended human dose of 8.9 mg/m$^2$. No histopathological changes were noted in the gastrointestinal epithelium. No gastrointestinal toxicity was observed in any of the mouse or rat toxicity studies.

4.3.3.3 Respiratory

In a respiratory safety study in rats, a single plerixafor dose of 10 mg/kg induced a transient decrease in respiratory rate at 30 minutes. A dose of 20 mg/kg induced a decrease in respiratory rate at 30 and 120 minutes and a decrease in tidal volume at 30 minutes.

In single- and repeat-dose toxicity studies, dyspnea or bradypnea were observed at or near the maximum tolerated single SC or IV dose in mice and rats. The time-course of these signs was similar to that of the neuromuscular clinical signs, suggesting a relationship to plasma $C_{max}$ rather than to systemic exposure.

Difficulty breathing was also noted in repeat-daily SC dose studies in dogs, but only at non-tolerated dose levels. No histopathologic findings were noted in the lungs in any rat or dog study.

4.3.3.4 Cardiovascular

Plerixafor showed no significant inhibition of hERG current *in vitro* at concentrations approximately 50 times the plasma $C_{max}$ (1 μg/mL) in humans at the recommended clinical dose. *In vitro* receptor binding and enzyme inhibition studies showed inhibition of ACE and an agonist response in the neuropeptide $Y_2$ and $Y_3$ assays in the low micromolar range, the biological relevance of which is unknown.

In the main cardiovascular safety study in conscious dogs, the continuous IV infusion of plerixafor for 8 hours (targeted to produce a steady state blood level of 7.5 μg/mL) caused no changes in heart rate, cardiac function, or blood pressure. One of two dogs did not tolerate a higher infusion rate targeted to produce steady state plasma level of 15 μg/mL. An increase in heart rate soon after initiation of infusion, and an increase in systemic blood pressure concomitant with the onset of neuromuscular signs several hours later were observed in both dogs. An increase in pulmonary wedge pressure was noted in one dog. The only ECG change noted was physiologic rate-associated PR shortening; there were no effects on the QRS or QTc intervals.

Measurements of blood pressure and ECG waveforms on Days 1 and 22 for dogs in the 4-week once daily dosing GLP toxicity showed no changes at doses up to 4 mg/kg. Histopathological evaluations of the heart were negative.

#### 4.3.3.5 Urinary System

In 2- and 4-week repeat daily dose studies in rats and dogs, plerixafor caused hypocalcemia, hypomagnesemia, and increased urinary excretion of calcium, magnesium, copper and zinc at doses ~2 fold below their respective MTDs and ~4 fold higher than the recommended human dose of 240 μg/kg. A reduction in bone mineral content and volume was also observed in a 4-week once-daily repeat-dose toxicity study in rats at 11.4 mg/kg; those rats also experienced reduced food consumption and body weight gain. No change in serum copper or zinc was noted. No histologic changes were found in the kidney or bladder.

#### 4.3.3.6 Local Irritation

An intracutaneous irritation study in rabbits showed that plerixafor hydrochloride at concentrations of ≥ 3 mg/mL produced slight irritation. Local irritation at the SC injection site was also observed in repeat-dose toxicity studies in rats and dogs.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

See Section 2 of this review.

4.4.2 Pharmacodynamics

4.4.2.1 Molecular actions on the CXCR4 receptor

The Applicant conducted the following *in vitro* studies:

Using the CCRFCEM cell line which endogenously expresses CXCR4, plerixafor inhibited SDF-1α binding to CXCR4, and inhibited SDF-1-mediated G-protein activation, calcium flux, and chemotaxis ($IC_{50}$ values of 572 ± 190 nM, 651 ± 37 nM, 15.4 ± 4.4 nM, and 51 ± 17 nM).

In similar studies with cells expressing other chemokine receptors, plerixafor did not inhibit calcium flux by CXCR1, CXCR2, CXCR3, CCR1, CCR2b, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, or CCR9. In addition plerixafor did not inhibit the binding of leukotriene B4 (chemoattractant for granulocytes) to its receptor, BLTR.

Receptor mutagenesis studies showed that plerixafor acts on the CXCR4 receptor through binding to the negatively charged amino acids Asp171 and Asp262 with each of its cyclam moieties.

4.4.2.2 Hematopoietic cell mobilization

4.4.2.2.1 Preclinical findings

The Applicant conducted a series of *in vivo* studies characterizing the ability of plerixafor to mobilize murine HSC and HPC, and the ability of both human and murine plerixafor-mobilized cells to reconstitute recipient bone marrow after transplantation.

A single 5 mg/kg SC injection of plerixafor to C3H/HeJ mice induced peak mobilization of HPC one hour post dosing. No desensitization was seen with repeat daily dosing for three days.

Donor cells collected from plerixafor-treated C57B1/6 ($CD45.2^+$) mice competed with native bone marrow cells for engraftment in lethally irradiated transplant recipient B6.BoyJ ($CD45.1^+$) mice. Greater than 8-fold higher chimerism was observed with plerixafor-mobilized donor cells compared with a saline control.

Self-renewal of plerixafor-mobilized HSC was demonstrated using a secondary repopulating assay in which donor cells obtained from the competitively engrafted mice above were re-injected into lethally-irradiated secondary mice. All secondary mice survived with > 50 % engrafted cells of donor origin.

$CD34^+$ cells mobilized from healthy human volunteers administered plerixafor, G-CSF, or G-CSF/plerixafor plus repopulated the bone marrow of lethally irradiated NOD/SCID mice after eight weeks.

$CD34^+$ cells mobilized from plerixafor-treated dogs had the ability to repopulate the bone marrow following myeloablative total body irradiation. Neutrophils and platelets engrafted at medians of 8 and 25 days following autologous transplantation and 8 and 26 days following allogeneic transplantation.

In rhesus monkeys, engraftment measured by gene marking was observed within 14 days and persisted up to 32 months after transplantation.

Using a parabiotic mouse model it was shown that upon treatment with 5 mg/kg plerixafor, bone marrow cells transited from one mouse to the marrow of the partner mouse. When recipient mice were treated with plerixafor before transplantation, donor cell engraftment was higher compared with controls, suggesting that plerixafor-induced release of HSC cells from the bone marrow increased the number of vacant niches in the bone marrow available for donor cell engraftment.

#### 4.4.2.2.2 Pharmacodynamic effects in healthy volunteers

In Study 1002, a single dose of plerixafor generated dose-dependent increases in circulating $CD34^+$ cells, all HPCs types (CFU-GM, BFU-E, and CFU-GEMM), neutrophils, lymphocytes, monocytes, eosinophils and basophils, with peak effects between 6 and 9 hours for all dose levels. $CD34^+$ counts returned to baseline by 24 hours except at 240 μg/kg. Peripheral $CD34^+$ counts peaked 15-fold above baseline nine hours after a single 240 μg/kg dose. Three consecutive daily doses of 80 μg/kg induced similar increases in mean $CD34^+$ counts at 6 hours, returning to baseline levels prior to the next dose. Cell cycle analysis by $[^3H]$-thymidine incorporation revealed no significant change in the percentage of HPCs in S-phase.

In Study 1003, four days of G-CSF followed by plerixafor produced larger mean increases in peripheral blood $CD34^+$ cells, all HPCs, and total leukocytes than G-CSF alone. Four days of G-CSF followed by 160 mg/kg of plerixafor induced a four-fold peak increase in $CD34^+$ cell levels at nine hours. The same dose of plerixafor alone produced a peak increase of approximately three-fold at six hours. Four days of G-CSF followed by 240 mg/kg of plerixafor produced a peak increase in $CD34^+$ cells at 10 to 14 hours.

In Study 1005, single SC doses of 240 μg/kg plerixafor induced an average 11-fold increase in peripheral $CD34^+$ cell count at 4 hours. A single dose of 320 μg/kg induced a maximal 12.7-fold increase at 8 hours. All four subjects at 240 μg/kg and four of five at 320 μg/kg achieved peak $CD34^+$ cell counts > 20/μl at 8 to 10 hours. Single doses of 240 or 320 μg/kg induced an approximately 4-fold increase in total WBC counts. At 320 μg/kg, WBC counts peaked between 6 and 12 hours, remained slightly elevated at 24 hours, and returned to baseline by 48-hours. Cell cycling assays following a 240 μg/kg dose showed no significant change in the percentage of CFU in S-phase.

4.4.2.3 Non-hematopoietic cell mobilization

In animal models, plerixafor at pharmacologically relevant doses mobilized non-hematopoietic CXCR4 cell populations into the blood, including angiogenic cells (endothelial progenitors, monocytes, $CD34^+$ cells), immunomodulatory cells (lymphocytes, neutrophils, monocytes, eosinophils), and tumor cells (acute lymphoblastic leukemia, acute promyelocytic leukemia, Namalwa B lymphoblastoid cells). The functional capacity of these mobilized cells was demonstrated in animal models of transplantation, ischemic limb or myocardial injury, asthma or rheumatoid arthritis, and tumorigenesis, respectively.

4.4.3 Pharmacokinetics

4.4.3.1 Sources of PK data

Four clinical studies (1002, C201, 2106, and 1101) contributed PK data to this application (Table 1). Three additional studies (98-01, 2001, and 1005) included PK analyses; however, audits of (b) (4) undertaken by Genzyme and a third party (b) (4) identified deficiencies in the conduct and reporting of their results. Findings from these audits were consistent with those identified by FDA in a Warning Letter to (b) (6) . PK results from these studies were therefore not reviewed.

**Table 1. Clinical studies contributing PK data (reviewer's table)**

| Study | N | Plerixafor dose | G-CSF dose |
|---|---|---|---|
| Phase 1 Study of the Safety, Pharmacokinetic and Hematological Activity of One Dose of AMD3100 Administered by Subcutaneous Injection to Healthy Volunteers (AMD3100-1002) | 18 | 40, 80, 160, and 240 µg/kg | None |
| Treatment with AMD3100 in Non-Hodgkin's Lymphoma and Multiple Myeloma Patients to Increase the Number of Peripheral Blood Stem Cells When Given a Mobilizing Regimen of G-CSF (AMD3100-C201) | 13 | 240 µg/kg | 10 µg/kg for 4 days prior to plerixafor; 10 µg/kg with plerixafor |
| Treatment with AMD3100 Added to a Mobilizing Regimen of G-CSF to Increase the Number of Peripheral Blood Stem Cells in Patients With Hodgkin's Disease (AMD3100-2106) | 9 | 240 µg/kg | 10 µg/kg for 4 days prior to plerixafor; 10 µg/kg with plerixafor |
| A Phase 1 Study of the Safety, Pharmacokinetics, and Hematological Activity of AMD3100 (240 µg/kg) in Subjects With Renal Impairment (AMD3100-1101) | 23 | 240 µg/kg | None |

4.4.3.2 Absorption

Following SC administration in the rat and dog, plasma $C_{max}$ was reached in 30 to 60 minutes and bioavailability was 100%. Plerixafor exposure following SC administration was dose proportional within the ranges of 0.3 to 12.1 mg/kg for rats and 0.25 to 4 mg/kg for dogs.

In clinical studies 1002, C201, and 2106, plasma $C_{max}$ was reached about 30 minutes following SC injection and increased dose-proportionally over the range of 40 to 240 µg/kg. Study 1101 showed that renal failure did not affect plasma $C_{max}$.

4.4.3.3 Distribution

Tissue distribution studies in rats following SC administration demonstrated drug-derived material in the majority of tissues evaluated, with the exception of brain, muscle, pancreas, renal fat, salivary gland, spinal cord and testis. Elimination from most tissues occurred between 4 and 24 hours; however, retention of drug-derived material in bone marrow, cartilage, spleen, liver, and kidney was noted for up to 144 hours. At 168 hours, up to 30% of drug-derived material remained in the rat and the dog. Accumulation of drug-derived material in rats was observed following 7 days of once daily 1 mg/kg SC doses in kidney, liver, cartilage, bone marrow and spleen, despite no significant increase in plasma $C_{max}$ or AUC.

Protein binding of plerixafor ranged from 33% to 58% in rat, dog, and human plasma. Partitioning of plerixafor into rat, dog and human red blood cells was negligible (partition coefficients $\leq 0.20$).

In clinical studies C201 and 2106, in patients with lymphoma or MM, the mean steady-state $V_D$ ranged from 22.2 to 52 L.

4.4.3.4 Metabolism

Studies conducted *in vitro* with rat, dog and human microsomes and hepatocytes demonstrated that plerixafor is metabolically stable and not subject to hepatic metabolism. Plerixafor was also found to be stable in rat, dog and human whole blood.

In [$^{14}$C]-plerixafor *in vivo* studies conducted in rat and dog, non-parent components present in plasma and urine were attributed to copper complexes with plerixafor. The 1:1 and 2:1 ratios of $Cu^{2+}$:plerixafor observed were consistent two potential chelating sites on plerixafor, the two cyclam rings.

4.4.3.5 Elimination

Plerixafor was eliminated rapidly from the blood, with half lives in mice, rats, and dogs of 0.75, 0.90 – 1.16 and 1.58 hours, respectively. The elimination half-life in humans is 4.83 hours.

Following SC and IV administration in rat and dog, the majority of the radioactivity (63 to 72%) was excreted in the urine within 48 hours. Fecal elimination accounted for < 12% of total radioactivity in both species.

Clinical studies C201 and 2106 found the clearance of plerixafor in patients with lymphoma or MM to range from 2954 to 6360 mL/hour and the terminal half life to range from 2.7 to 11.7 hours. Following a 240 mg/kg dose to healthy volunteers with normal renal function, approximately 70% of the dose was excreted in urine as parent drug during the first 24 hours.

Study 1101 showed that compared to subjects with normal renal function, subjects with mild, moderate, or severe renal impairment had average respective increases in $AUC_{0\text{-}24\ h}$ of 21.7%, 51.4%, and 69.5%. The serum half life of plerixafor increased from 4.9 hours in subjects with normal renal function to 15.9 hours in those with severe impairment. Because of these findings, the Office of Clinical Pharmacology recommends a dose reduction of one-third (160 mcg/kg) across all body weights for patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min).

# 5 Sources of Clinical Data

The efficacy database for this application consisted of patients enrolled in two randomized, placebo-controlled trials (3101 and 3102) plus supportive data from two open-label studies in patients with NHL (2101) or MM (2106). The safety database was composed of patients from those four studies plus four studies assessing safety and PK in healthy volunteers (98-01, 1002, 1003, and 1005), eight single-arm, open-label studies of plerixafor with or without G-CSF in patients with NHL, HD, and/or MM (1004, 2102, 2103, 2104, 2105, 2108, C201, EU21), one single-arm open-label study of G-CSF/plerixafor in poor mobilizers with malignancies (2112), one study of G-CSF/plerixafor with rituximab (2113), one study in renally impaired patients (1101), and one study in patients with HIV (2001).

## 5.1 Tables of Clinical Studies

**Table 2. Clinical studies submitted to support this NDA (reviewer's table)**

| Study | Design | Population | N | Treatment | 1$^{O}$ Endpoints |
|---|---|---|---|---|---|
| AMD3100-98-01 | Open-label, dose escalation | Healthy vol. | 13 | Single dose 10, 20, 40, or 80 mg/kg IV; 40 or 80 mg/kg SC; or 10 mg/kg orally | Safety, PK |
| AMD3100-1002 | Open-label, dose escalation | Healthy vol. | 24 | Single dose 40, 80, 160, or 120 µg/kg SC | Safety, PK, PD |
| AMD3100-1003 | Open-label, dose escalation | Healthy vol. | 31 | Single-dose 140 or 240 µg/kg SC | Safety, PD |
| 06-H-0156 | Open-label, dose escalation | Healthy vol. | 17* | 2 doses of 240, 320, or 480 µg/kg SC | Thorough QT |
| AMD3100-1004 | Open-label | MM, NHL | 21 | Up to 5 doses of 160, 240, or 320 µg/kg SC | Safety, PD, efficacy |
| AMD3100-1005 | Open-label, fixed dose | Healthy vol. | 10 | Single dose 240 or 320 µg/kg SC | Safety, PK, PD |
| AMD3100-2101 | Open-label crossover | NHL, MM | 25 | G-CSF alone and with up to 4 days of plerixafor 160 or 240 µg/kg | Safety, efficacy |
| AMD3100-2102 | Open-label, fixed dose | Poor mobilizers with MM | 20 | Up to 7 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-2103 | Open-label, fixed dose | NHL | 13 | Up to 5 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-2104 | Open-label, fixed dose | MM, NHL | 44 | Up to 4 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-2105 | Open-label, fixed dose | MM, NHL | 49 | Up to 5 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-2106 | Open-label, fixed-dose | HD | 22 | Up to 5 doses of 240 µg/kg SC with G-CSF | Safety, PK, prelim efficacy |
| AMD3100-2108 | Open-label, fixed dose | MM | 9 | Up to 4 doses of 240 µg/kg SC | Safety, PK, prelim efficacy |
| AMD3100-2109 | Open-label fixed dose | Poor mobilizers with MM or NHL | 5 | Up to 3 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-2113 | 2-arm, open-label, non | HD, NHL | 20* | Up to 4 doses of 240 µg/kg SC with G-CSF and | Safety, prelim efficacy |

| | | | | | |
|---|---|---|---|---|---|
| | randomized | | | rituximab | |
| AMD3100-C201 | Open-label, fixed dose | MM, NHL | 23 | Up to 5 doses of 240 µg/kg SC with G-CSF | Safety, PK |
| AMD3100-EU21 | Open-label, fixed dose | MM, NHL | 35 | Up to 5 doses of 240 µg/kg SC with G-CSF | Safety |
| AMD3100-1101 | Open-label, fixed dose | Renally impaired non-cancer | 23 | Single dose 240 µg/kg SC | Safety, PK, PD |
| AMD3100-2112 | Open-label, fixed dose | Poor mobilizers with non-AML/ CLL cancer | 40* | Up to 7 doses of 240 µg/kg SC | Safety, PK |
| AMD3100-2113 | 2-arm, open-label, non-randomized | HD, NHL | 20* | Up to 4 doses of 240 µg/kg SC with G-CSF and rituximab | Safety |
| AMD3100-3101 | Double-blind, placebo-control | NHL | 298 | Up to 4 doses of 240 µg/kg SC | Safety, efficacy |
| AMD3100-3102 | Double-blind, placebo-control | MM | 302 | Up to 4 doses of 240 µg/kg SC | Safety, efficacy |
| AMD3100-CUP001 | Open label, fixed dose | Any cancer but AML or CLL | 368* | Up to 4 doses of 240 µg/kg SC (160 if renally impaired) | Compassionate use |
| AMD3100-2001 | Open-label, escalating dose | HIV | 40 | 10 daily doses of 2.5, 5, 10, 20, 40, 80, or 160 µg/kg/h IV | Safety, PK |

* enrollment ongoing

## 5.2 Review Strategy

The applicant submitted all primary data electronically. Using this submitted material, this reviewer

- Examined all clinical study reports and amendments;
- Subjected datasets to queries using JMP;
- Examined approximately 30 patient CRFs, selected at random;
- Studied the Applicant's presentation to the FDA dated August 5, 2008.

In addition,

- The regulatory history of NDA #22-311 and the Annual Report for IND #55,851 were reviewed.
- A literature search was performed and the information was compared against primary data submitted by the applicant.
- The FDA Division of Scientific Investigation was consulted (see section 3.2)

## 5.3 Discussion of Individual Studies

### 5.3.1 AMD3100-2101

#### 5.3.1.1 Title

Comparison of the Number of Peripheral Blood $CD34^+$ Cells Collected for Transplantation of Multiple Myeloma and Non-Hodgkin's Lymphoma Patients in a Crossover Design Given a Mobilization Regimen of G-CSF Alone Followed by a Mobilization Regimen of AMD3100 Plus G-CSF

#### 5.3.1.2 Objectives

The primary objective was to evaluate the difference in the number of $CD34^+$ cells/kg collected after mobilization with G-CSF/plerixafor compared with that collected after mobilization of G-CSF alone. Secondary objectives were to compare between treatment arms the number of apheresis days required to collect $\geq 5 \times 10^6$ $CD34^+$ cells/kg, the rate and neutrophil engraftment kinetics.

#### 5.3.1.3 Study design

Study 2101 began as an open-label, crossover study conducted at six sites in the United States. The initial randomized crossover design was based on the premise that the first mobilization would not affect the $CD34^+$ cell yield from the crossover regimen. However, the first 4 patients who had successful collection with the first but not the second regimen all received G-CSF/plerixafor first (see Section 6.1.4.1 of this review for details), raising concern of a sequence effect. As a result, the protocol was amended to eliminate the randomization so that the first mobilization was with G-CSF alone in the remaining patients. However, five patients who were accrued after randomization was discontinued did not achieve the minimum cell dose with G-CSF alone but then subsequently were successful in the G-CSF/plerixafor collection. In retrospect, it became clear that the earlier observation was probably an artifact of a small sample size, rather than a true sequence effect.

#### 5.3.1.4 Population

Study 2101 was open to patients age 18 to 75 years with NHL or MM in first or second complete or partial remission and eligible for autologous HSCT. Patients must have had no more than three prior chemotherapy regimens (not including thalidomide and dexamethasone) and have recovered from all acute toxicity, have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, be HIV seronegative, and have adequate hematologic, renal, hepatic, cardiac and pulmonary function (WBC > 3,000/μL; ANC > 1,500/μL; platelets > 100,000/μL; serum creatinine ≤ 2.2 mg/dL; AST, ALT, and total bilirubin < 2 x ULN, LVEF >45% $FEV_1$ >50% of predicted). Key exclusion criteria included receipt of a cytokine within one week or

pegfilgrastim within 21 days, central nervous system lymphoma, and unwillingness to adhere to contraceptive practice.

Patients who did not complete the first treatment or the crossover treatment phase or whose $CD34^+$ cells could not be mobilized by either treatment were to be removed from the study and replaced. If a patient developed a medical problem between the first treatment phase and the crossover treatment phase, a 1-week delay was permitted (i.e. 21 to 24 days rest interval). However, if more extended delay was required, the patient was to be withdrawn from the study and replaced.

***Reviewer's comment:*** *The eligibility criteria did not address prior HSC mobilization attempt(s).*

5.3.1.5 Treatment

Study treatment consisted of five sequential phases: first treatment, rest interval, crossover treatment, ablative chemotherapy and transplantation, and follow-up.

5.3.1.5.1 First treatment

Patients in both treatment arms received a G-CSF run-in period. The first eight patients enrolled received three (subsequently amended to four) consecutive days of G-CSF 10 μg/kg as a SC injection each morning. The day following the run-in period, patients returned to the clinic and underwent apheresis (3-volume ± 10%) daily for up to four days or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected.

After eight patients had been enrolled, the study was amended to increase the 160 μg/kg dose of plerixafor to 240 μg/kg. This decision was based on results from a dose-finding study in healthy volunteers (1003) showing that when given after a 4 days of G-CSF, a plerixafor dose of 240 μg/kg resulted in a similar peak mobilization of $CD34^+$ cells compared to 160 μg/kg, but the observed peak response was broader, which should widen the optimal time window for apheresis to between 6 and 16 hours after administration of plerixafor. In addition, preliminary data from cancer patients (Study 1004) demonstrated that 240 μg/kg of plerixafor alone was safe and appeared to result in a greater increase in circulating $CD34^+$ cells than 160 μg/kg of plerixafor alone.

5.3.1.5.2 *Rest period*

After the final apheresis, there was a rest interval during which no protocol treatment was administered. This interval lasted 13 to 16 days depending on the number of aphereses required to reach the target number of cells (e.g., if one apheresis day was required, the rest interval was 16 days; if four were required, the rest interval was 13 days). The rationale for this time frame was to allow blood and bone marrow $CD34^+$ levels to return to baseline yet minimize the risk of disease progression.

5.3.1.5.3 Crossover treatment phase

Patients received G-CSF 10 μg/kg as a SC injection each morning for four days (three days before the change in study design). Patients returned to the clinic the next day and received a morning dose of G-CSF 10 μg/kg plus plerixafor 160 μg/kg, followed six hours later by a morning dose of G-CSF and apheresis (3-volume ± 10%). Patients continue to receive morning doses of G-CSF/plerixafor followed in six hours by apheresis for up to four days or until ≥ 5 × $10^6$ $CD34^+$ cells/kg were collected.

5.3.1.5.4 Myeloablative chemotherapy and HSCT

A minimum of 2 x $10^6$ $CD34^+$ cells/kg was required for transplantation, although the preferred number was 5 x $10^6$ cells/kg. Ablative chemotherapy was to begin within 14 days of the last apheresis. The choice of myeloablative regimen was left to investigator discretion. HSCT was performed according per standard local procedures (a copy of each procedure was provided to the Sponsor) using the product obtained from the G-CSF/plerixafor mobilization (the product obtained from the G-CSF alone mobilization was retained as a back-up). G-CSF administration began 24 hours after hematopoietic stem cell administration at 5 μg/kg per day SC.

5.3.1.5.5 Post-transplantation follow-up

No further study treatment was administered post-transplantation. See Section 6.1.3.1.8 of this review for the follow-up schedule.

5.3.1.6 Dose modification for toxicity

Adverse events were graded using the WHO Adverse Event Grading Scale and were coded according to the MedDRA version 10.0 adverse event dictionary. The study design did not allow dose modification for toxicity.

5.3.1.7 Concomitant medications

No medications were restricted. Supportive care (antimicrobial prophylaxis, antiemetics, etc.) was per local institutional standards.

5.3.1.8 Scheduled visits and observations

Blood counts and circulating $CD34^+$ cell counts were checked prior to each dose of study treatment, within 30 minutes following completion of apheresis and as clinically indicated. Graft durability was assessed by follow-up telephone calls at 3, 6, and 12 months post-transplantation.

5.3.1.9 Statistical considerations and analytic plan

A total of 24 patients were to be enrolled. The primary efficacy parameter was the total number of $CD34^+$ cells/kg collected by apheresis as measured by fluorescent activated cell sorting (FACS) analysis. To avoid inter-laboratory variability, $CD34^+$ values from a central laboratory were used for analyses, unless that information was missing, in which case, local laboratory data were to be used.

Secondary efficacy endpoints were

- The number of apheresis days required to reach $\geq 5 \times 10^6$ $CD34^+$ cells/kg
- Time to neutrophil engraftment, as defined by individual study site (Table 3)

**Table 3. Study 2101 Engraftment criteria (reviewer's table)**

| Site | Engraftment criteria | |
|---|---|---|
| | **Neutrophils** | **Platelets** |
| (b) (4) | First of 3 consecutive days of ANC > 500/μL | First day of platelets ≥ 20,000/μL (un-transfused for 7 days) |
| (b) (4) | First of 3 consecutive days of ANC > 500/μL | First of 3 consecutive days of platelets ≥ 20,000/μL (un-transfused for 7 days) |
| (b) (4) | Second of 3 consecutive days of ANC > 500/μL | First day of platelets ≥ 20,000/μL (un-transfused for 5 to 20 days) |
| (b) (4) | Third of 3 consecutive days of ANC > 500/μL | First day of platelets > 20,000/μL (un-transfused for 7 days) |
| (b) (4) | First of 3 consecutive days of ANC > 500/μL | First day of 3 consecutive days of platelets > 20,000/μL (un-transfused for 7 days) |
| (b) (4) | First of 3 consecutive days of ANC > 500/μL | First day of platelets > 100,000/μL (un-transfused for 7 days) |

Exploratory endpoints

- Time to platelet engraftment (Table 3)
- Peripheral blood $CD34^+$ cell count immediately before G-CSF dosing, before plerixafor dosing, four and six hours after plerixafor dosing, and within 30 minutes after completion of apheresis
- The percentage of patients with durable engraftment three and six months post-transplant
    - Patients with missing data were considered to have durable engraftment until the last time that durable engraftment was documented.
    - Infusions of cells occurring within 30 days of the initial infusion date were considered a single transplant event, the date of which was taken as the date of the first infusion. Infusions of cells occurring 30 or more days after the initial infusion and following a second course of ablative chemotherapy were considered a second or tandem transplant event.

- Durability was only assessed for transplants performed exclusively with the G-CSF/plerixafor apheresis product.
- For patients with multiple transplants, only the durability of the second transplant was calculated.

For continuous variables, within-patient differences across the two mobilization regimens were to be analyzed parametrically using the paired t-test, and non-parametrically using the Wilcoxon signed rank test at a nominal two-sided significance level of ≤ 0.05. Assuming a standard deviation of 2, 24 patients would provide 80% power to detect a 19% increase in $CD34^+$ cell yield.

5.3.1.10 Study amendments

The original version of the protocol, dated June 27, 2002, was amended six times. Amendments 1 (Oct. 21, 2002) and 2 (Nov. 19 2002) were implemented before the first patient was enrolled (Jan. 2, 2003) in the study. Amendment 5 was not implemented.

Key changes introduced were to increase the G-CSF run-in period from 3 to 4 days, escalate the dose of plerixafor from 160 to 240 μg/kg, change from a randomized to a fixed treatment order, and extend post-transplantation follow-up from 6 months to 12 months (Table 4).

**Table 4. Study 2101 amendments (reviewer's table)**

| | | Patients enrolled (n) | | |
|---|---|---|---|---|
| **Amendment** | **Date** | **That amendment** | **Cumulative** | **Major changes** |
| 1 | Oct. 21, 2002 | 0 | 0 | Not applicable |
| 2 | Nov. 19, 2002 | 8 | 8 | Not applicable |
| 3 | Mar. 13, 2003 | 4 | 12 | ↑ G-CSF run-in from 3 days to 4 days<br>↑ plerixafor dose from 160 to 240 μg/kg |
| 4 | June 17, 2003 | 13 | 25 | Eliminated randomization |
| 6 | Feb. 3, 2004 | 0 | 25 | Extended follow-up to 12 months |

5.3.2 AMD3100-2106

5.3.2.1 Title

Treatment with AMD3100 Added to a Mobilizing Regimen of G-CSF to Increase the Number of Peripheral Blood Stem Cells in Patients with Hodgkin's Disease

5.3.2.2 Objectives

The primary objective was to determine the proportion of patients with HD who collected ≥ 5 x $10^6$ $CD34^+$ cells/kg after mobilization with G-CSF/plerixafor. Secondary objectives were to:

- Determine the safety of plerixafor when added to G-CSF for the mobilization of HSCs in patients with HD patients undergoing autologous HSCT
- Determine the proportion of HD patients who collected ≥ 2 x $10^6$ $CD34^+$ cells/kg after HSC mobilization with G-CSF/plerixafor
- Determine the change in circulating $CD34^+$ cell count from baseline to 10 – 11 hours after a dose of plerixafor
- Determine the number of days required to collect ≥ 5 x $10^6$ $CD34^+$ cells/kg
- To determine the times to neutrophil and platelet engraftment
- Evaluate graft durability at 3, 6, and 12 months
- Examine the PK and PD of a single 240 μg/kg dose of plerixafor administered after 4 days of G-CSF in patients with HD

5.3.2.3 Study design

This was an open-label, nonrandomized study conducted at a single site in the United States.

5.3.2.4 Population

Study 2106 enrolled patients age 18 to 70 years with HD eligible for autologous HSCT. Patients must have had no more than three prior chemotherapy regimens (not including rituximab) and have recovered from all acute toxicity, have an ECOG performance status 0 or 1, be HIV seronegative, and have adequate hematologic, renal, hepatic function, cardiac and pulmonary function (WBC > 3,000/μL; ANC > 1,500/μL; platelets > 100,000/μL; serum creatinine ≤ 2.2 mg/dL; AST, ALT, and total bilirubin < 2 x ULN, LVEF >45% $FEV_1$ >50% of predicted). Key exclusion criteria included failure to achieve the desired number of $CD34^+$ cells in prior collections, central nervous system lymphoma, and unwillingness to adhere to contraceptive practice.

5.3.2.5 Treatment

5.3.2.5.1 G-CSF mobilization

Patients received four consecutive days of G-CSF 10 μg/kg as a SC injection each morning.

5.3.2.5.2 Study drug treatment phase

On Day 4, patients received plerixafor 240 μg/kg or placebo as a SC injection. Patients returned to the clinic the next day (Day 5) and underwent 3-volume ± 10% apheresis after receiving a

morning dose of G-CSF (i.e. 10 to 11 hours after plerixafor or placebo). Patients continued to receive an evening dose of plerixafor followed by morning G-CSF and apheresis for up to four days or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected. $CD34^+$ cell counts determined by the local laboratory were used for all clinical decision making. The study design did not allow dose modification for toxicity.

5.3.1.5.3 Myeloablative chemotherapy and HSCT

All patients were treated with high-dose chemotherapy followed by transplantation with the G-CSF/plerixafor-mobilized apheresis product. A minimum of 2 x $10^6$ $CD34^+$ cells/kg was required for transplantation. The choice of myeloablative regimen was left to investigator discretion. The HSCT was performed per standard local procedures. No further study treatment was administered post-transplantation.

***Reviewer's comments***

1. *The protocol specified a minimum number of $CD34^+$ cells required for transplantation but did not specify the preferred number.*
2. *The protocol did not provide guidelines regarding the post-transplant administration of hematopoietic growth factors.*

5.3.2.6 Concomitant medications

No medications were restricted. Supportive care (antimicrobial prophylaxis, antiemetics, etc.) was according to local institutional standards.

5.3.2.7 Scheduled visits and observations

Blood counts and circulating $CD34^+$ cell counts were checked prior to each dose of plerixafor, before each apheresis, and as clinically indicated. Graft durability was assessed by follow-up telephone calls at 3, 6, and 12 months post-transplantation.

5.3.2.8 Statistical considerations and analytic plan

Between 16 and 22 patients were to be enrolled. The primary efficacy variable was the proportion of patients who collected total of ≥ 5 x $10^6$ $CD34^+$ cells/kg measured by FACS at the central laboratory

***Reviewer's comments:*** *$CD34^+$ cell counts determined by the local laboratory were used for treatment decisions, but values determined by the central laboratory were to be used for efficacy analyses.*

Secondary efficacy endpoints were

- The proportion of patients who collected total of ≥ 2 x $10^6$ $CD34^+$ cells/kg

- The change in number of $CD34^+$ cells/μL in peripheral blood 10 to 11 hours after a dose of plerixafor and the proportion of patients achieving a ≥ 2-fold increase
- Time to neutrophil engraftment
- Graft durability at 3, 6 and 12 months

***Reviewer's comment:*** *The protocol did not adequately define engraftment and graft durability.*

Results of the primary and secondary endpoints were to be presented descriptively. Formal statistical analyses were not planned.

#### 5.3.2.9 Study amendments

The original version of the protocol, dated March 3, 2004, was amended three times. Five patients were enrolled on the original protocol. Amendments 1, 2 and 3 enrolled 3, 2, and 12 patients, respectively. Changes introduced included the use of a new study drug formulation, the addition of PK analyses, and the addition of include graft durability as a secondary objective (Table 5).

**Table 5. Study 2101 amendments (reviewer's table)**

| | | Patients enrolled (n) | | |
|---|---|---|---|---|
| **Amendment** | **Date** | **That version** | **Cumulative** | **Major changes** |
| 1 | Feb. 22, 2005 | 3 | 8 | • Added graft durability at 3, 6, and 12 months as a secondary endpoint<br>• Introduced a new study drug formulation<br>• Extended AE and SAE reporting from 30 days to 6 months post transplant in patients who undergo transplantation |
| 2 | June 6, 2005 | 2 | 10 | • Added of blood samples for PK analysis |
| 3 | Sept. 15, 2005 | 12 | 22 | • Revised PK timepoints and requisite patient sample size<br>• Added CD34+ FACS analysis |

### 5.3.3 AMD3100-3101

#### 5.3.3.1 Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (240 μg/kg) plus G-CSF (10 μg/kg) versus G-CSF (10 μg/kg) plus Placebo to Mobilize and Collect ≥ $5 \times 10^6$ $CD34^+$ cells/kg in Non-Hodgkin's Lymphoma Patients for Autologous Transplantation

5.3.3.2 Objectives

The primary objective was to determine if NHL patients are more likely to collect $\geq 5 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days with G-CSF/plerixafor than with G-CSF/placebo. Secondary objectives were to compare the two treatment arms with respect to safety, the proportion of patients who collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, neutrophil and platelet engraftment times, and graft durability.

5.3.3.3 Study design

This was a prospective, randomized, placebo-controlled add-on study conducted at 32 sites in the United States.

5.3.3.4 Population

The trial was open to patients age 18 to 75 years with NHL in first or second complete remission or partial remission and eligible for autologous HSCT. Patients must have been at least four weeks since prior chemotherapy, have an ECOG performance status 0 or 1, be HIV seronegative, and have adequate hematologic, renal and hepatic function (WBC > 3,000/μL; ANC > 1,500/μL; platelets > 100,000/μL; serum creatinine ≤ 2.2 mg/dL; and AST, ALT, and total bilirubin < 2 x ULN). Key exclusion criteria included failed prior stem cell collections attempts, central nervous system lymphoma.

5.3.3.5 Randomization

A minimum of 300 patients were to be randomized in a 1:1 ratio to G-CSF/plerixafor vs. G-CSF/placebo. Only the pharmacist was to know the treatment assigned.

Up to 40 additional patients (20 per treatment arm) at selected sites were allowed to receive rituximab prior to, during, and post-apheresis. Data from these patients were not to be analyzed for efficacy, but were included in the safety database.

***Reviewer's comment:*** *G-CSF alone was an acceptable control regimen for this randomized trial to demonstrate efficacy.*

5.3.3.6 Treatment

Study treatment consisted of four sequential phases: mobilization, treatment/apheresis, myeloablative chemotherapy, transplantation, and post-transplantation/follow-up.

*Mobilization*

Patients received G-CSF 10 µg/kg as a SC injection each morning for 4 days. At approximately 10:00 p.m. on Day 4, patients received plerixafor 240 µg/kg or placebo as a SC injection.

*Treatment/apheresis*
Patients returned to the clinic the next day (Day 5) and received a morning dose of G-CSF followed by 3-volume ± 10% apheresis. Patients continued to receive an evening dose of study treatment followed by morning G-CSF and apheresis for up to four days or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected.

*Myeloablative chemotherapy*
Ablative chemotherapy consisted of one of the following regimens per local institutional standards:

- Carmustine, etoposide, cytarabine, and melphalan
- Cyclophosphamide, etoposide, and total body irradiation
- Carmustine, etoposide, cytarabine, and melphalan
- Busulfan, melphalan, and thiotepa
- Cyclophosphamide, carmustine, and etoposide
- Busulfan, cyclophosphamide, and etoposide

*Stem cell transplantation*
Transplantation was to occur within one month of the last apheresis session using local standard institutional procedures. All collected $CD34^+$ cells collected could be administered. Patients with excess cells ($> 5 \times 10^6$/kg) could have some of the collection saved for future use.

*Post-transplantation*
Beginning the sixth day after cell transplantation, G-CSF 5 µg/kg was administered daily until neutrophil engraftment (ANC ≥ 500/µL for 3 days or ≥ 1000/µL for one day).

5.3.3.7 Rescue procedure

Patients who did not collect $\geq 0.8 \times 10^6$ $CD34^+$ cells/kg after two apheresis days or $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days had the option of, after a minimum 7-day rest period, receiving another course of G-CSF/plerixafor followed by HSC collection. Treatment assignment remained blinded for the rescue procedure.

5.3.3.8 Dose modification for toxicity

Adverse events were graded using the WHO Adverse Event Grading Scale. The study design did not allow dose modification for toxicity.

5.3.3.9 Concomitant medications

Patients had to have been off carmustine for at least 6 weeks and must not have received G-CSF or GM-CSF within 3 weeks of the first dose of G-CSF for mobilization. With the exception of up to 40 patients in the study, rituximab was prohibited until at least 90 days after transplantation. No other medications were restricted.

5.3.3.10 Scheduled visits and observations

After transplantation, neutrophils and platelets were monitored daily until neutrophil engraftment and then at least three times weekly until platelet engraftment. Peripheral $CD34^+$ cell counts were measured by local and central (b) (4) laboratories prior to G-CSF administration on Day 4, prior to G-CSF administration on each apheresis day, and daily from the apheresis product.

5.3.3.11 Statistical considerations and analytic plan

Three hundred patients (150 per treatment arm) were to be entered. An additional 40 patients permitted to use rituximab were to be entered for inclusion in the safety database. Patients who did not complete the 4 days of G-CSF mobilization were to be dropped from the protocol and replaced.

The primary efficacy endpoint was the collection of $\geq 5 \times 10^6$ $CD34^+$ cells/kg within four apheresis days. Secondary endpoints were:

- The percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days
- The number of apheresis days required to collect $\geq 5 \times 10^6$ $CD34^+$ cells/kg
- Time to neutrophil engraftment (ANC $\geq$ 500/μL for 3 days or $\geq$ 1000/μL for one day) and to platelet engraftment (the first day of platelets $\geq$ 20,000/μL for seven consecutive days without a transfusion)
- The percentage of patients with durable engraftment at post-transplant Day 100, defined as at least two of the following three criteria:
    1. Platelets > 50,000/μL without transfusion for at least two weeks
    2. Hemoglobin ≥ 10 g/dL with no EPO or transfusions for at least one month
    3. ANC > 1,000/μL with no G-CSF for at least one week

The Cochran/Mantel-Haenzel chi-square test was to be used for between-group comparisons, stratified by investigator. McNemar's chi-square test was to be used for within-group differences in bivariate responses. Time-to-event parameters were to be summarized using Kaplan-Meier methods, while treatment group differences in the resulting survival curves were to be analyzed using the Wilcoxon and log-rank tests. Any patient for whom no event was observed was to be censored on the last day he/she was evaluated for the event.

The sample size was based on data from AMD3100-2101 suggesting that at least 50% of patients receiving G-SCF/plerixafor in the per-protocol population would mobilize ≥ 5 x $10^6$ $CD34^+$ cells/mL compared to 30% for G-CSF/placebo. Assuming 20% of enrolled patients would be excluded from the per-protocol analysis but included as treatment failures in the ITT analysis reduced the effective difference between treatment groups from 20% to 16%. Three hundred patients provided 80% power to detect this 16% difference at a 2-sided significance level of 0.05.

5.3.3.11 Study amendments

Study 3101 was amended a total of seven times (Table 6).

**Table 6. Study 3101 amendments (reviewer's table)**

| Amendment | Date | Changes Instituted |
|---|---|---|
| **#1** | **Nov. 12, 2004** | • Allowed up to 40 patients at selected centers to receive rituximab pre- and post-apheresis<br>• Specified that the percentage of patients with durable engraftment would be assessed at six months in addition to at 100 days<br>• Defined graft durability and graft failure |
| **#2** | **Dec. 1, 2004** | • Specified that analysis of the primary endpoint would be based on the ITT population<br>• Specified that a 20-point difference in treatment success rate between treatment arms in the ITT population would be considered clinically significant, but that the planned sample size was chosen to demonstrate statistical significance in the per protocol analysis |
| **#3** | **Jan. 21, 2005** | • Excluded patients for whom post-transplant chemotherapy and/or radiotherapy was anticipated<br>• Decreased the washout period for G-CSF prior to the first dose of mobilizing G-CSF dose from 21 to 14 days<br>• Disallowed post-transplant chemotherapy and/or radiotherapy except to treat relapse or if radiotherapy was low-dose and localized to lesions above the diaphragm (in which case, the radiotherapy must be administered no earlier than Day 100 and must be completed by Day 150).<br>• Added recording of concomitant medications taken in the month prior to each follow-up visit<br>• Specified that patients would be randomized centrally<br>• Added BEP to the permitted pre-transplant chemotherapy regimens<br>• Refined the definitions of graft durability and graft failure<br>• Specified that post-transplant platelet monitoring would continue until platelets reached ≥ 50,000/mL without transfusion<br>• Specified that the WHO scale rather than NCI-CTCAE would be used to grade AEs<br>• Specified that the percentage of patients with durable engraftment would be |

| | | |
|---|---|---|
| | | assessed at 12 month in addition to at 100 days and six months |
| **#4** | **June 28, 2005** | • Increased the upper age limit for study eligibility from 75 to 78 years<br>• Clarified that biopsy-confirmed diagnosis of NHL documentation more than 30 days prior to first mobilization was permitted<br>• Reduced lower limit for qualifying WBC count from 3000 to 2500/μL<br>• Increased the qualifying upper limit for ALT, AST, and total bilirubin from 2 to 2.5 times the ULN<br>• Excluded patients who had prior autologous or allogeneic HSCT<br>• Added BVAC and BEAC to the permitted pre-transplant chemotherapy regimens<br>• Changed the start of G-CSF administration post-transplant from Day 6 to Day 5 or 6<br>• Extended the interval between last apheresis and HSCT from one month to five weeks<br>• Clarified that either an automated or a manual white cell differential was permitted |
| **#5** | **Aug. 5, 2005** | • Single center amendment (b) (4) to add collection of 50 mL of blood prior to the first apheresis to be examined by FACS for endothelial progenitor cells |
| **#6 and 7** | **Aug 11, 2005 and Sept. 25, 2005** | • Clarified that biopsy confirmation of NHL diagnosis must have occurred prior to the first mobilization<br>• Excluded patients with clinically significant arrhythmias or conduction abnormality in the last year<br>• Specified that no further apheresis was permitted between the fourth collection and transplant, unless criteria for failed collection were met<br>• Added BuCy to the permitted pre-transplant chemotherapy regimens |

***Reviewer's comment:*** *These protocol amendments were all relatively minor and should have had little impact on the overall study findings.*

5.3.4 AMD3100-3102

5.3.4.1 Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (240 μg/kg) plus G-CSF (10 μg/kg) versus G-CSF (10 μg/kg) plus Placebo to Mobilize and Collect ≥ $5 \times 10^6$ $CD34^+$ cells/kg in Multiple Myeloma Patients for Autologous Transplantation

5.3.4.2 Objectives

The primary objective was to determine if MM patients are more likely to collect $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days with G-CSF/plerixafor than with G-CSF/placebo. Secondary objectives were to compare the two treatment arms with respect to safety, the proportion of patients collecting $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days and $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the number of days required to collect $\geq 6 \times 10^6$ $CD34^+$ cells/kg, neutrophil and platelet engraftment times, and graft durability at 100 days, 6 months, and 12 months.

5.3.4.3 Study design

Study 3102 was a prospective, randomized, double-blind, placebo-controlled, and conducted at 32 sites in the United States.

5.3.4.4 Population

Study 3102 was open to patients age 18 to 75 years with MM in first or second complete remission or partial remission and eligible for autologous HSCT. Patients must have been at least four weeks since prior chemotherapy (or one week since thalidomide, lenalidomide, dexamethasone, or bortezomib), have an ECOG performance status 0 or 1, be HIV seronegative, and have adequate hematologic, renal and hepatic function (WBC > 2,500/μL; ANC > 1,500/μL; platelets > 100,000/μL; serum creatinine ≤ 2.2 mg/dL; and AST, ALT, and total bilirubin < 2.5 x ULN). Key exclusion criteria included prior autologous or allogeneic transplant, receipt of more than two cycles of alkylating agent combinations, failed prior stem cell collection attempts, central nervous system MM, and receipt of G-CSF within 14 days or GM-CSF or pegfilgrastim within three weeks.

5.3.4.5 Randomization

Prior to receiving the first dose of G-CSF for mobilization, patients were to be randomized in a 1:1 ratio to receive G-CSF/plerixafor or G-CSF/placebo. Only the pharmacist was to know the treatment assigned. Randomization was stratified by study center, baseline platelet count (< vs. ≥ 200,000/μL) and type of transplant planned (single or tandem).

***Reviewer's comment:*** *G-CSF alone was an acceptable control regimen for this randomized trial to demonstrate efficacy.*

5.3.4.6 Treatment

Study treatment consisted of four sequential phases: mobilization, treatment/apheresis, myeloablative chemotherapy, transplantation, and post-transplantation/follow-up.

*Mobilization*
Patients received G-CSF 10 μg/kg as a SC injection each morning for 4 consecutive days. At approximately 10:00 p.m. on Day 4, patients received plerixafor 240 μg/kg or placebo as a SC injection.

*Treatment/apheresis*
Patients returned to the clinic Day 5 and received a morning dose of G-CSF followed by a 3-volume (± 10%) apheresis. Patients continued to receive an evening dose of study treatment (plerixafor 240 μg/kg or placebo SC) followed by morning G-CSF and apheresis for up to four days or until $\geq 6 \times 10^6$ $CD34^+$ cells/kg were collected.

*Myeloablative chemotherapy*
Ablative chemotherapy consisted of one of the following regimens per local institutional standards:

- Melphalan 140 or 200 $mg/m^2$
- Carmustine, etoposide, cytarabine, and melphalan
- Busulfan and melphalan
- Arsenic and melphalan
- Busulfan and cyclophosphamide

*Stem cell transplantation*
Transplantation was take place within five weeks of the last apheresis session using local institutional procedures. In the event of a tandem transplant, the first transplantation had to occur within 5 weeks after the last apheresis session and the subsequent transplantation within 6 months of the first transplantation. All $CD34^+$ cells collected could be administered. Any excess cells collected ($> 5 \times 10^6$/kg) could be saved for future use.

*Post-transplantation*
Beginning the sixth day after cell transplantation, G-CSF 5 μg/kg was administered daily until neutrophil engraftment.

5.3.4.7 Rescue procedure

Patients who mobilized $< 0.8 \times 10^6$ $CD34^+$ cells/kg after two apheresis days or $< 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, or were planned for tandem transplant and collected $< 4 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days had the option of, after a minimum 7-day rest period, receiving another course of G-CSF plus open-label plerixafor in the same doses and schedule followed by stem cell collection. The initial study treatment assignment remained blinded for the rescue procedure.

5.3.4.8 Dose modification for toxicity

Adverse events were graded using the WHO Adverse Event Grading Scale. The study did not allow dose modification for toxicity.

5.3.4.9 Concomitant medications

Chemotherapy and radiation therapy were not permitted after transplant except to treat relapse or if the radiation therapy was low dose and localized to lesions above the diaphragm. In this case, the radiation therapy was administered no earlier than Day 100 and was completed by Day 150. However, at one selected site, up to 30 additional patients (15 per treatment group) could receive cytoreductive chemotherapy after 90 days post-transplant (only one patient was enrolled in this category.). No other medications were restricted.

5.3.4.10 Scheduled visits and observations

After transplantation, the neutrophils and platelets were monitored daily until neutrophil engraftment (ANC ≥ 500/μL for 3 days or ≥ 1000/μL for 1 day). After neutrophil engraftment, platelets were monitored at least three times weekly until ≥ 20,000/μL for 7 days and then every 3 to 4 days until ≥ 50,000/μL without transfusion. Peripheral blood $CD34^+$ cells counts were measured by local and central **(b) (4)** laboratories prior to G-CSF administration on Day 4, prior to G-CSF administration on each apheresis day, and daily from the apheresis product.

5.3.4.11 Statistical considerations and analytic plan

Three hundred patients (150 per treatment arm) were to be entered. Patients who did not complete 4 days of G-CSF mobilization were to be dropped from the protocol and replaced.

The primary efficacy endpoint was the collection of a total of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days. Secondary endpoints were:

- The percentage of patients collecting $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days
- The percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days
- The number of apheresis days required to collect $\geq 6 \times 10^6$ $CD34^+$ cells/kg
- Time to neutrophil engraftment (ANC ≥ 500/μL for 3 days or ≥ 1000/μL for one day) and to platelet engraftment (the first day of platelets ≥ 20,000/μL for seven consecutive days without a transfusion)
- The percentage of patients with graft durability at 100 days, 6 months, and 12 months, defined by at least two of the three following criteria:
    1. Platelets > 50,000/μL without transfusion for at least 2 weeks
    2. Hemoglobin level ≥ 10 g/dL with no EPO or transfusions for at least 1 month
    3. ANC > 1,000/μL with no G-CSF for at least 1 week

$CD34^+$ cell yields were to be calculated based on measurements from the central laboratory. If that value was missing, the corresponding local laboratory value was to be used.

All primary comparisons were to be stratified by baseline platelet counts (< vs. ≥ 200,000/μl). Binomial proportions were to be analyzed by Pearson's chi-square test, not corrected for continuity; Fisher's exact test was to be used if test assumptions were not met. Time-to-event parameters were to be summarized using Cox proportional hazards regression. Any patient for whom no event was observed was to be censored on the last day he/she was evaluated for the event.

The sample size was chosen based on data from AMD3100-2101 suggesting that at least 50% of patients receiving G-SCF/plerixafor in the per-protocol population would mobilize ≥ 5 x $10^6$ $CD34^+$ cells/mL compared to 30% for G-CSF/placebo. Assuming that 20% of enrolled patients would be excluded from the per-protocol analysis but included as treatment failures in the ITT analysis reduced the effective difference between treatment groups from 20% to 16%. Three hundred patients provided 80% power to detect this 16% difference at a 2-sided significance level of 0.05.

Up to 30 additional (15 per treatment group) could be enrolled and permitted to receive cytoreductive chemotherapy following HSCT. To allow for these extra patients, the maximum sample size was 330 patients.

5.3.4.12 Study amendments

Study 3102 was amended eight times (Table 7).

**Table 7. Study 3102 amendments**

| Amendment | Date | Changes Instituted |
|---|---|---|
| **#1 – 3** | **Nov. 10-30, 2004** | • None (these amendments occurred before enrollment of any patients on study) |
| **#4** | **Mar. 14, 2005** | • Allowed up to 30 additional patients at one selected site to receive cyto-reductive chemotherapy 90 days post-transplant, per the standard of care at that site. |
| **#5** | **June 27, 2005** | • Removed the upper limit on the number of cells to be collected within four days to provide more opportunity to collect additional cells for tandem transplants<br>• Allowed patients up to 78 years of age (previously 75 years), with WBC counts >2,500/μL (previously >3,000/μL), and with AST, ALT and total bilirubin < 2.5 x ULN (previously 2.0)<br>• Specified that ablative chemotherapy could be any regimen approved for the study<br>• Specified that G-CSF could be started on Day 5 or 6 after transplant (previously 6), and that HSCT could occur up to 5 weeks after the last |

| | | |
|---|---|---|
| | | apheresis section (previously 1 month) |
| **#6** | **Aug. 5, 2005** | Added a blood sample immediately prior to the first apheresis procedure, used to assess endothelial progenitor cells at one selected site |
| **#7** | **Sept. 2, 2005** | Was never sent to study sites. Typographical errors were subsequently noted and corrected in Amendment #8 |
| **#8** | **Sept. 16, 2005** | • Added lenalidomide to the drugs patients could not have received for 7 days prior to the first dose of G-CSF for mobilization<br>• Specified that no further mobilization and apheresis was permitted between the fourth apheresis and transplant, unless criteria for a failed collection were met<br>• Added procedures for rescue of mobilization failures<br>• Specified that the diagnosis of MM must have been confirmed by bone marrow biopsy prior to first mobilization<br>• Specified that clinically significant abnormal ECGs within the last year (previously 3 years) would exclude patients from participation |

***Reviewer's comments:***

1. *The changes introduced in Amendments 1 through 8 should have had a relatively minor impact on the efficacy and safety endpoints of the study.*
2. *Amendment 5 made the study more generalizable by expanding the study population and accepting standards of care across study sites.*

# 6 Review of Efficacy

## ***Efficacy Summary***

2101 was a crossover study that enrolled 25 patients age 18 to 75 years with NHL or MM in first or second complete or partial remission and eligible for autologous HSCT. Its primary objective was to evaluate the difference in the number of $CD34^+$ cells/kg collected after mobilization with G-CSF/plerixafor compared with that collected after mobilization of G-CSF alone. In patients with NHL, the mean average daily $CD34^+$ collection was $2.9 \times 10^6$ cells/kg with G-CSF/ plerixafor, compared to $1.0 \times 10^6$ cells/kg with G-CSF alone ($p < 0.001$, paired t-test). In patients with MM, the mean average daily $CD34^+$ collection was $6.6 \times 10^6$ cells/kg with G-CSF/ plerixafor, compared to $2.5 \times 10^6$ cells/kg with G-CSF alone ($p = 0.025$, paired t-test).

Study 2106 was designed to determine the proportion of patients with HD who collected ≥ $5 \times 10^6$ $CD34^+$ cells/kg with G-CSF/plerixafor. The median number of $CD34^+$ cells collected was $6.9 \times 10^6$/kg. Fifteen of 22 patients (68%) met the primary efficacy endpoint of collecting a total of ≥ $5 \times 10^6$ $CD34^+$ cells/kg.

Study 3101 randomized 298 patients with NHL who were planning to undergo autologous HSCT to G-CSF/plerixafor versus G-CSF/placebo. The primary endpoint was the collection of ≥ 5 ×

$10^6$ $CD34^+$ cells/kg within 4 apheresis days. Secondary endpoints were the percentage of patients achieving $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the number of apheresis days required to reach $\geq 5 \times 10^6$ $CD34^+$ cells/kg, times to neutrophil and platelet engraftment, and the percentage of patients with durable engraftment at post-transplant Day 100.

The combination arm showed a statistically significant improvement in the primary endpoint. Eighty nine (59%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $\geq 5 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 29 (20%) patients randomized to G-CSF/placebo ($p < 0.001$). One hundred and thirty (87%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of mobilization of $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 70 (47%) patients randomized to G-CSF/placebo ($p < 0.001$). The median number of apheresis days required to mobilize 5 x $10^6$ $CD34^+$ cells/kg was 3.0 in the G-CSF/plerixafor group and could not be estimated in the G-CSF/placebo group because less than half of the patients in that group reached the target in four days. One hundred and thirty five of 150 (90%) patients randomized to G-CSF/plerixafor underwent transplantation, compared with 82/148 (55%) in the G-CSF/placebo group. The addition of plerixafor did not appear to affect the likelihood of engraftment, the median times to neutrophil or platelet engraftment, or among surviving patients, the likelihood of graft durability at 100 days, at 6 months, or at one year.

Study 3102 randomized 302 patients with MM who were planning to undergo autologous HSCT to G-CSF/plerixafor versus G-CSF/placebo. The primary efficacy endpoint was the collection of a total of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days. Secondary endpoints were the percentage of patients collecting $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, the number of apheresis days required to reach $\geq 6 \times 10^6$ $CD34^+$ cells/kg, time to neutrophil and to platelet engraftment, and the percentage of patients with graft durability at 100 days, 6 months, and 12 months.

The combination arm showed a statistically significant improvement in the primary endpoint. One hundred and six (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($P < 0.001$). One hundred and twelve (76%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of mobilization of $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, compared to 79 (51%) patients randomized to G-CSF/placebo ($p < 0.001$). One hundred and forty-one (95%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of mobilization of $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 136 (88%) patients randomized to G-CSF/placebo ($p < 0.028$). The median number of apheresis days required to mobilize $\geq 6$ x $10^6$ $CD34^+$ cells/kg was one day in the G-CSF/plerixafor group and four days in the G-CSF/placebo group ($p < 0.001$). One hundred and forty two of the Of 148 patients randomized to G-CSF/plerixafor (96%) underwent transplantation, compared with 136/154 (88%) in the G-CSF/placebo group. The addition of plerixafor did not appear to affect on the likelihood of engraftment, the median times to neutrophil or platelet engraftment, or among surviving patients the likelihood of graft durability at 100 days, at 6 months, or at one year.

The results of the randomized studies 3101 and 3102 showed that the addition of plerixafor to G-CSF increased the proportion of patients who were able to collect a minimum transplantable cell dose (defined prospectively as $\geq 2 \times 10^6$ $CD34^+$ cells/kg) and an optimal number for transplantation (defined prospectively as $\geq 5 \times 10^6$ $CD34^+$ cells/kg in < 4 apheresis days for NHL patients and as $\geq 6 \times 10^6$ $CD34^+$ cells/kg in < 2 apheresis days of for MM patients). As a result, more patients treated with G-CSF/plerixafor underwent transplantation. Following transplantation, approximately 99% of all transplanted patients achieved neutrophil and platelet engraftment. The number of days to neutrophil and platelet engraftment and graft durability rates through 12 months post-transplant were similar between the G-CSF/plerixafor and G-CSF/placebo groups.

The addition of plerixafor reduced the median number of apheresis sessions required to collect an optimum transplantable cell dose compared to G-CSF/placebo. This reduction should theoretically allow more optimal use of apheresis machines and related resources, as well as reduce the morbidity associated with apheresis.

## 6.1 Indication

### 6.1.1 Methods

#### 6.1.1.1 Focus of efficacy review

This review focuses primarily on efficacy and safety data from two non-randomized studies in patients with NHL and MM (2101) and HD (2106) and from two randomized clinical trials comparing G-CSF/plerixafor to G-CSF/placebo in patients with NHL (3101) and MM (3102). Results from prior dose-finding studies (see Section 4.4.2.2.2 of this review) demonstrated that plerixafor doses up to 240 µg/kg produced dose proportional increases in circulating $CD34^+$ cells in healthy volunteers and in patients with lymphoma or MM, with peak responses extending from 6 to 16 hours post-injection. No clear benefit of 320 µg/kg plerixafor over 240 µg/kg, either alone or with G-CSF, was seen in healthy volunteers or patients with lymphoma or MM. The combination of G-CSF/plerixafor increased circulating $CD34^+$ cell counts in volunteers and cancer patients more than plerixafor alone.

#### 6.1.1.2 General discussion of endpoints

##### 6.1.1.2.1 Primary endpoints

The primary endpoints of Studies 3101 and 3102 were the percentage of patients achieving collection of $\geq 5 \times 10^6$ $CD34^+$ cells/kg within four apheresis days and $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two apheresis days. These endpoints are clinically meaningful because these values are

within the range where the likelihood of and time to engraftment maximize, and thus represent preferred quantities of $CD34^+$ cells for infusion.[8-11]

### 6.1.1.2.2. Secondary endpoints

A secondary endpoint of Studies 3101 and 3102 was the percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days. This endpoint is clinically meaningful because it is approximately the minimum number $CD34^+$ cells/kg required for adequate hematopoietic rescue following myeloablative chemotherapy and thus represents the threshold at which HSCT can safely be performed.[8]

Other secondary endpoints were time to neutrophil and to platelet engraftment and the percentage of patients with durable engraftment at post-transplant Day 100. The time to neutrophil and platelet engraftment is clinically meaningful because it correlates with the need for supportive care. Graft status at Day 100 correlates well with long-term graft function.

### 6.1.1.2.3 Exploratory endpoints

Peripheral blood $CD34^+$ cell counts were an exploratory endpoint of Study 2101. Peripheral blood $CD34^+$ cell counts are predictive of $CD34^+$ cell apheresis yield, and are often followed clinically to avoid unnecessary, low-yield apheresis procedures. A circulating $CD34^+$ cell count $\geq$ 40-50/μL is predictive of being able to collect 2.5 x $10^6$ $CD34^+$ cells in a single apheresis session.[48,49]

### 6.1.1.2.4 Regulatory precedent

BLA #103,353 for *E. coli*-derived G-CSF (filgrastim) was supported by two single-arm clinical trials and one open-label randomized trial involving a total of 97 pretreated patients with NHL, HD, acute lymphoblastic leukemia, or breast cancer undergoing myeloablative chemotherapy. Key study endpoints were numbers of progenitor cells harvested, time to engraftment, and transfusion requirement. Patients treated with G-CSF mobilized a median of 25.3 to 63.9 x $10^4$ CFU-GM/kg and 2.80 to 3.11 x $10^6$ $CD34^+$ cells/kg, respectively. In the randomized study, patients in the G-CSF arm had fewer days of platelet transfusions (median 6 vs. 10), shorter time to a sustained platelet count > 20,000/μL (median 16 vs. 23 days) shorter time to recovery of a sustained ANC > 500/μL (median 11 vs. 14 days), fewer days of red blood cell transfusions (median 2 vs. 3) and a shorter duration of post-transplant hospitalization. The Agency concluded that mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with unmobilized apheresis or bone marrow harvest, and that this may result in a decreased need for supportive care.

BLA #103,362 for yeast-derived GM-CSF (sargramostim) was supported by a single-center retrospective review of patients with cancer undergoing leukapheresis for collection of either mobilized (n = 196) or unmobilized (n = 100) HPC. GM-CSF produced a dose-dependent increase in numbers of mobilized CFU-GM and BFU-E, which translated to shorter times to myeloid and platelet engraftment. The Agency concluded that mobilization allows for the

collection of increased numbers of progenitor cells capable of engraftment, and that this can lead to more rapid engraftment, which may decrease the need for supportive care.

## 6.1.2 Demographics

### 6.1.2.1 AMD3100-2101

A total of 25 patients, 25 with NHL and 10 with MM, were enrolled on Study 2101. Seven patients in each group (47% in the NHL group and 70% in the MM group) were male. The overall median age was 60 years, and the majority of patients were Caucasian. All patients had received prior chemotherapy (Table 8).

**Table 8. Study 2101 patient characteristics**

| Characteristic | Patients with NHL (n = 15) | Patients with MM (n = 10) | All patients (n = 25) |
|---|---|---|---|
| **Gender**[a] | | | |
| Male | 7 (47%) | 7 (70%) | 14 (56%) |
| Female | 8 (53%) | 3 (30%) | 11 (44%) |
| **Age (years)**[a] | | | |
| Mean | 56 | 61 | 58 |
| Median | 59 | 64 | 60 |
| Range | 31-66 | 43-72 | 31-72 |
| **Race/ethnicity**[a] | | | |
| Caucasian | 14 (93%) | 5 (50%) | 19 (76%) |
| African-American | 0 (0%) | 4 (40%) | 4 (16%) |
| Hispanic/Latino | 1 (7%) | 1 (10%) | 2 (8%) |
| **Pre-treatment weight (kg)**[a] | | | |
| Mean | 86 | 92 | 88 |
| Median | 90 | 93 | 91 |
| Range | 62-105 | 60-124 | 60-124 |
| **Disease stage**[b] | | | |
| I | 0 (0%) | 2 (20%) | NA |
| II | 2 (13%) | 4 (40%) | NA |
| III | 4 (26%) | 4 (40%) | NA |
| IV | 8 (53%) | NA | NA |
| **Time since diagnosis (months)**[b] | | | |
| Mean | 43 | 17 | 32 |
| Median | 28 | 8 | 21 |
| Range | 5-126 | 3-73 | 3-126 |
| **Time since last progression/relapse (mo)**[b] | | | |
| Mean | 5 | 17 | 7 |
| Median | 4 | 6 | 4 |
| Range | 3-7 | 5-40 | 3-40 |
| **Prior chemotherapy**[b] | | | |
| Yes | 15 (100%) | 10 (100%) | 25 (100%) |
| No | 0 (0%) | 0 (0%) | 0 (0%) |
| **Prior radiotherapy**[b] | | | |
| Yes | 4 (27%) | 4 (40%) | 8 (32%) |

| | | | |
|---|---|---|---|
| No | 11 (73%) | 5 (50%) | 16 (64%) |
| Missing | 0 | 1 (10%) | 1 (4%) |

[a] DEMOG1.xpt by DIAGNTP, SEX, AGE, ETHNIC, and PRETRTWT
[b] ONCTX1.xpt by CURRSTG, DXCNFDT, and PROGDT
[c] PRCH1 by PATID, DIAGTYP, and CHEMO
[d] PRRADO by PATID, DIAGTYP, and RADC

### 6.1.2.2 AMD3100-2106

Twenty two patients with HD were enrolled on Study 2106. Thirteen patients (59%) were male, their median age was 34 years, and all were Caucasian (Table 9).

**Table 9. Study 2106 patient and disease characteristics**

| Characteristic | All patients (n = 22) |
|---|---|
| **Gender**[a] | |
| Male | 13 (59%) |
| Female | 9 (41%) |
| **Age (years)**[a] | |
| Mean | 34 |
| Median | 32 |
| Range | 18-57 |
| **Race/ethnicity**[a] | |
| Caucasian | 22 (100%) |
| **Pre-treatment weight (kg)**[a] | |
| Mean | 92 |
| Median | 87 |
| Range | 58-143 |
| **Disease stage**[b] | |
| I | 0 (0%) |
| II | 5 (23%) |
| III | 7 (32%) |
| IV | 8 (36%) |
| Missing | 2 (9%) |
| **Time since diagnosis (months)**[b] | |
| Mean | 24 |
| Median | 16 |
| Range | 9-102 |
| **Time since last progression/relapse (mo)**[b] | |
| Mean | 4 |
| Median | 4 |
| Range | 2-16 |
| **Prior treatment** | |
| Chemotherapy[b] | 22 (100%) |
| Radiotherapy[b] | 9 (41%) |

[a] DEMOG1.xpt by DIAGNTP, SEX, AGE, ETHNIC, and PRETRTWT
[b] ONCTX1.xpt by CURRSTG, DXCNFDT, and PROGDT
[c] PRCH1 by PATID, DIAGTYP, and CHEMO
[d] PRRADO by PATID, DIAGTYP, and RADC

Eighteen patients (82%) had one or more minor protocol violations (data not shown). No patient had a major protocol violation.

6.1.2.3 AMD3100-3101

Enrollment onto Study 3101 took place from January 18, 2005 to October 19, 2006. The clinical cutoff date was April 6, 2007, at which time, median patient follow-up was 421 days.

Study 3101 was conducted at 32 centers in the United States. No center contributed more than 14% of patients. In both treatment arms (b) (4) contributed the most patients. Stratified randomization ensured balanced treatment assignment at each study site (Table 10).

**Table 10. Study 3101 enrollment by site**

| Study center | Treatment arm G-CSF/plerixafor | G-CSF/placebo | Total |
|---|---|---|---|
| (b) (4) | 21 (14%) | 21 (14%) | 42 (14%) |
| (b) (4) | 18 (12%) | 18 (12%) | 36 (12%) |
| (b) (4) | 12 (8%) | 12 (8%) | 24 (8%) |
| (b) (4) | 11 (7%) | 12 (8%) | 23 (8%) |
| (b) (4) | 10 (7%) | 9 (6%) | 19 (6%) |
| (b) (4) | 8 (5%) | 10 (7%) | 18 (6%) |
| (b) (4) | 9 (6%) | 8 (5%) | 17 (6%) |
| Other 25 sites | 61 (41%) | 58 (39%) | 119 (40%) |
| **Total** | **150 (100%)** | **148 (100%)** | **298 (100%)** |

Source: (blchar1.xpt where PATNUM ≠ missing and RITUX = missing) by (SITENUM and TRTGRPRC)

The ITT population consisted of 298 patients randomized to G-CSF/plerixafor (n = 150) or G-CSF/placebo (n = 148). Two additional randomized patients were excluded because of randomization errors. Approximately 19% of the ITT population were over age 65, and 7% were non-Caucasian. Males outnumbered females by about 2 to 1. Almost all patients had received prior chemotherapy, and patients were approximately evenly divided between first or second remission. Patient characteristics generally appeared well-balanced between treatment arms.

**Table 11. Study 3101 baseline patient characteristics (ITT pop.)**

| Characteristic | G-CSF/plerixafor (n = 150) | G-CSF/placebo (n = 148) | Total |
|---|---|---|---|
| **Demography** | | | |
| **Median age (years)** | 56 | 59 | 58 |
| **Sex** | | | |
| M | 100 (67%) | 102 (69%) | 202 (68%) |
| F | 50 (33%) | 46 (31%) | 96 (32%) |
| **Race** | | | |
| Caucasian | 136 (91%) | 140 (95%) | 276 (93%) |
| Black | 6 (4%) | 1 (1%) | 7 (2%) |
| Hispanic | 5 (3%) | 4 (3%) | 9 (3%) |
| Asian | 2 (1%) | 2 (1%) | 4 (1%) |
| Other | 1 (1%) | 1 (1%) | 2 (1%) |

| | | | |
|---|---|---|---|
| **Pathology** | | | |
| **Disease stage at initial diagnosis** | | | |
| I | 15 (10%) | 10 (7%) | 25 (8%) |
| II | 15 (10%) | 32 (22%) | 47 (16%) |
| III | 29 (19%) | 44 (30%) | 73 (24%) |
| IV | 86 (57%) | 61(41%) | 147 (49%) |
| Missing | 5 (3%) | 1 (1%) | 6 (2%) |
| **Current stage of disease** | | | |
| I | 6 (4%) | 12 (8%) | 18 (6%) |
| II | 15 (10%) | 28 (19%) | 33 (13%) |
| III | 32 (21%) | 34 (23%) | 66 (22%) |
| IV | 72 (48%) | 52 (35%) | 124 (42%) |
| Missing | 25 (17%) | 22 (15%) | 47 (16%) |
| **Treatment history** | | | |
| **Time interval** | | | |
| From initial diagnosis to randomization | 12 mo | 13 mo | 13 mo |
| From last progression/relapse to random. | 4 mo | 4 mo | 4 mo |
| **Prior treatment** | | | |
| Chemotherapy | 145 (97%) | 140 (95%) | 295 (96%) |
| Radiotherapy | 25 (17%) | 29 (20%) | 54 (18%) |
| Surgery | 149 (99%) | 148 (100%) | 297 (99%) |
| **Current remission status** | | | |
| 1st CR | 51 (34%) | 44 (30%) | 95 (32%) |
| 1st PR | 26 (17%) | 19 (13%) | 45 (15%) |
| 2nd CR | 30 (20%) | 29 (20%) | 59 (20%) |
| 2nd PR | 43 (29%) | 54 (36%) | 97 (33%) |
| Missing | 0 (0%) | 2 (1%) | 2 (1%) |

Source: (blchar1.xpt where RANDDT missing and RITUX = missing) by ([TRTGRPC] and [AGE, SEX, ETHNICC, DZSTAGE, CURRSTG, or CREMSTTC])

### 6.1.2.4 AMD3100-3102

Enrollment onto Study 3102 took place from February 4, 2005 to July 7, 2006. The clinical cutoff date was April 6, 2007, at which time, median patient follow-up was 435 days.

Study 3102 was conducted at 40 centers, 38 of which were in the United States and one each in Canada and Germany. No center contributed more than 11% of patients. In both treatment arms **(b) (4)** contributed the most patients. Stratified randomization ensured balanced treatment assignment at each study site (Table 12).

**Table 12. Study 3102 enrollment by site**

| | Treatment arm | | |
|---|---|---|---|
| **Study center** | **G-CSF/plerixafor** | **G-CSF/placebo** | **Total** |
| **(b) (4)** | 17 (11%) | 17 (11%) | 34 (11%) |
| **(b) (4)** | 16 (11%) | 17 (11%) | 33 (11%) |
| **(b) (4)** | 12 (8%) | 10 (6%) | 22 (7%) |
| **(b) (4)** | 8 (5%) | 6 (4%) | 14 (5%) |
| **(b) (4)** | 8 (5%) | 6 (4%) | 14 (5%) |
| **(b) (4)** | 6 (4%) | 7 (5%) | 13 (4%) |
| Other 36 sites | 81 (55%) | 91 (59%) | 179 (59%) |

| | | | |
|---|---|---|---|
| **Total** | **148 (100%)** | **154 (100%)** | **302 (100%)** |

Source: (blchar1.xpt where PATID ≠ 25-401) by (SITENUM and TRTGRPRC)

The ITT population consisted of 302 patients randomized to G-CSF/plerixafor (n = 148) or G-CSF/placebo (n = 154). One additional randomized patient (25-401) was excluded from the ITT population because she was scheduled to receive post-transplantation cytoreductive chemotherapy. Approximately 20% of the population was over age 65, and 19% were non-Caucasian. Males outnumbered females by about 2 to 1. Almost all patients had received prior chemotherapy, and most were in their first partial remission. Patient characteristics generally appeared well-balanced between treatment arms (Table 13).

**Table 13. Study 3102 baseline patient characteristics (ITT pop.)**

| Characteristic | G-CSF/plerixafor (n = 148) | G-CSF/placebo (n = 154) | Total (n = 302) |
|---|---|---|---|
| **Demography** | | | |
| **Median age (years)** | 58 | 59 | 59 |
| **Sex** | | | |
| M | 100 (66%) | 107 (69%) | 202 (68%) |
| F | 48 (32%) | 47 (31%) | 95 (32%) |
| **Race** | | | |
| Caucasian | 117 (79%) | 128 (83%) | 245 (81%) |
| Black | 18 (12%) | 14 (9%) | 32 (11%) |
| Hispanic | 11 (7%) | 4 (3%) | 15 (5%) |
| Asian | 1 (1%) | 3 (1%) | 4 (1%) |
| Other | 1 (1%) | 5 (3%) | 6 (2%) |
| **Pathology** | | | |
| **Disease stage at initial diagnosis**[c] | | | |
| I | 27 (18%) | 14 (9%) | 41 (14%) |
| II | 25 (17%) | 42 (27%) | 67 (22%) |
| III | 83 (56%) | 83 (54%) | 166 (55%) |
| Missing | 13 (9%) | 15 (10%) | 28 (9%) |
| **Current stage of disease**[c] | | | |
| I | 28 (19%) | 19 (12%) | 47 (16%) |
| II | 29(20%) | 44 (29%) | 73 (24%) |
| III | 91 (61%) | 90 (58%) | 181 (60%) |
| Missing | 0 (0%) | 1 (1%) | 1 (1%) |
| **Treatment history** | | | |
| **Median time from initial diagnosis to rand.** | 7 mo | 7 mo | 7 mo |
| **Prior treatment** | | | |
| Chemotherapy | 144 (97%) | 148 (96%) | 292 (97%) |
| Radiotherapy | 40[a] (27%) | 47[b] (31%) | 87 (29%) |
| Surgery | 147 (99%) | 153 (99%) | 300 (99%) |
| **Current remission status** | | | |
| 1st CR | 11 (7%) | 18 (12%) | 29 (10%) |
| 1st PR | 129 (87%) | 126 (82%) | 255 (84%) |
| 2nd PR | 8 (5%) | 10 (6%) | 18 (6%) |

Source: blchar1.xpt by TRTGRPC and AGE, SEX, ETHNICC, DZSTAGE, CURRSTG, or CREMSTTC
[a] 2 missing
[b] 1 missing
[c] Durie-Salmon stage if different from ISS stage

## 6.1.3 Patient Disposition

### 6.1.3.1 AMD3100-2101

#### 6.1.3.1.1 Study Populations

All but one patient (01-102 with MM) received G-CSF run-in treatment, and all 25 received plerixafor. Most patients who began plerixafor treatment completed the treatment period and had 12 months of follow-up (Table 14).

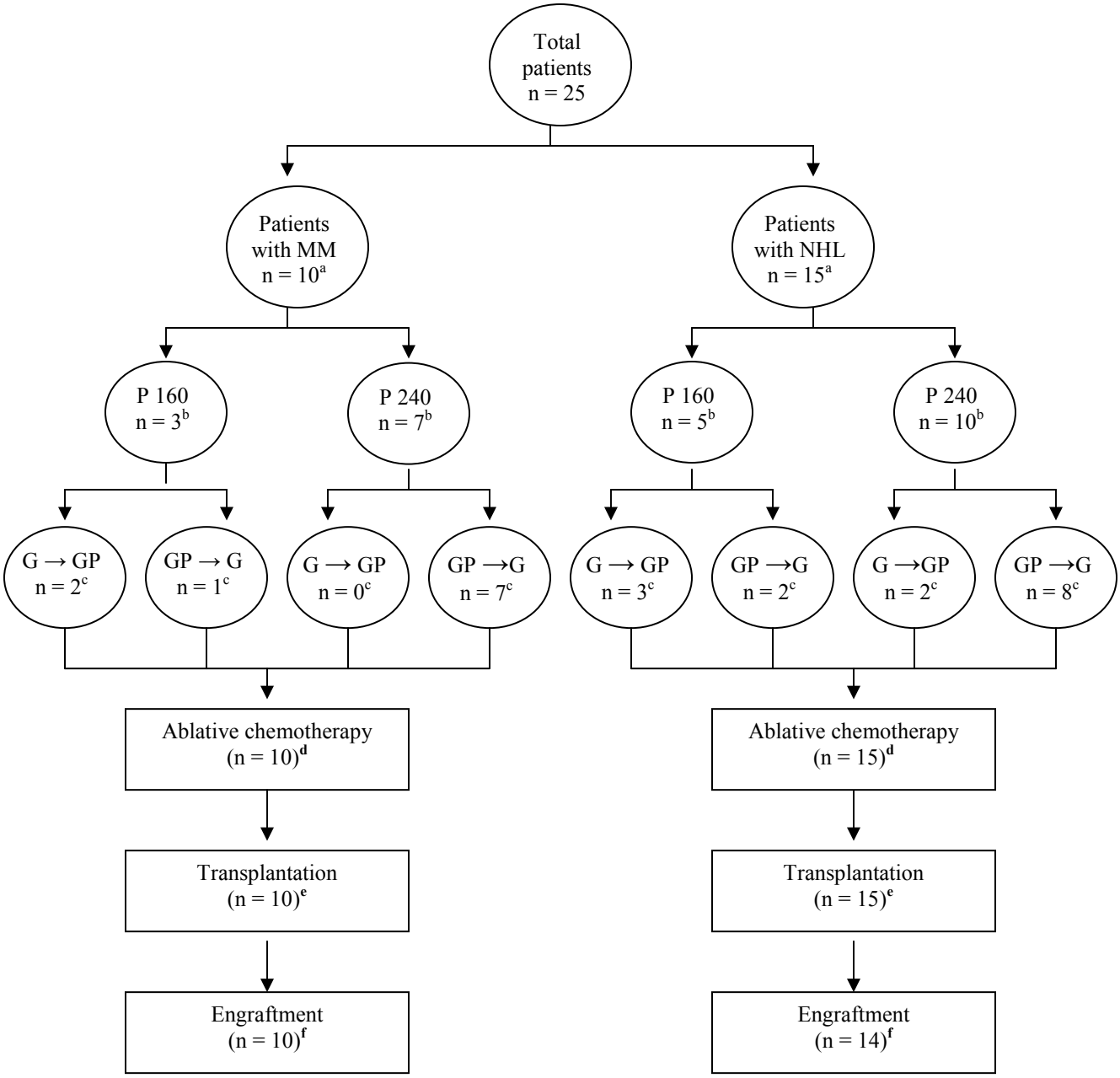
**Table 14. Study 2101 patient disposition**

| Category | Patients with NHL (n = 15) | Patients with MM (n = 10) | All patients (n = 25) |
|---|---|---|---|
| Met criteria for G-CSF run-in[a] | 11 (73%) | 8 (80%) | 19 (76%) |
| Received daily G-CSF[b] | 15 (100%) | 9 (90%) | 24 (96%) |
| Met criteria for treatment phase[c] | 14 (93%) | 9 (90%) | 23 (92%) |
| Continued crossover run-in[d] | 15 (100%) | 10 (100%) | 25 (100%) |
| Treated with plerixafor[e] | 15 (100%) | 10 (100%) | 25 (100%) |
| Completed treatment period[f] | 11 (73%) | 8 (80%) | 19 (76%) |
| Had 3 month follow-up[g] | 14 (93%) | 10 (100%) | 24 (96%) |
| Had 6 month follow-up[g] | 14 (93%) | 9 (90%) | 23 (92%) |
| Had 12 month follow-up[g] | 10 (67%) | 10 (100%) | 20 (80%) |

[a] ELGMOB1 by DIAGTYP, and ELIGCSFG
[b] CROSSQ1 by DIAGTYP, and GCSFDOS
[c] ELGMOB1 by DIAGTYP, and ELIGTX
[d] CROSSQ1 by DIAGTYP, and CRPTCON
[e] CROSSQ1 by DIAGTYP, and CRHLTH
[f] STDYCP1 by DIAGTYP and STYCP
[g] FUP1 by DIAGTYP, FPTMP, and PFMETH

Changes made during the study with regard to sequencing and dosing of study drug (see Sections 6.1.3.1.3, 6.1.3.1.5 and 6.1.3.1.10 of this review) resulted in the distribution of the 25 study patients to eight treatment groups. All 25 patients enrolled received myeloablative chemotherapy followed by HSCT (Figure 1).

**Figure 1. Study 2101 patient distribution**




[a] (PTCOUNT2.xpt by PATID and DIAGTYP) by DIAGTYP
[b] (PTCOUNT2.xpt by PATID, DIAGTYP, and DOSE) by (DIAGTYP and DOSE)
[c] (PTCOUNT2.xpt by PATID, DIAGTYP, and TRTGRP) by (DIAGTYP and TRTGRP)
[d] (PTCOUNT2.xpt where VISIT = Chemotherapy pre-transplant) by (PATID, DIAGTYP and VISCOMP)
[e] (PTCOUNT2.xpt where VISIT = Transplantation1) by (PATID, DIAGTYP and VISCOMP)
[f] (PTCOUNT2.xpt where VISIT = PLT Engraft and PMN Engraft) by (PATID, DIAGTYP and VISCOMP)

6.1.3.1.2 Protocol deviations

Six patients failed to meet all protocol eligibility criteria (Table 15).

**Table 15. Study 2101 eligibility violations**

| Patient ID | Disease | Reason ineligible |
|---|---|---|
| 02-103 | MM | >150% ideal body weight |
| 03-225 | NHL | >150% ideal body weight |
| 03-227 | NHL | $FEV_1$ 42% predicted |
| 03-426 | NHL | WBC 2,100/μL, ANC 1,100/μL |
| 04-762 | MM | Age 72 years |
| 06-683 | NHL | Had not attained PR status but had stable disease |

Source: ELGMOB1 by DIAGTYP, ELIGCSF, and WAVSPEC

***Reviewer's comment:*** *These eligibility violations should not have compromised the integrity of the study results of because co-morbidities generally tend to worsen rather than improve efficacy of cancer therapy.*

Four major and 219 minor protocol violations were reported during the course of the study. All patients had at least one minor protocol violation and three patients had major violations (Table 16). All major protocol violations involved the timing or blood volume of apheresis (Table 17). Most of the minor violations involved failure to complete a required procedure or laboratory study with its specified window (Table 18).

**Table 16. Study 2101 protocol violations**

| | Patients with NHL (n = 15) | Patients with MM (n = 10) | All patients (n = 25) |
|---|---|---|---|
| Patients with any protocol violation | 15 (100%) | 10 (100%) | 25 (100%) |
| Patients with minor violation | 15 (100%) | 10 (100%) | 25 (100%) |
| Patients with major violation | 0 (0%) | 3 (30%) | 3 (12%) |
| Patients with major and minor violations | 0 (0%) | 3 (30%) | 3 (12%) |

Source: PV1.xpt by PATID, DIAGTYP, and DEVSEV

**Table 17. Study 2101 major protocol violations**

| Patient | Nature of violation |
|---|---|
| 01-756 | 4 blood volumes were processed on treatment Days 5 and 6 |
| 01-756 | 5 blood volumes were processed on crossover treatment Day 26 |
| 02-750 | Apheresis initiated 3 hours and 10 minutes after administration of plerixafor on crossover Day 26 |
| 05-751 | 3 blood volumes were not processed during the G-CSF treatment or during the G-CSF/plerixafor crossover |

Source: (PV1 where DEVSEV = "major") by PATID, DEVRESN1, and DIAGTYP

**Table 18. Study 2101 minor protocol violations**

| Nature of violation | Patients with NHL (n = 15) | Patients with MM (n = 10) | All patients (n = 25) |
|---|---|---|---|
| Required protocol procedure not completed | 15 (100%) | 10 (10%) | 25 (100%) |
| Other | 14 (93%) | 9 (9%) | 23 (92%) |
| Measurements/labs taken outside of window | 9 (60%) | 9 (9%) | 18 (72%) |
| Subject did not meet entry criteria | 6 (40%) | 3 (3%) | 9 (36%) |
| Visit not done | 3 (20%) | 2 (2%) | 5 (20%) |
| Plerixafor medication error/non-compliance | 5 (33%) | 0 (0%) | 5 (20%) |
| G-CSF medication error/ non-compliance | 0 (0%) | 3 (3%) | 3 (12%) |
| Informed consent/assent | 1 (7%) | 1 (1%) | 2 (8%) |
| Subject took a prohibited medication/treatment | 0 (0%) | 2 (2%) | 2 (8%) |
| Visit is outside of specified window | 2 (13%) | 0 (0%) | 2 (8%) |

6.1.3.2 AMD3100-2106

Fifteen of the 22 enrolled patients met all protocol eligibility criteria. Six of the other seven were granted waivers to be treated and the seventh was treated without a waiver (Table 19)

**Table 19. Study 2106 eligibility violations**

| Category | Number of patients |
|---|---|
| Met all eligibility criteria | 15 (68%) |
| Received a waiver to begin treatment | 7 (32%) |
| Prior mobilization attempt unsuccessful due to improper cell processing | 1 (7%) |
| ANC 1,300/mL | 1 (7%) |
| Platelets 82,000/mL | 1 (7%) |
| Actual body weight exceeded 150% ideal body weight | 2 (13%) |
| History of ventricular arrhythmia | 1 (7%) |
| Was treated without a waiver | 1 (%) |
| **Total** | **22 (100%)** |

Source: ELIGMOB1.xpt by ELIGCSF and VAWSPEC

All 22 enrolled patients received and completed treatment with both G-CSF and plerixafor. Twelve-month follow-up data were available for approximately two thirds of patients (Table 20).

**Table 20. Study 2106 patient disposition**

| Category | All patients (n = 22) |
|---|---|
| Received daily G-CSF[b] | 22 (100%) |
| Met criteria for treatment phase[b] | 22 (100%) |
| Treated with plerixafor[c] | 22 (100%) |
| Completed treatment period[d] | 21 (95%) |
| Had 3 month follow-up[e] | 14 (64%) |
| Had 6 month follow-up[e] | 15 (68%) |
| Had 12 month follow-up[f] | 15 (68%) |

[a] (ELGMOB1.xpt where PATID ≠ 01-107) by GCSFDOS
[b] (ELGMOB1.xpt where PATID ≠ 01-107) by ELIGTX
[c] (APHSDDG1.xpt where PATID ≠ 01-107) by PATID and SD1DT
[d] (STDYCP1.xpt where PATID ≠ 01-107) by STYCP

[e] (FUP1.xpt where PATID ≠ 01-107) by FPTMP and PFMETH
[f] FUP12M1.xpt by PFMETH

### 6.1.3.2 AMD3100-3101

A total of 30 patients (10%) had major violations of one or more eligibility criteria, as defined by the Sponsor. These violations appeared well balanced between treatment arms and are unlikely to have significantly affected the study results (Table 21).

**Table 21. Study 3101 major eligibility violations**

| Violation | G-CSF/plerixafor (n = 150) | G-CSF/placebo (n = 148) | All patients (n = 298) |
|---|---|---|---|
| Platelets < 100,000/μL | 0 (0%) | 1 (1%) | 1 (<1%) |
| ANC < 1500/μL | 1 (1%) | 1 (1%) | 2 (1%) |
| Unable to verify if last dose of chemotherapy > 4 weeks from start of study drug | 7 (5%) | 5 (3%) | 14 (5%) |
| Patient was in 3rd CR | 0 (0%) | 2 (1%) | 2 (1%) |
| Received chemotherapy within 4 weeks of or after starting study drug | 3 (12%) | 3 (2%) | 5 (2%) |
| Not specified laboratory result, patient not dosed | 0 (0%) | 2 (1%) | 2 (1%) |
| ALT > 2.5 x ULN | 0 (0%) | 1 (1%) | 1 (<1%) |
| Prior bone marrow transplant | 1 (1%) | 0 (0%) | 1 (<1%) |
| Not treated due to an SAE | 2 (1%) | 0 (0%) | 2 (1%) |
| **Total** | **14 (9%)** | **15 (10%)** | **29 (10%)** |

Source: (PROTVOL1.xpt where TIMEPT = SC) by (TRTGRP and TEXT1)

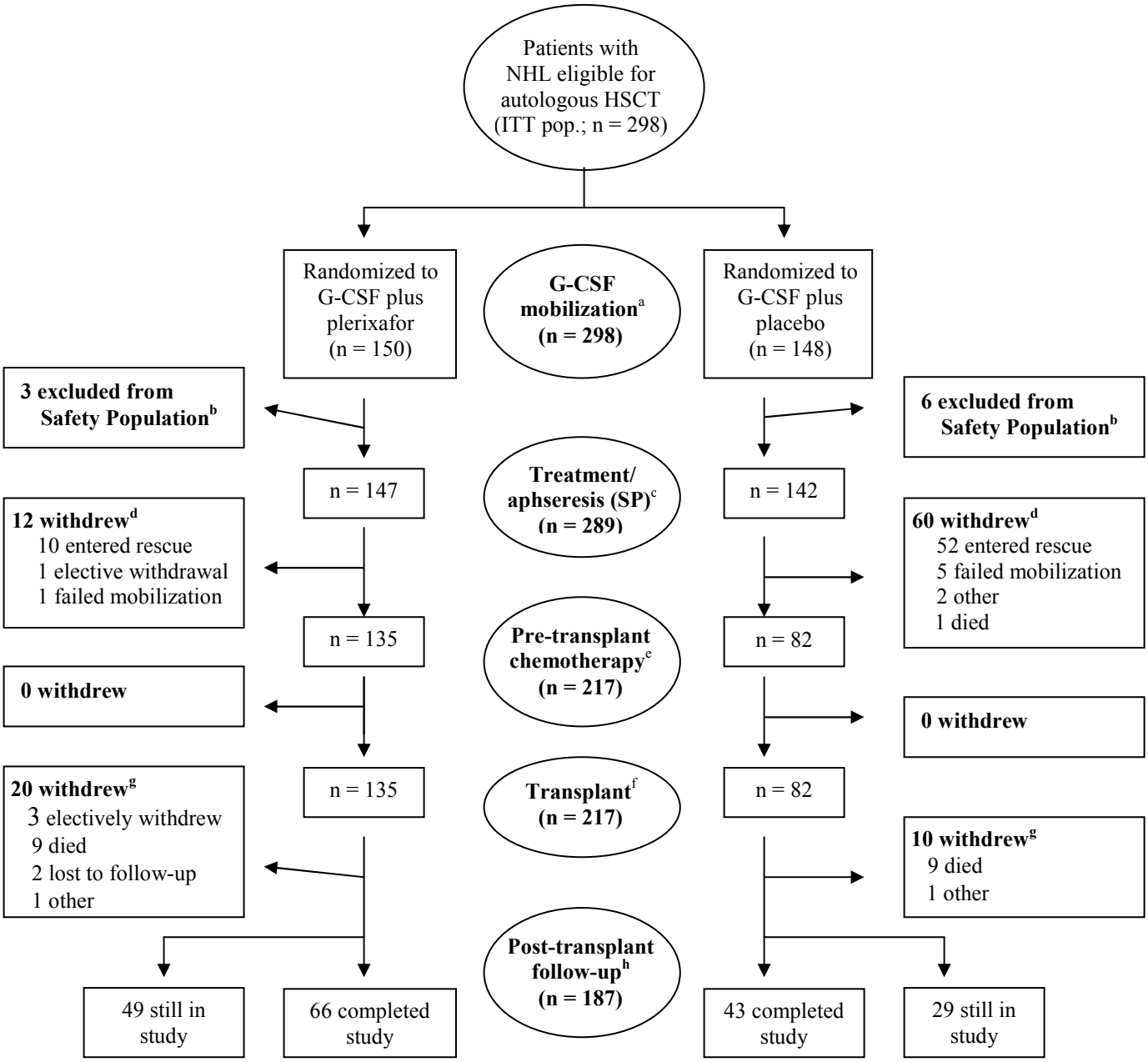
All 298 patients in the ITT population began G-CSF mobilization. Nine (3%) were excluded from the safety population for having failed to receive at least one dose of study drug.

Of 289 patients who began treatment/apheresis, 72 (12 randomized to G-CSF/plerixafor and 60 randomized to G-CSF/placebo) did not complete treatment/apheresis. This difference was driven by a larger number of patients from the G-CSF/placebo group entering the rescue procedure.

In each treatment group, all patients who completed apheresis also completed pre-transplant chemotherapy and transplantation (135 patients in the G-CSF/plerixafor group and 82 in the G-CSF/placebo group). After transplantation, 20 patients in the G-CSF/plerixafor group and 10 patients in the G-CSF/placebo group withdrew from the study. Death caused post-transplantation withdrawal in 14 of 135 (10%) patients in the G-CSF/plerixafor group and 9 of 82 (11%) in the G-CSF/placebo group.

In the G-CSF/plerixafor group, 66 patients completed the study and 49 are still in the study. In the G-CSF/placebo group, 43 completed the study and 29 are still on study. The CRFs suggest that most patients whom the dataset listed the reason for withdrawal as “other” likely had AEs. The disposition of patients during the rescue procedure is presented in Section 6.1.6.1.2 of this review.

**Figure 2. Study 3101 patient populations**




[a] (DISP1.xpt where RANDDT ≠ missing and RITUX = missing) by TRTGRPC
[b] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, and ITT1 = 0) by TRTGRPC
[c] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, and ITT1 = 1) by TRTGRPC
[d] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, ITT1 = 1, and ITT2 = 0) by TRTGRPC
[e] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, ITT1 = 1, and ITT2 = 1) by TRTGRPC
[f] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, ITT1 = 1, ITT2 = 1, and COMP4 = 1) by TRTGRPC
[g] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, ITT1 = 1, ITT2 = 1, and OFFTXYN = 1) by TRTGRPC
[h] (DISP1.xpt where RANDDT ≠ missing, RITUX = missing, ITT1 = 1, ITT2 = 1, and OFFTXYN = 2) by TRTGRPC

Of the 298 randomized patients, 98 (33%) had major protocol violations (Table 22). Thirteen patients had more than one major protocol violation. Approximately 80% of major protocol violations occurred during screening, G-CSF mobilization, or apheresis (data not shown).

**Table 22. Study 3101 major protocol violations**

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

Source: (PROTVOL1 where RITUX = missing and SEV = Major) by TRTGRP and TYPE

***Reviewer's comment:*** *These protocol violations are unlikely to have biased the study results for the following reasons.*

1. *Their numbers are not surprising, given the complex designs of the randomized trials.*
2. *In general, violations in eligibility, administration of study drug and follow-up tend to cause the treatment arm in which they occur appear less efficacious. An exception is apheresis with > 3 blood volumes, which would favor the primary endpoint in that arm. In addition, the performance of extra apheresis sessions would favor long-term engraftment. There were only five instances of either of those violations (three in the plerixafor arm and two in the placebo arm).*
3. *The nature and timing of these violations were well-balanced between treatment arms.*

6.1.3.4 AMD3100-3102

A total of 36 patients (12%) had major violations of one or more eligibility criteria. These violations appeared well balanced between treatment arms and are unlikely to have significantly affected the study results (Table 23).

**Table 23. Study 3102 major eligibility violations**

| Violation | G-CSF/plerixafor (n = 148) | G-CSF/placebo (n = 154) | All patients (n = 292) |
|---|---|---|---|
| Differential was not done | 0 (0%) | 2 (1%) | 2 (1%) |
| ANC < 1500/μL or WBC < 2,000/μL | 1 (1%) | 2 (1%) | 3 (1%) |
| Unable to verify if last dose of chemotherapy > 4 weeks from start of study drug | 11 (7%) | 2 (1%) | 13 (4%) |
| Prior radiation to >50% of pelvis | 0 (0%) | 1 (1%) | 1 (<1%) |
| Received chemotherapy within 4 weeks of or after starting study drug | 2 (1%) | 6 (4%) | 8 (3%) |
| Received or may have received glucocorticoid within 7 days of study drug | 3 (2%) | 2 (1%) | 5 (2%) |
| Insufficient cardiac function | 1 (1%) | 0 (0%) | 1 (<1%) |
| ALT > 2.5 x ULN | 1 (1%) | 0 (0%) | 1 (<1%) |
| Rescue consent signed instead of main version | 1 (1%) | 0 (0%) | 1 (<1%) |

| | | | |
|---|---|---|---|
| Not treated due to an insurance issue | 0 (0%) | 1 (1%) | 1 (<1%) |
| **Total** | **20 (14%)** | **16 (10%)** | **36 (12%)** |

Source: (PROTVOL1.xpt where TIMEPT = SC) by (TRTGRP and TEXT1)

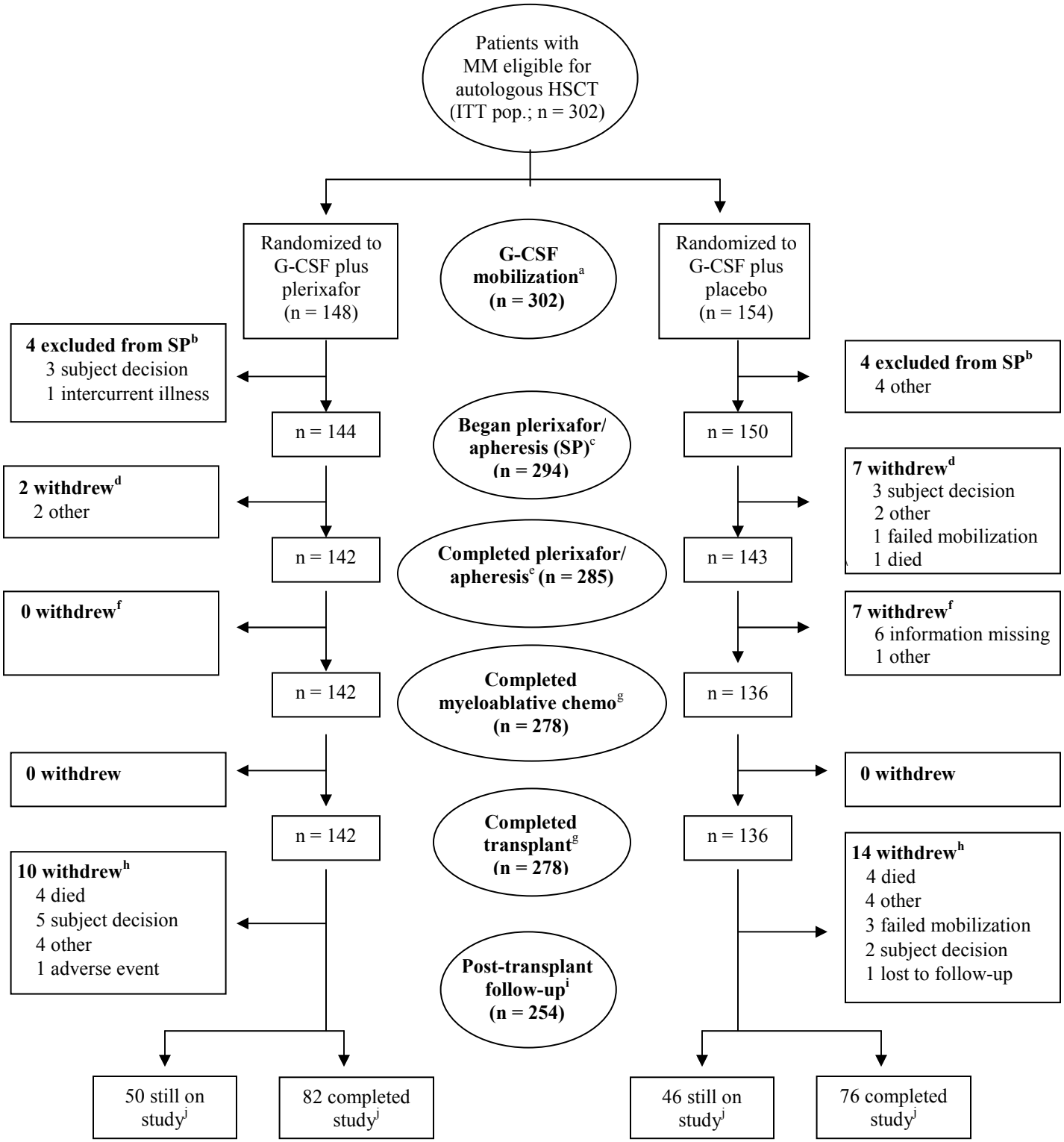
All 302 patients in the ITT population entered the G-CSF mobilization phase of the study. Eight (3%) were excluded from the safety population for having failed to receive at least one dose of study drug. Of 294 patients who began treatment/apheresis, nine (two randomized to G-CSF/plerixafor and seven randomized to G-CSF/placebo) did not complete treatment/apheresis.

Two hundred and seventy eight patients completed myeloablative chemotherapy (142 in the G-CSF/plerixafor group and 136 in the G-CSF/placebo group) and all 278 of them went on to HSCT. After transplantation, 10 patients in the G-CSF/plerixafor group and 14 patients in the G-CSF/placebo group withdrew from the study.

In the G-CSF/plerixafor group, 82 patients completed the study and 50 remain on study. In the G-CSF/placebo group, 76 completed the study and 46 remain on study. For the disposition of patients during the rescue procedure, see Section 6.1.6.2.2 of this review.

***Reviewer's comment:*** *The submitted datasets and CRFs did not fully identify the factor(s) that drove study discontinuation for many patients after plerixafor administration. Nonetheless, relatively few patients dropped out early, and those that did appeared well balanced between treatment arms, so dropouts seem unlikely to have significantly biased the study results.*

**Figure 3. Study 3102 patient populations**




[a] (DISP1.xpt where PATID ≠ 25-401) by TRTGRPC

[b] (DISP1.xpt where PATID ≠ 25-401 and ITT1 = 2) by TRTGRPC
[c] (DISP1.xpt where PATID ≠ 25-401 and ITT1 = 1) by TRTGRPC
[d] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, and COMP2 = 2) by TRTGRPC and ORRTXRNC
[e] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, COMP2 = 1) by TRTGRPC
[f] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, and COMP2 = 1, COMP3 = 1, RCOMP1 = 1, and RCOMP3 = 1) by TRTGRPC
[g] (DISP1.xpt where PATID ≠ 25-401 ITT1 = 1, COMP2 = 1, and RCOMP3 = 1) by TRTGRPC
[h] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, COMP2 = 1, RCOMP3 = 1, and COMP5 = 2) by TRTGRPC and OFFTXRNC
[i] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, COMP2 = 1, RCOMP3 = 1, and COMP5 = 1 or 3) by TRTGRPC
[j] (DISP1.xpt where PATID ≠ 25-401, ITT1 = 1, COMP2 = 1, and RCOMP5 = 1 or 3) by TRTGRPC and RCOMP5

Of the 302 randomized patients, 117 (39%) had major protocol violations (Table 24). Nineteen patients (6%) had more than one major protocol violation. Approximately 76% of the major protocol violations occurred during screening, G-CSF mobilization, or apheresis (data not shown).

**Table 24. Study 3102 major protocol violations**

| Category | G-CSF/plerixafor (n = 148) | G-CSF/placebo (n = 154) |
|---|---|---|
| Eligibility | 21 (14%) | 14 (9%) |
| Apheresis | 16 (11%) | 15 (10%) |
| Missing data | 7 (5%) | 10 (6%) |
| G-CSF dosing | 11 (7%) | 7 (5%) |
| Treatment dosing | 1 (1%) | 4 (3%) |
| Timing | 7 (5%) | 3 (1%) |
| Concurrent therapy | 0 (0%) | 0 (%) |
| Unknown | 0 (0%) | 1 (1%) |
| **Total** | **63 (43%)** | **54 (35%)** |

Source: (PROTVOL1.xpt where PATID ≠ 25-401 and SEV contains "Major") by (TRTGRP and TYPE)

***Reviewer's comment:*** *These protocol violations are unlikely to have biased the study results for the following reasons.*

1. *Their numbers are not surprising, given the complex designs of the randomized trials.*
2. *In general, violations in eligibility, administration of study drug and follow-up tend to cause the treatment arm in which they occur appear less efficacious. An exception is apheresis with > 3 blood volumes, which would favor the primary endpoint in that arm. In addition, the performance of extra apheresis sessions would favor long-term engraftment. There were only five instances of either of those violations (three in the plerixafor arm and two in the placebo arm).*
3. *The nature and timing of these violations were well-balanced between treatment arms.*

### 6.1.4 Analysis of Primary Endpoints

#### 6.1.4.1 AMD3100-2101

The primary efficacy parameter was the cumulative number of $CD34^+$ cells/kg collected by apheresis as measured by FACS. Central laboratory data were used for this analysis, unless that information was missing, in which case, local data were used.

In both the NHL and MM patient subgroups and overall, the G-CSF/plerixafor regimen resulted in a significantly greater total $CD34^+$ cell/kg collection than G-CSF alone. In patients with NHL, the mean average daily $CD34^+$ collection was 2.9 x $10^6$ cells/kg with G-CSF/plerixafor, compared to 1.0 x $10^6$ cells/kg with G-CSF alone ($p < 0.001$, paired t-test). In patients with MM, the mean average daily $CD34^+$ collection was 6.6 x $10^6$ cells/kg with G-CSF/plerixafor, compared to 2.5 x $10^6$ cells/kg with G-CSF alone ($p = 0.025$, paired t-test). The mean within-patient difference in total $CD34^+$ cells/kg collected with G-CSF/plerixafor versus G-CSF alone (i.e. the treatment effect) for patients with NHL was 3.1 x $10^6$ cells/kg ($p = 0.011$, paired t-test) and for patients with MM was 4.1 x $10^6$ cells/kg ($p < 0.001$, paired t-test).

**Table 25. Study 2101 cumulative $CD34^+$ cells collected**

| | Patients with NHL (n = 15) | | Patients with MM (n = 10) | | All patients (n = 25) | |
|---|---|---|---|---|---|---|
| | **G-CSF/plerix.** | **G-CSF alone** | **G-CSF/plerix.** | **G-CSF alone** | **G-CSF/plerix.** | **G-CSF alone** |
| **Cumulative $CD34^+$ cells collected ($10^6$/kg)** | | | | | | |
| Mean | 5.8 | 2.8 | 10.4 | 6.3 | 7.7 | 4.2 |
| Median | 5.5 | 1.5 | 7.9 | 4.9 | 6.6 | 4.3 |
| Range | 2.7, 3.7 | 0, 9.1 | 5.5, 25.4 | 0.5, 17.2 | 2.7, 25.4 | 0, 17.2 |
| **Within patient difference in cumulative $CD34^+$ cells collected ($10^6$/kg)** | | | | | | |
| Mean | 3.1 | | 4.1 | | 3.5 | |
| Median | 2.7 | | 4.1 | | 3.4 | |
| Range | -3.9, 13.0 | | 0.1, 8.2 | | -3.9, 13.0 | |
| t-test P | 0.011 | | <0.001 | | <0.001 | |
| Signed rank P | 0.005 | | 0.002 | | <0.001 | |
| **Average $CD34^+$ cells collected per day of apheresis ($10^6$/kg)** | | | | | | |
| Mean | 3.2 | 0.9 | 6.2 | 2.4 | 4.4 | 1.5 |
| Median | 1.9 | 0.4 | 4.4 | 1.2 | 3.3 | 1.0 |
| Range | 0.6 – 7.2 | 0 – 2.5 | 0.8 – 25.4 | 0.3 – 9.2 | 0.6 – 25.4 | 0 – 9.2 |
| **Within patient difference in average $CD34^+$ cells collected per day of apheresis ($10^6$/kg)** | | | | | | |
| Mean | 2.4 | | 4.2 | | 2.8 | |
| Median | 1.5 | | 2.3 | | 1.6 | |
| Range | 0.1-6.8 | | 0.6-16.8 | | 0.1-16.8 | |
| t-test P | <0.001 | | 0.039 | | <0.001 | |
| Signed rank P | <0.001 | | 0.002 | | <0.001 | |

Source: (EAPH3.xpt by DIAGTYP) Fit Y by X: Y response = TCD34GA and TCD34G], X factor = MOBTRT

6.1.4.2 AMD3100-2106

The median number of $CD34^+$ cells collected was 6.9 x $10^6$/kg. Fifteen of 22 patients (68%) succeeded in meeting the primary efficacy endpoint of collecting a total of ≥ 5 x $10^6$ $CD34^+$ cells/kg.

Note that Patient 01-107 was mobilized a second time due to a problem with handling of the first collection. Combining the yield of the first collection (4.9 x $10^6$ cells/kg) with the second collection (< 2 x $10^6$ cells/kg), the patient had enough cells for transplantation but data from the second cell collection was used for analysis, so the patient was counted as a failure.

6.1.4.3 AMD3100-3101

Eighty nine (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 ($p < 0.001$; Table 26).

**Table 26: Study 3101 total $CD34^+$ cells mobilized within four apheresis days (ITT pop.)**

| $CD34^+$ cells mobilized | G-CSF/plerixafor (n = 150) | G-CSF/placebo (n = 148) |
|---|---|---|
| ≥ 5 × $10^6$ /kg | 89 (59%) | 29 (20%) |
| < 5 × $10^6$/kg | 61 (41%) | 119 (80%) |
| Estimate of treatment effect | 39.7% | |
| 95% CI of estimate of treatment effect | 29.6% – 49.9% | |
| Pearson's Chi-square *P*-value | < 0.001 | |

Source: (DISP1.xpt where RANDDT ≠ missing and RITUX = missing) joined including non-matches with (EAPH1.xpt where RITUX = missing)
Y response: if (CD34DAY5 + CD34DAY6 + CD34DAY7 + CD34DAY8) ≥ 5, "Yes"; else "No"
X factor: TRTGRPC

6.1.4.4 AMD3100-3102

One hundred and six (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of ≥ 6 × $10^6$ $CD34^+$ cells/kg within two apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($p < 0.001$; Table 27).

**Table 27: Study 3102 collection of 6 x $10^6$ $CD34^+$ cells within two apheresis days (ITT pop.)**

| $CD34^+$ cells mobilized | G-CSF/plerixafor (n = 148) | G-CSF/placebo (n = 154) |
|---|---|---|
| ≥ 6 × $10^6$/kg within 2 apheresis days | 106 (72%) | 53 (34%) |
| < 6 × $10^6$/kg within 2 apheresis days | 42 (28%) | 101 (66%) |
| Estimate of treatment effect | 37.2% | |
| 95% CI of estimate of treatment effect | 26.7% – 47.7% | |
| Cochran-Mantel-Haenszel *P*-value | <0.001 | |
| Pearson's Chi-square *P*-value | < 0.001 | |

Source: (DISP1.xpt where PATID ≠ 25-401) join including non-matches (EAPH1.xpt where PATID ≠ 25-401)
Y response: if (CD34DAY5 + CD34DAY6) ≥ 5,

X factor: TRTGRPC

## 6.1.5 Analysis of Secondary Endpoints

### 6.1.5.1 AMD3100-2101

#### 6.1.5.1.1 Number of apheresis days required to reach ≥ 5 × $10^6$ $CD34^+$ cells/kg

The number of days to reach 5 × $10^6$ $CD34^+$ cells/kg was calculated using central laboratory data with the exception of one entry (Patient 03-881, Day 3, G-CSF/plerixafor regimen) for which that value was missing and the local laboratory value was used.

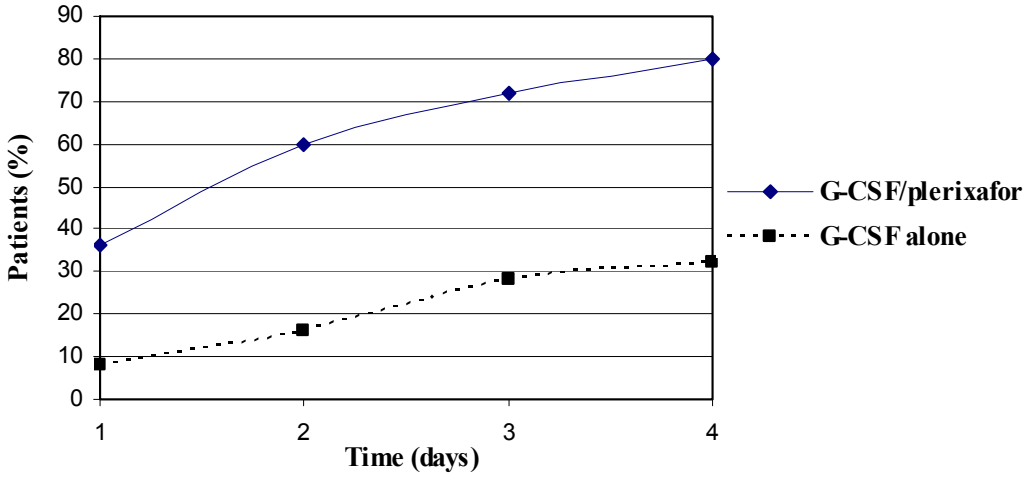
Overall, and within NHL and MM patient subgroups, more patients successfully mobilized ≥ 5 and ≥ 2 x $10^6$ $CD34^+$ cells/kg with G-CSF/plerixafor than G-CSF alone. In addition, times to reach those targets were consistently shorter with G-CSF/plerixafor than G-CSF alone (Table 28 and Figure 4). Because the sample size was small, this reviewer did not analyze these differences statistically.

**Table 28. Study 2101 apheresis product**

| | Patients with NHL (n = 15) | | Patients with MM (n = 10) | | All patients (n = 25) | |
|---|---|---|---|---|---|---|
| | G-CSF/plerix. | G-CSF alone | G-CSF/plerix. | G-CSF alone | G-CSF/plerix. | G-CSF alone |
| **Daily number of patients to collect ≥ 5 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| Day 1 | 5 (33%) | 0 (0%) | 4 (40%) | 2 (20%) | 9 (36%) | 2 (8%) |
| Day 2 | 3 (20%) | 1 (7%) | 3 (30%) | 1 (10%) | 6 (24%) | 2 (8%) |
| Day 3 | 1 (7%) | 1 (7%) | 2 (20%) | 2 (20%) | 3 (12%) | 3 (12%) |
| Day 4 | 1 (7%) | 1 (7%) | 1 (10%) | 0 (0%) | 2 (8%) | 1 (4%) |
| **Cumulative number of patients to collect ≥ 5 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| Day 1 | 5 (33%) | 0 (0%) | 4 (40%) | 2 (20%) | 9 (36%) | 2 (8%) |
| Day 2 | 8 (53%) | 1 (7%) | 7 (70%) | 3 (30%) | 15 (60%) | 4 (16%) |
| Day 3 | 9 (60%) | 2 (13%) | 9 (90%) | 5 (50%) | 18 (72%) | 7 (28%) |
| Day 4 | 10 (67%) | 3 (20%) | 10 (100%) | 5 (50%) | 20 (80%) | 8 (32%) |
| **Number of apheresis days to collect ≥ 5 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| N | 10 | 3 | 10 | 5 | 20 | 8 |
| Mean | 1.8 | 3.0 | 2.0 | 2.0 | 1.9 | 2.4 |
| Median | 1.5 | 3.0 | 2.0 | 2.0 | 2.0 | 2.5 |
| Range | 1.0, 4.0 | 2.0, 4.0 | 1.0, 4.0 | 1.0, 3.0 | 1.0, 4.0 | 1.0, 4.0 |
| **Daily number of patients to collect ≥ 2 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| Day 1 | 7 (47%) | 2 (13%) | 7 (70%) | 3 (30%) | 14 (56%) | 5 (20%) |
| Day 2 | 8 (53%) | 5 (33%) | 3 (30%) | 6 (60%) | 11 (44%) | 11 (44%) |
| **Cumulative number of patients to collect ≥ 2 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| Day 1 | 7 (47%) | 2 (13%) | 7 (70%) | 3 (30%) | 14 (56%) | 5 (20%) |
| Day2 | 15 (100%) | 7 (47%) | 10 (100%) | 9 (90%) | 25 (100%) | 16 (64%) |
| **Number of apheresis days to collect ≥ 2 x $10^6$ $CD34^+$ cells/kg** | | | | | | |
| N | 15 | 7 | 10 | 9 | 25 | 16 |
| Mean | 1.5 | 1.7 | 1.3 | 1.7 | 1.4 | 1.7 |
| Median | 2.0 | 2.0 | 1.0 | 2.0 | 1.0 | 2.0 |
| Range | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 |

Source: EAPH2.xpt using variables PATID, ELTIMPN, DIAGTYP, MOBTRT, ACD34TOT, and SEQDAY

**Figure 4. Study-2101 cumulative patients collecting 5 x $10^6$ $CD34^+$ cells/kg**




6.1.5.1.2 Time to neutrophil engraftment

All 25 patients (100%) on Study 2101 underwent autologous HSCT. Eleven of 15 (73%) in the NHL group and 9 of 10 (90%) in the MM group did so with apheresis products mobilized exclusively using G-CSF/plerixafor and were therefore evaluable for neutrophil engraftment. Of those 20 evaluable patients, 19 engrafted within 12 days. The one exception was Patient 03-225 with NHL who experienced delayed neutrophil engraftment and died of sepsis.

**Table 29. Study 2101 neutrophil engraftment**

| Parameter | Patients with NHL (n = 15) | Patients with MM (n = 10) | All patients (n = 25) |
|---|---|---|---|
| **Patients transplanted (n)** | 15 | 10 | 25 |
| **Transplants performed (n)** | | | |
| Total | 15 | 11[a] | 26 |
| With only G-CSF/plerixafor product | 11 | 9 | 20 |
| **Days to neutrophil engraftment (n)[b]** | | | |
| Mean | 12.6 | 10.6 | 11.7 |
| Median | 10.0 | 11.0 | 10.5 |
| Range | 10 – 35 | 9 – 12 | 9 – 35 |
| **Days to neutrophil engraftment (n)[b]** | | | |
| Mean | 26.0 | 14.6 | 20.6 |
| Median | 18.5 | 17.0 | 17.0 |
| Range | 10 – 89 | 1 – 18 | 1 – 89 |

Source: TPL1.xpt, variables PATID, DIAGTYP, TPPROD, DAYSPMN, and DAYSPLT
[a] Patient 06-754 had second transplant with G-CSF alone but engrafted following the first transplant and is included twice
[b] Calculated only for patients transplanted with G-CSF/plerixafor product

6.1.5.2 AMD3100-2106

6.1.5.2.1 Number of apheresis days required to reach ≥ 2 × $10^6$ $CD34^+$ cells/kg

Eighteen of 22 patients (82%) met the secondary efficacy endpoint of collecting a total of ≥ 2 x $10^6$ $CD34^+$ cells/kg by central laboratory data (Table 30). This result compared favorably with historical controls.[50]

6.1.5.2.2 Change in number of circulating $CD34^+$ cells/μL

Peripheral blood $CD34^+$ cell counts increased a median three-fold 10 – 11 hours after the first dose of plerixafor. Target mobilizations of ≥ 2 and ≥ 5 x $10^6$ $CD34^+$ cells/kg were reached in means of 1.3 and 1.7 days, respectively.

**Table 30. Study 2106 total $CD34^+$ cell mobilization (ITT pop.)**

| Parameter | Patients (n = 22) |
|---|---|
| **Number of patients mobilizing a total of ≥ 2 x $10^6$ $CD34^+$ cells/kg[a]** | 18 (82%) |
| **Absolute CD34+ cell count** | |
| Before first plerixafor dose[b] | |
| N | 20 |
| Mean | 21.4 x $10^6$/μL |
| Median | 13.0 x $10^6$/μL |
| Range | 0 – 74.0 x $10^6$/μL |
| Following first plerixafor dose[b] | |
| N | 21 |
| Mean | 61.1 x $10^6$/μL |
| Median | 40.0 x $10^6$/μL |
| Range | 6 – 156.0 x $10^6$/μL |
| N-fold increase in CD34+ cell count[b] | |
| N | 19 |
| Mean | 3.2 x $10^6$/μL |
| Median | 3.0 x $10^6$/μL |
| Range | 1.7 – 5.7 x $10^6$/μL |
| **Time to reach target total $CD34^+$ cell collection[c]** | |
| ≥ 5 x $10^6$ $CD34^+$ cells/kg | |
| N | 13 |
| Mean | 1.7 days |
| Median | 1.0 days |
| Range | 1.0 – 3.0 days |
| ≥ 2 x $10^6$ $CD34^+$ cells/kg | |
| N | 18 |
| Mean | 1.3 days |
| Median | 1.0 days |
| Range | 1.0 – 3.0 days |

[a] APHPAT2.xpt: APHCELL1 + APHCELL2 + APHCELL3 + APHCELL4 + APHCELL5
[b] LABAPHL2.xpt variables LBTEST and APHVISIT
[c] APHPAT2.xpt variables TARGET2 and TARGET5

Twenty-one of 22 (95%) patients proceeded to transplantation with G-CSF/plerixafor mobilized product. The remaining patient (Patient 01-113) withdrew during the follow-up phase because of insufficient cell collection.

6.1.5.2.3 Time to neutrophil engraftment

All 21 (100%) transplanted patients achieved successful neutrophil engraftment, all but one by Day 12. The remaining patient had neutrophil engraftment on Day 14. This patient had been granted a waiver to mobilize a second time due to a problem with handling of the first collection.

Twenty of 21 (95%) transplanted patients achieved platelet engraftment. Of those 20 patients, 19 (95%) achieved platelet engraftment by Day 22; the remaining patient (Patient 01-119) engrafted on Day 29.

6.1.5.2.4 Graft durability at 3, 6 and 12 months

Patient follow-up was ongoing at the time this NDA was submitted. On August 28, 2008, the Applicant submitted final 12-month graft durability reports for Studies 3101 and 3102 but not for Study 2106.

As of the data cut-off of 05 April 2007, 12-month post-transplant follow-up data were available for 15 patients on Study 2106, all of whom had durable grafts. No instance of graft failure was reported (Table 31).

**Table 31. Study 2106 engraftment**

| Parameter | Value |
|---|---|
| **Time to engraftment**[a] | |
| **Neutrophils** | |
| N | 21 |
| Mean | 9.3 days |
| Median | 9.0 days |
| Range | 8.0 – 14.0 days |
| **Platelets** | |
| N | 20 |
| Mean | 18.6 days |
| Median | 19 days |
| Range | 11.0 – 29.0 days |
| **Graft durability**[b] | |
| **3 months post-transplant** | |
| N evaluable | 15/22 (71%) |
| Durable | 15/22 (71%) |
| **6 months post-transplant** | |
| N evaluable | 15/22 (71%) |
| Durable | 15/22 (71%) |
| **12 months post-transplant** | |
| N evaluable | 15/22 (71%) |
| Durable | 15/22 (71%) |

[a] TP2.xpt variables DAYSPMN and DAYSPLT
[b] FUPDUR.xpt by DUR3, DUR6, and DUR12

### 6.1.5.3 AMD3100-3101

#### 6.1.5.3.1 Mobilization of ≥ 2 × $10^6$ $CD34^+$ cells/kg within 4 apheresis days

One hundred and thirty (87%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of mobilization of ≥ 2 × $10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 70 (47%) patients randomized to G-CSF/placebo (P < 0.001; Table 32).

**Table 32. Study 3101 collection of 2 × $10^6$ $CD34^+$ cells/kg within 4 apheresis days (ITT pop.)**

| $CD34^+$ cells mobilized | G-CSF/plerixafor (n = 150) | G-CSF/placebo (n = 148) |
|---|---|---|
| **Secondary efficacy endpoint** | | |
| ≥ 2 × $10^6$ /kg | 130 (87%) | 70 (47%) |
| < 2 × $10^6$/kg | 20 (13%) | 78 (53%) |
| Estimate of treatment effect | 39.4% | |
| 95% CI of estimate of treatment effect | 29.7% – 49.1% | |
| Cochran-Mantel-Haenszel P-value | <0.001 | |
| Pearson chi-square P-value | < 0.001 | |

Source: (DISP.xpt where RANDDT ≠ missing and RITUX = missing) joined including non-matches with (EAPH1.xpt where RITUX = missing)
Y response: if (CD34DAY5 + CD34DAY6) ≥ 2, "Yes"; else "No"
X factor: TRTGRPC

#### 6.1.5.3.2 Number of apheresis days required to mobilize ≥ 5 x $10^6$ $CD34^+$ cells/kg

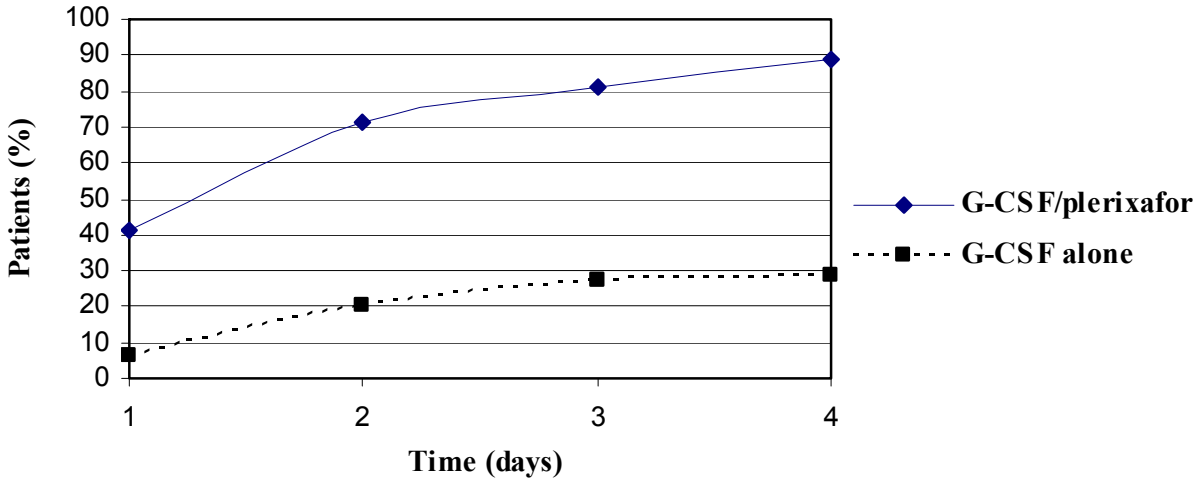
The median number of apheresis days required to mobilize ≥ 5 x $10^6$ $CD34^+$ cells/kg was 3.0 in the G-CSF/plerixafor group and could not be estimated in the G-CSF/placebo group because less than half of the patients in that group reached the target in four days (Table 33 and Figure 5).

**Table 33. Study 3101 apheresis days required to mobilize 5 x $10^6$ $CD34^+$ cells/kg (ITT pop.)**

| | G-CSF/plerixafor (n = 147) | G-CSF/placebo (n = 142) |
|---|---|---|
| **Patients reaching target by day** | | |
| Apheresis Day 1 | 41 (28%) | 6 (4%) |
| Apheresis Day 2 | 71 (49%) | 20 (14%) |
| Apheresis Day 3 | 81 (58%) | 27 (22%) |
| Apheresis Day 4 | 89 (66%) | 29 (24%) |
| **Median time to reach target** | | |
| Median | 3 days | Not estimable |
| HR | 3.6 | |
| 95% CI of HR | 2.4, 5.5 | |
| Log-rank P | <0.001 | |

Source: (EAPH1.xpt where RITUX = missing) by (TRTGRPR, CD34DAY5, CD34DAY6, CD34DAY7, and CD34DAY8)

**Figure 5. Study 3101 apheresis days required to mobilize 5 x $10^6$ $CD34^+$ cells/kg**




6.1.5.3.3 Time to engraftment

The addition of plerixafor increased the likelihood of patients going on to transplantation. Of the ITT population, 135/150 (90%) randomized to G-CSF/plerixafor underwent transplantation, compared with 82/148 (55%) in the G-CSF/placebo group.

Of the transplanted patients, 129 (96%) in the G-CSF/plerixafor group and 65 (44%) in the G-CSF/placebo group collected ≥ 2 x $10^6$ $CD34^+$ cells/kg within four apheresis days. In addition, six patients in the G-CSF/plerixafor group and 16 in the G-CSF/placebo group mobilized ≥ 2 x $10^6$ $CD34^+$ cells in more than four days. One patient randomized to G-CSF/placebo underwent transplantation after having collected 1.9 x $10^6$ $CD34^+$ cells/kg. The median number of days to neutrophil and platelet engraftment was the same in each treatment arm (Table 34)

**Table 34. Study 3101 neutrophil and platelet engraftment (non-rescue transplanted pop.)**

| | G-CSF/plerixafor (n = 135) | G-CSF/placebo (n = 82) |
|---|---|---|
| **Neutrophil engraftment** | | |
| Achieved (y/n)[a] | 135 (100%) | 82 (100%) |
| Median time to achieve (days)[b] | 10 | 10 |
| **Platelet engraftment** | | |
| Achieved (y/n)[c] | 132 (98%) | 81 (99%) |
| Median time to achieve[d] | 20 | 20 |

Source: [a] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PMNGFTYN)
[b] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PMNGFTTT)
[c] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PLTGFTYN)
[d] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PLTGFTTT)

6.1.5.3.4 Graft durability

Among surviving patients, graft durability was similar in both treatment arms at 100 days, at 6 months, or at one year (Table 35).

**Table 35. Study 3101 graft durability (transplanted pop.)**

| | G-CSF/plerixafor (n = 135) | G-CSF/placebo (n = 82) |
|---|---|---|
| **Graft durability at 100 days** | | |
| N | 135 | 82 |
| Yes | 128 (95%) | 78 (95%) |
| **Graft durability at 6 months** | | |
| N | 123 | 78 |
| Yes | 120 (98%) | 77 (99%) |
| **Graft durability at 1 year** | | |
| N | 112 | 65 |
| Yes | 110 (98%) | 65 (100%) |

Source: (GRFTDR01.xpt and COMMONV.xpt) and Sponsor's program 14.2.6.1.1.2

### 6.1.5.4 AMD3100-3102

#### 6.1.5.4.1 Percentage of patients mobilizing ≥ $6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days

One hundred and twelve (76%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of collecting ≥ $6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, compared to 79 (51%) patients randomized to G-CSF/placebo (P < 0.001; Table 36).

**Table 36. Study 3102 collection of 6 x $10^6$ $CD34^+$ cells within four apheresis days (ITT pop.)**

| $CD34^+$ cells mobilized | G-CSF/plerixafor (n = 148) | | G-CSF/placebo (n = 154) |
|---|---|---|---|
| ≥ $6 \times 10^6$/kg within 4 apheresis days | 112 (76%) | | 79 (51%) |
| < $6 \times 10^6$/kg within 4 apheresis days | 36 (24%) | | 75 (49%) |
| Estimate of treatment effect | | 24.4% | |
| 95% CI of estimate of treatment effect | | 13.9% – 34.9% | |
| Pearson's Chi-square P-value | | < 0.001 | |
| Cochran-Mantel-Haenszel P-value | | < 0.001 | |

Source: (EAPH1.xpt where PATID ≠ 25-401) join including non-matches (DISP1.xpt where PATID ≠ 25-401)
Y response: (CD34DAY5 + CD34DAY6 + D34DAY7 + CD34DAY8)
X factor: TRTGRPC

#### 6.1.5.4.2 Percentage of patients mobilizing ≥ $2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days

One hundred and forty-one (95%) patients randomized to G-CSF/plerixafor met the secondary efficacy endpoint of mobilization of ≥ $2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, compared to 136 (88%) patients randomized to G-CSF/placebo (P < 0.028; Table 37).

**Table 37: Study 3102 collection of 2 x $10^6$ $CD34^+$ cells within four apheresis days (ITT pop.)**

| $CD34^+$ cells mobilized | G-CSF/plerixafor (n = 148) | | G-CSF/placebo (n = 154) |
|---|---|---|---|
| ≥ $2 \times 10^6$/kg within 4 apheresis days | 141 (95%) | | 136 (88%) |
| < $2 \times 10^6$/kg within 4 apheresis days | 7 (5%) | | 18 (12%) |
| Estimate of treatment effect | | 7% | |
| 95% CI of estimate of treatment effect | | 0.8% – 13.1% | |
| Pearson's Chi-square P | | < 0.028 | |

Source: (DISP1.xpt where PATID ≠ 25-401) join including non-matches (EAPH1.xpt where PATID ≠ 25-401)
Y response: if (CD34DAY5 + CD34DAY6 + CD34DAY7 + CD34DAY8) ≥ 2
X factor: TRTGRPC

6.1.5.4.3 Number of apheresis days required to mobilize ≥ 6 x $10^6$ $CD34^+$ cells/kg

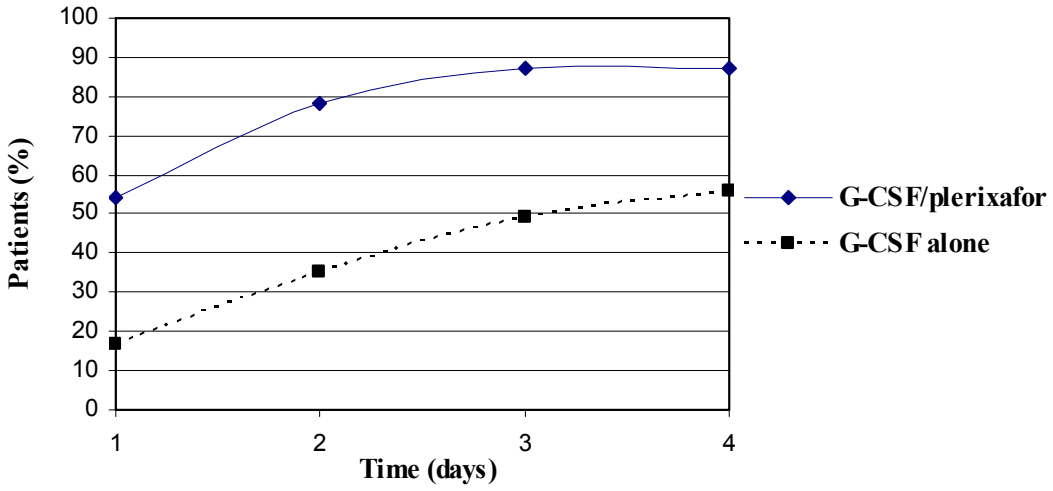
The median number of apheresis days required to mobilize ≥ 6 x $10^6$ $CD34^+$ cells/kg was one in the G-CSF/plerixafor group and four in the G-CSF/placebo group (P < 0.001; Table 38 and Figure 6).

**Table 38. Study 3102 apheresis days required to mobilize 6 x $10^6$ $CD34^+$ cells/kg (safety pop.)**

| | G-CSF/plerixafor (n = 144) | G-CSF/placebo (n = 150) |
|---|---|---|
| **Patients reaching target by day** | | |
| Apheresis Day 1 | 78 (54%) | 26 (17%) |
| Apheresis Day 2 | 106 (78%) | 53 (35%) |
| Apheresis Day 3 | 112 (87%) | 71 (49%) |
| Apheresis Day 4 | 112 (87%) | 79 (56%) |
| **Median time to reach target** | | |
| Median | 1.0 day | 4.0 days |
| HR | 2.6 | |
| 95% CI of HR | 1.88, 3.46 | |
| Log-rank P | <0.001 | |

Source: (EAPH1.xpt where PATID ≠ 25-401) by (TRTGRPR, CD34DAY5, CD34DAY6, CD34DAY7, and CD34DAY8)

**Figure 6. Study 3102 apheresis days required to mobilize 6 x $10^6$ $CD34^+$ cells/kg**




6.1.5.4.4 Time to engraftment

One hundred and forty two of the 148 (96%) randomized to G-CSF/plerixafor went on to transplantation, compared with 136/154 (88%) in the G-CSF/placebo group (Table 39). Of the 278 transplanted patients, 139 (94%) in the G-CSF/plerixafor group and 127 (82%) in the G-CSF/placebo group collected ≥ 2 x $10^6$ $CD34^+$ cells/kg within four apheresis days. Five

additional patients in the G-CSF/placebo group and none in the G-CSF/plerixafor group collected ≥ 2 x $10^6$ $CD34^+$ cells/kg after further apheresis (Table 40). Among transplanted patients, the addition of plerixafor did not appear to affect on the likelihood of engraftment or the median number of days to neutrophil or platelet engraftment (Table 41).

**Table 39. Study 3102 proportion of patients transplanted (ITT pop.)**

| Patients | G-CSF/plerixafor | G-CSF/placebo |
|---|---|---|
| Transplanted | 142 (96%) | 136 (88%) |
| Not transplanted | 6 (4%) | 18 (12%) |
| **Total** | **148 (100%)** | **154 (100%)** |

Source: (DISP1.xpt where PATID ≠ 25-401) by TRTGRP and ITT2

**Table 40. Study 3102 $CD34^+$ cell collection (transplanted pop.)**

| Apheresis product of transplanted patients | G-CSF/plerixafor | G-CSF/placebo |
|---|---|---|
| ≥ 2 x $10^6$ $CD34^+$ cells/kg within 4 apheresis days[a] | 139 | 127 |
| ≥ 2 x $10^6$ $CD34^+$ cells/kg after additional aphereses[b] | 0 | 5 |
| < 2 x $10^6$ $CD34^+$ cells/kg after additional aphereses[c] | 1 | 1 |
| < 2 x $10^6$ $CD34^+$ cells/kg and underwent no additional apheresis[d] | 2 | 3 |
| **Total** | **142** | **136** |

Source: CSR Table 11-9

**Table 41. Study 3102 neutrophil and platelet engraftment (transplanted pop.)**

| | G-CSF/plerixafor (n = 142) | G-CSF/placebo (n = 136) |
|---|---|---|
| **Neutrophil engraftment** | | |
| Achieved (n)[a] | 141 (99%) | 136 (100%) |
| Median time to achieve (days)[b] | 11 | 11 |
| **Platelet engraftment** | | |
| Achieved (n)[c] | 141 (99%) | 135 (99%) |
| Median time to achieve (days)[d] | 18 | 18 |

Source: [a] (ENGRAFT1.xpt where PATID ≠ 25-401 and, ITT2 = 1) by (TRTGRPC and PMNGFTYN)
[b] (ENGRAFT1.xpt where PATID ≠ 25-401 and ITT2 = 1) by (TRTGRPC and PMNGFTTT)
[c] (ENGRAFT1.xpt where PATID ≠ 25-401 and ITT2 = 1) by (TRTGRPC and PLTGFTYN)
[d] (ENGRAFT1.xpt where PATID ≠ 25-401 and ITT2 = 1) by (TRTGRPC and PLTGFTTT)

### 6.1.5.4.5 Graft durability

Among surviving patients, graft durability at 100 days, at 6 months, or at one year was similar in both treatment arms (Table 42).

**Table 42. Study 3102 graft durability (transplanted pop.)**

| Graft durability | G-CSF/plerixafor (n = 142) | G-CSF/placebo (n = 136) |
|---|---|---|
| **At 100 days** | | |
| Number of patients transplanted | 142 | 136 |
| Number of patients with durable graft | 140 (99%) | 133 (98%) |
| **At 6 months** | | |
| Number of patients transplanted | 135 | 127 |
| Number of patients with durable graft | 133 (98%) | 125 (98%) |

| | | |
|---|---|---|
| **At 1 year** | | |
| Number of patients transplanted | 128 | 120 |
| Number of patients with durable graft | 127 (99%) | 119 (99%) |

Source: (GRFTDUR1.xpt and COMMOMV.xpt) and Applicant's 14.2.7.1.2.sas

## 6.1.6 Other Endpoints

### 6.1.6.1 AMD3101-3101

#### 6.1.6.1.1 Overall survival

OS was an exploratory endpoint of AMD3100-3101. At a median follow-up of 421 days, 134 (89%) patients in the original ITT population randomized to G-CSF/plerixafor and 131 (88%) in the G-CSF/placebo group were alive. Because the number of deaths was small, median OS could not be estimated for either group. Findings were similar censoring patients who entered the rescue procedure at the time of consent for rescue (Table 43).

**Table 43. Study 3101 overall survival (ITT pop.)**

| | **G-CSF/plerixafor (n = 150)** | **G-CSF/placebo (n = 148)** |
|---|---|---|
| **Primary ITT population** | | |
| Patients alive | 134 (89%) | 131 (88%) |
| Median survival time (days) | Not estimable | Not estimable |
| **Censoring patients who entered rescue** | | |
| Patients alive | 136 (91%) | 138 (93%) |
| Median survival time (days) | Not estimable | Not estimable |

Source: (SURV1.xpt where [PATID ≠ 03-006 or 03-021] and RITUX = missing) fit proportional hazards: Time to Event = DEATHTT, Censor where DEATH = 1, Add TRTGRPC

#### 6.1.6.1.2 Rescue treatment

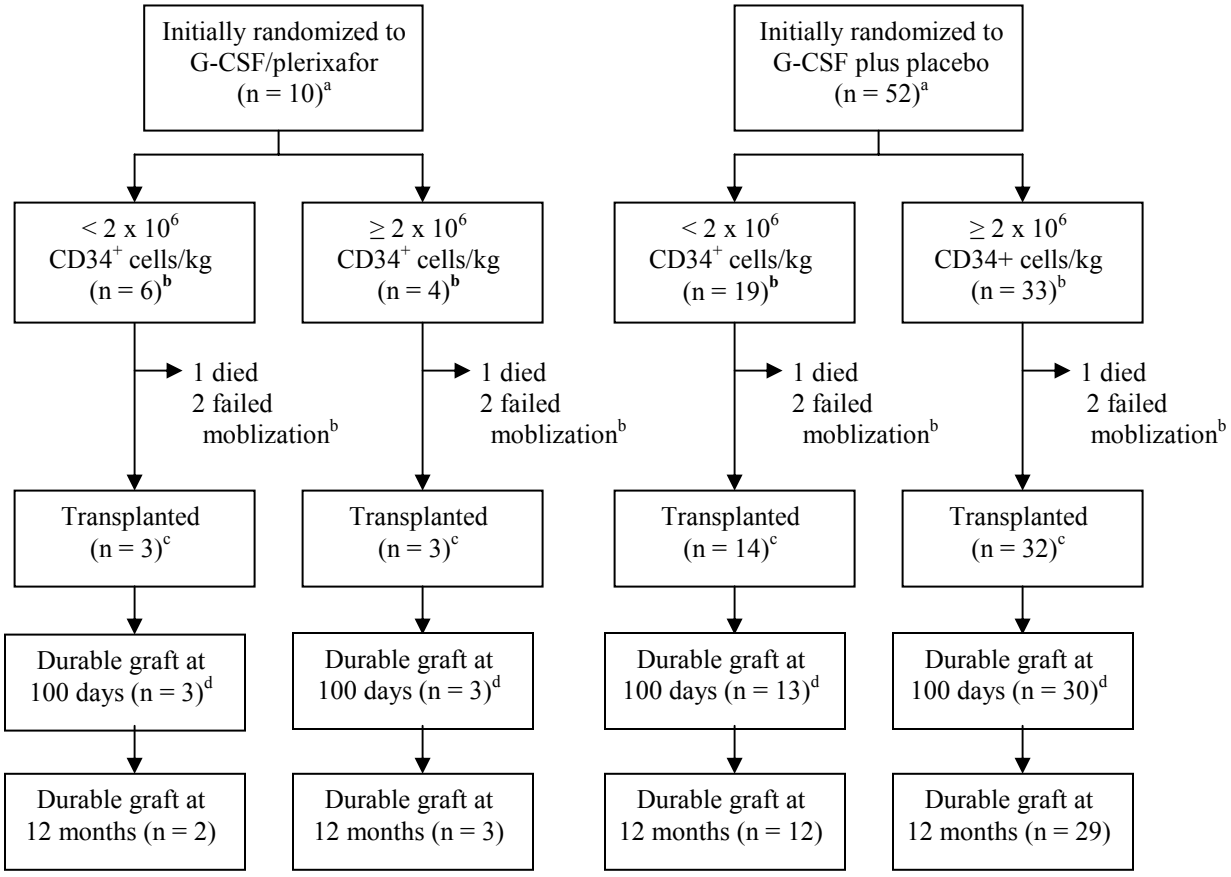
A total of 62 patients – 10 of 150 (7%) in the G-CSF/plerixafor group and 52 of 148 (35%) in the G-CSF/placebo group – who initially failed to collect either $\geq 2 \times 10^6$ $CD34^+$ cells/kg within two apheresis days or $\geq 5 \times 10^6$ $CD34^+$ cells/kg within five days entered rescue treatment. During the rescue procedure, 37 (60%) patients collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days, and seven (11%) collected $\geq 5 \times 10^6$ $CD34^+$ cells/kg.

Fifty two of the 62 (84%) patients who underwent rescue treatment went on to transplantation: 35 of the patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the rescue procedure and 17 who collected $< 2 \times 10^6$ $CD34^+$ cells/kg (Figure 7). Five of those who collected $< 2 \times 10^6$ $CD34^+$ underwent further mobilization with G-CSF alone and/or bone marrow harvest (data not shown).

Fifty of 52 (98%) patients who underwent HSCT following rescue treatment engrafted. Median times to neutrophil and platelet engraftment were 11.0 and 22.0 days, respectively.

***Reviewer's comment:*** *Rescue treatment increased the proportion of patients able to undergo HSCT. Initial transplantation results for the rescue population appear comparable to those of patients who underwent transplantation without the rescue procedure.*

**Figure 7. Study 3101 rescue procedure**




[a] (REAPH1.xpt where RITUX = missing) by TRTGRPC
[b] REAPH1.xpt where RITUX = missing by (TRTGRP and T2CD34)
[c] ([REAPH1 where RITUX = missing] joined with GRFTDR01) by (TRTGRP and T2CD34)
[d] ([REAPH1 where RITUX = missing] joined with GRFTDR01 where DURGRAF = 1) by (TRTGRP and T2CD34)

### 6.1.6.2 AMD3101-3102

#### 6.1.6.2.1 Overall survival

OS was an exploratory endpoint of AMD3100-3102. At a median follow-up of 385 days, 144 (99%) patients randomized to G-CSF/plerixafor survived (including patients who entered rescue treatment and/or received tandem transplants) compared with 148 (96%) patients of those in the G-CSF/placebo group were alive. Because the number of deaths was small, median OS could not

be estimated for either group. An analysis excluding patients who entered rescue treatment was not performed because numbers of patients and deaths in that subpopulation were small.

**Table 44. Study 3102 overall survival (ITT pop.)**

| | G-CSF/plerixafor (n = 148) | G-CSF/placebo (n = 154) |
|---|---|---|
| **Primary ITT population** | | |
| Patients alive | 144 (97%) | 148 (96%) |
| Median survival time (days) | Not estimable | Not estimable |

6.1.6.2.2 Rescue treatment

Seven patients randomized to G-CSF/placebo collected insufficient numbers of $CD34^+$ cells and entered the rescue procedure, compared to no patient randomized to G-CSF/plerixafor. During rescue treatment all patients collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg within four apheresis days, two (29%) collected $\geq 6 \times 10^6$ $CD34^+$ cells/kg within two days and three (43%) collected $\geq 6 \times 10^6$ $CD34^+$ cells/kg within four apheresis days. All rescue patients underwent transplant (four underwent tandem transplant), and four of four (100%) of those for whom 6-month data were available had all maintained engraftment.

***Reviewer's comment:*** *Initial transplantation results for the rescue population appear comparable to those of patients who underwent transplantation without the rescue procedure.*

## 6.1.7 Subpopulations

### 6.1.7.1 AMD3100-3101

The primary efficacy endpoint (mobilization of $\geq 5 \times 106$ $CD34^+$ cells/kg within 4 apheresis days) was met by slightly greater proportions of men than women and in patients under age 65 than 65 or older. These differences, however, were small and of unlikely clinical significance (Table 45). A separate analysis by race was not performed because non-Caucasian patients comprised only 7% of the patient population.

**Table 45: Study 3101 primary efficacy analysis by patient subgroup (ITT pop.)**

| | Men | | Women | |
|---|---|---|---|---|
| **$CD34^+$ cells mobilized** | **Plerixafor (n = 100)** | **Placebo (n = 102)** | **Plerixafor (n = 50)** | **Placebo (n = 46)** |
| $\geq 5 \times 10^6$ /kg | 62 (62%) | 18 (18%) | 27 (54%) | 11 (24%) |
| $< 5 \times 10^6$/kg | 38 (38%) | 84 (82%) | 23 (46%) | 35 (76%) |
| | **Age 18 – 64** | | **Age ≥ 65** | |
| **$CD34^+$ cells mobilized** | **Plerixafor (n = 117)** | **Placebo (n = 111)** | **Plerixafor (n = 33)** | **Placebo (n = 37)** |
| $\geq 5 \times 10^6$ /kg | 72 (62%) | 23 (18%) | 17 (52%) | 6 (16%) |
| $< 5 \times 10^6$/kg | 45 (38%) | 88 (82%) | 16 (48%) | 31 (84%) |

Source: ([DISP1.xpt where RANDDT ≠ missing} joined including non-matches with EAPH1.xpt] where RITUX = missing]) by (SEX or AGE [< vs. 65])
Y response: if (CD34DAY5 + CD34DAY6 + CD34DAY7 + CD34DAY8) ≥ 5, "Yes"; else "No"
X factor: TRTGRPC

### 6.1.7.2 Study 3102

The primary efficacy endpoint (mobilization of ≥ $6 \times 10^6$ $CD34^+$ cells/kg within 4 apheresis days) was met by slightly higher proportions of men and in patients over age 65 compared to women and younger patients, respectively (Table 46). However, no statistical or clinical significance can be inferred from this exploratory analysis. Racial subgroups were not analyzed because only 19% of the patient population was non-Caucasian.

**Table 46: Study 3102 primary efficacy analysis by patient subgroup (ITT pop.)**

| | Men | | Women | |
|---|---|---|---|---|
| **$CD34^+$ cells mobilized** | **Plerixafor (n = 100)** | **Placebo (n = 107)** | **Plerixafor (n = 48)** | **Placebo (n = 47)** |
| ≥ $6 \times 10^6$/kg within 4 days | 79 (79%) | 56 (52%) | 33 (69%) | 23 (49%) |
| < $6 \times 10^6$/kg within 4 days | 21 (21%) | 51 (48%) | 15 (31%) | 24 (51%) |
| | **Age 18 – 64** | | **Age ≥ 65** | |
| **$CD34^+$ cells mobilized** | **Plerixafor (n = 115)** | **Placebo (n = 116)** | **Plerixafor (n = 33)** | **Placebo (n = 38)** |
| ≥ $6 \times 10^6$/kg within 4 days | 87 (76%) | 66 (57%) | 25 (76%) | 13 (34%) |
| < $6 \times 10^6$/kg within 4 days | 28 (24%) | 50 (43%) | 8 (24%) | 25 (66%) |

Source: ([DISP1.xpt joined including non-matches with EAPH1.xpt] where PATID ≠ 25-401) by (SEX or AGE [< vs. ≥ 65])
Y response: if (CD34DAY5 + CD34DAY6) ≥ 2, "Yes"; else "No"
X factor: TRTGRPC

## 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

None of the four clinical trials submitted to demonstrate efficacy in patients with lymphoma or MM were designed to evaluate plerixafor exposure-response relationships. The chief sources of clinical data in this regard are three earlier phase I open-label dose-escalation studies in healthy volunteers (1002, 1003, and 1005) and one in patients with NHL and MM (1004). These studies showed that plerixafor doses up to 240 μg/kg produced dose-proportional increases in circulating $CD34^+$ cells, with no clear benefit of 320 μg/kg over 240 μg/kg, and the combination of G-CSF/plerixafor increased circulating $CD34^+$ cell counts more than plerixafor alone (Table 47).

**Table 47. Clinical studies contributing exposure-response data**

| Study | Population | Treatment | Results |
|---|---|---|---|
| 1002 | Healthy volunteers (n = 24) | Plerixafor 40, 80, 160, or 240 μg/kg SC x 1 or 80 μg/kg daily x 3 | Dose dependent increases were observed for CFU-GM, BFU-E and CFU-GEMM between 3 and 9 hours post-dose.<br><br>Common AEs were injection site-erythema, nausea, headache and oral paresthesia. No SAEs were reported. |
| 1003 | Healthy volunteers (n = 31) | G-CSF 10 μg/kg/day x 4 days followed on Day 5 by plerixafor 160 μg/kg plus G-CSF, plerixafor 160 μg/kg alone, plerixafor 240 μg/kg plus G-CSF, or G-CSF alone | G-CSF/plerixafor was superior to either drug alone in mobilizing $CD34^+$ cells. Plerixafor 160 μg/kg on Day 5 increased peripheral blood $CD34^+$ cells ~ 3-fold at 6 hours and 9 hours post-dose. Plerixafor 160 μg/kg plus G-CSF increased the $CD34^+$ cell yield to ~ 4-fold at 9 hours post-dose, and increased CFU-GM, BFU-E and CFU-GEMM ~ 5-fold, 3-fold and 3-fold, respectively, at 6 hours post-dose. Administration of 240 μg/kg plerixafor with G-CSF increased $CD34^+$ cells 4-fold at 12 hours post-dose.<br><br>Common AEs were injection site erythema, headache, paresthesia and nausea. No SAEs were reported. |
| 1004 | Patients with NHL or MM (n = 21) | Plerixafor single dose of 160, 240, or 320 μg/kg; the 320 μg/kg dose was followed by a rest period and mobilization with G-CSF /plerixafor | No clear relationship was shown between the plerixafor doses studied and the magnitude of the $CD34^+$ cell response. NHL and MM patients receiving 320 μg/kg plerixafor had mean peak increases in $CD34^+$ cells of 9.3- and 12.3-fold, respectively, 8-10 hours post-dose. Mean peak increases at 6 hours ranged from 4.4- to 9.4-fold.<br><br>All doses were well tolerated. |
| 1005 | Healthy volunteers (n = 10) | Plerixafor single dose of 240 or 320 μg/kg | Single plerixafor doses of 240 and 320 μg/kg increased $CD34^+$ counts ~ 11-fold at 4 hours and 12.7-fold at 8 hours post-dose, respectively. This difference was not clinically significant, as all subjects who received 240 μg/kg and all but one who received 320 μg/kg had a $CD34^+$ cell count > 20/μl, which predicts successful apheresis.<br><br>Common AEs were injection-site erythema, paresthesia, and atypical chest discomfort, all more frequent at 320 μg/kg. All AEs were resolved spontaneously; no SAEs were reported. |

## 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Plerixafor is intended to be used as a single course lasting no more than four days. None of the clinical studies conducted to date were designed to evaluate persistence of efficacy or tolerance, as these issues should not be relevant to the proposed indication.

### 6.1.10 Additional Efficacy Issues/Analyses

None

# 7 Review of Safety

## ***Safety Summary***

The safety database was reviewed in the context of the HSCT process, which consists of three sequential periods associated with unique risks. Period 1 comprises mobilization and apheresis. Period 2 comprises myeloablative chemotherapy, transplantation, and the post-transplant period through engraftment. Period 3 is from engraftment through the clinical cutoff date. Toxicities observed in Period 1 are generally more likely than those occurring during other periods to be attributed to plerixafor because of their temporal proximity to dosing and the increasing contributions of other treatments and procedures at later time points.

Plerixafor was generally well tolerated, with overall incidences of AE and Grade 3 or 4 AEs similar between treatment arms in the two randomized trials during each period of study. The majority of SAEs occurred during and following administration of ablative chemotherapy when patients were no longer receiving study drug. No deaths were attributed to plerixafor.

The most frequently reported (> 10% in either treatment group) AEs during study drug administration (Period 1) were diarrhea, nausea, bone pain, fatigue, injection site erythema, headache, paresthesia, back pain, hypokalemia, arthralgia, catheter site pain and dizziness. Common AEs with an incidence ≥ 2% higher in the G-CSF/plerixafor group compared to G-CSF/placebo during Period 1 were diarrhea (38 vs. 17%), nausea (34 vs. 22%), vomiting (10 vs. 6%), flatulence (7 vs. 4%), injection site erythema (26 vs. 5%), injection-site pruritus (6 vs. 1%), and dizziness (10 vs. 6%). Common AEs with an incidence ≥ 2% higher in the G-CSF/placebo group compared to G-CSF/plerixafor during Period 1 were catheter site pain (14 vs. 11%), bone pain (36 vs. 32%), back pain (22 vs. 18%), and extremity pain (7 vs. 5%).

One percent of all AEs reported during Period 1 in the two randomized trials were Grade 3 or 4. Grade 3-4 AEs reported by more than one patient randomized to G CSF/plerixafor were atrial fibrillation (n = 2), thrombocytopenia (n = 3), nausea (n = 2), and bone pain (n = 3).

AEs reported in ≥ 5% of patients in either treatment group during administration of myeloablative chemotherapy and before engraftment (Period 2) of the randomized studies were mucosal inflammation, febrile neutropenia, nausea, vomiting and diarrhea. Events reported in more than one patient in the G-CSF/plerixafor group were mucosal inflammation, febrile neutropenia, nausea and vomiting. Events reported in more than one patient in the G-CSF/placebo group were neutropenia and pyrexia. These events are typical complications of myeloablative chemotherapy. Post-engraftment (Period 3), the only event that occurred in ≥ 5% of patients in either treatment group was pyrexia in two of 32 (6.3%) patients in the G-

CSF/plerixafor group. No post-engraftment events were considered serious or related to study treatment.

The most common AEs (≥ 5% of patients in either treatment group) occurring during Period 1 in the subgroup of patients on all oncology studies and in the poor mobilizer population were similar to those in the pooled randomized studies except for slightly higher incidences of anemia and thrombocytopenia. No clinically meaningful differences in incidences or types of AEs between the NHL and MM subgroups were apparent. AEs were generally less frequent in patients with HD compared with the NHL and MM subgroups.

There was no evidence that age or gender affected the risks of any toxicities. Although no racial or ethnic groups were excluded from the randomized studies, most patients (87%) were Caucasian. The safety and efficacy of plerixafor in persons under age 18 and in pregnant or breast feeding women has not been established. Because of preclinical teratogenicity findings, plerixafor will be characterized pregnancy Category D.

## 7.1 Methods

### 7.1.1 Clinical Studies Used to Evaluate Safety

The safety database for this application consists of primary data from the following sources:

- 14 clinical studies conducted in patients with lymphoma and MM who were eligible for autologous HSCT (2101, 2102, 2103, 2104, 2105, 2106, 2108, 2109, 2112, 2113, EU21, C201, 3101, and 3102).
- One study in non-oncology patients with renal impairment (1101)
- One study in patients with HIV, an indication no longer being pursued (2001)

In addition, narrative summaries were provided for five studies conducted in healthy volunteers (98-01, 1002, 1003, 1004, 1005) and an interim narrative summary was provided for the ongoing Compassionate Use Program (CUP) available to patients in the US, Australia, Canada, and New Zealand. As of the respective data cut-off dates of these studies, a total of 1426 patients were enrolled and treated in the 21 studies plus the CUP. Of them, 1161 received plerixafor; 265 received either G-CSF/placebo or G-CSF alone.

On October 15, 2008, the Sponsor submitted a four-month safety update covering the period from March 1 through July 31, 2008. That four-month safety update was fully incorporated into this review.

### 7.1.2 Adequacy of Data

During the course of the registration studies, data regarding AEs, vital signs and other physical findings, laboratory values, drug exposure, and concomitant medications were recorded on case report forms. The Sponsor submitted this information in datasets containing the pooled safety population. AEs were categorized appropriately using the MedDRA version 10.0 dictionary of adverse events. Datasets were generally complete and well organized.

### 7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

The overall safety of plerixafor must be analyzed in the context of the HSCT process, which consists of the following sequential periods associated with unique risks:

- Period 1 comprises mobilization and apheresis. This period is defined as from the first dose of G-CSF for mobilization to 30 days after the last apheresis or to the day before starting the first dose of ablative chemotherapy, whichever occurred first. AEs observed in Period 1 are generally more likely than those occurring during other periods to be attributed to plerixafor because of their temporal proximity to dosing and the increasing contributions of other treatments and procedures at later time points.

  Period 1 is also associated with risks of G-CSF and apheresis. Frequent side effects of G-CSF are bone pain, fatigue, and headache. G-CSF causes transient spleen enlargement,[51,52] and spontaneous splenic rupture has been reported.[28,29] Rare complications include thrombosis, flare of autoimmune disease, and precipitation of sickle-cell crisis. G-CSF can also cause laboratory abnormalities such as thrombocytopenia, increases in alkaline phosphatase and lactate dehydrogenase, and decreases in serum potassium and magnesium.

  Adverse events associated with apheresis include complications of vascular access (peripheral or central) such as infections, thrombosis, pneumothorax, and bleeding; effects of replacement solutions (crystalloids, albumin, plasma), such as changes in coagulation times, hypofibrinogenemia, and hypocalcemia; and citrate (anticoagulant) toxicity (paresthesias, nausea, vomiting, chills, hyperreflexia, arrhythmias, and metabolic acidosis). Transient neutropenia and thrombocytopenia usually follow apheresis.[53]

- Period 2 comprises myeloablative chemotherapy, transplantation, and the post-transplant period through engraftment. This period is defined as from the first day of ablative chemotherapy to the first day of successful neutrophil or platelet engraftment (whichever was later). The protocols required collection of AEs only Grade 3 or greater (except for febrile neutropenia and hemorrhage – collected if Grades 4 or 5; and neutropenia, thrombocytopenia, and anemia – collected if outcome was death).

  Myeloablative chemotherapy and radiation therapy cause increased cytopenias (susceptibility to infection and bleeding), fatigue, anorexia, nausea, vomiting, mucositis,

alopecia, skin reactions, and neurotoxicity. Infusion of the previously harvested cryopreserved apheresis product can cause allergic reactions, thrombosis, and hemolysis.

- Period 3 comprises the post-engraftment period. This period is defined as from the first day following neutrophil and platelet engraftment until the clinical cutoff date (for single transplants) *or* until the day before starting chemotherapy in preparation for a tandem transplant (if planned). The protocols required collection of only SAEs.

  Patients during this period are at risk of late infections, graft failure, and long-term complications of the myeloablative regimen (infertility, cataracts, myelodysplasia, secondary cancers, etc.).

- Periods 4 and 5 are analogous to Periods 2 and 3 for patients undergoing tandem transplant. The protocols required collection of only SAEs.

The safety database consisted of data from a total of 983 patients enrolled in 16 clinical studies (Table 45 displays those 16 studies in bold type). The Applicant did not provide safety datasets for patients enrolled in the phase 1 dose escalation studies (98-01, 1002, 1003, 1004, and 1005) or the CUP.

Datasets and Case Report Forms submitted were in general consistent; relatively few data were missing. For each AE reported, the Applicant provided its MedDRA version 10.0 System Organ Class, Preferred Term, and Lower Level Term, its severity, dates of onset and termination, and the investigator's assessment of attribution.

The main focus of this safety review will be subgroups of patients from the randomized, placebo-controlled studies of G-CSF/plerixafor (n = 593), all oncology patients (n = 835), and poor mobilizers (Table 48).

**Table 48. Studies contributing data and pooling strategy for safety analyses**

| | **Randomized, placebo-controlled studies; n = 593** | **Oncology subgroups receiving G-CSF/plerixafor; n = 835** | **Poor mobilizers; n = 131** | **Rescue patients for repeat mobilization; n = 69** | **Compassionate use program; n = 368** | Healthy subjects; n = 76 | Phase 1 oncology study; n = 21 | **Plerixafor monotherapy; n = 9** | **Renally impaired, non-oncology; n = 17** | **HIV; n = 40** | Pediatric; n = 8 | **G-CSF/plerixafor/rituximab; n = 15** | **Chemo mobilization prior to G-CSF/plerixafor; n = 44** | **Formulation comparison; n = 234** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3101** | **X** | **X** | **X** | **X** | | | | | | | | **X** | | |
| **3102** | **X** | **X** | **X** | **X** | | | | | | | | | | |
| **2101** | | **X** | **X** | | | | | | | | | | | **X** |
| **2102** | | **X** | **X** | | | | | | | | | | | **X** |
| **2103** | | **X** | **X** | | | | | | | | | | | **X** |
| **2104** | | | | | | | | | | | | | **X** | |
| **2105** | | **X** | | | | | | | | | | | | **X** |
| **2106** | | **X** | | | | | | | | | | | | **X** |
| **2108** | | | | | | | | **X** | | | | | | |
| **2109** | | **X** | | | | | | | | | | | | **X** |
| **2112** | | **X** | **X** | | | | | | | | | | | **X** |
| **2113** | | **X** | | | | | | | | | | **X** | | **X** |
| **EU21** | | **X** | | | | | | | | | | | | **X** |
| **C201** | | **X** | | | | | | | | | | | | **X** |
| **2001** | | | | | | | | | | **X** | | | | |
| 98-01 | | | | | | X | | | | | | | | |
| 1002 | | | | | | X | | | | | | | | |
| 1003 | | | | | | X | | | | | | | | |
| 1004 | | | | | | | X | | | | | | | |
| 1005 | | | | | | X | | | | | | | | |
| **1101** | | | | | | | | | **X** | | | | | |
| CUP | | | | | X | | | | | | X | | | |

The group of patients enrolled on randomized studies was pooled from studies 3101 and 3102 comparing G-CSF/plerixafor versus G-CSF/placebo for mobilization at the 240 μg/kg plerixafor dose level. Excluded from this group are 1) seven patients (3 from Study 3101 and 4 from Study 3102) were enrolled but did not receive either G-CSF mobilization or randomized study treatment, 2) 13 rituximab-treated patients from Study 3101, 3) one patient from Study 3102 who received cytoreductive chemotherapy as part of the mobilization regimen, and 4) the rescue periods for the 69 patients who entered the rescue arms of the randomized studies.

The group of all oncology patients is pooled from the randomized studies (3101 and 3102) and 12 non-randomized studies evaluating the combination of G-CSF and plerixafor for HSC mobilization for autologous HSCT. Plerixafor doses ranged from 160 μg/kg to 320 μg/kg, with most patients (> 95%) receiving 240 μg/kg. This group excludes patients treated with plerixafor but not G-CSF (study 2108), phase 1 oncology patients (study 1004), patients whose mobilization regimen also included chemotherapy (study 2104 and one patient on 3102) or

rituximab (15 patients from 3101 and 2113), and rescue treatment periods during the randomized studies. The data for this group was also analyzed by underlying cancer type (NHL, MM, or HD).

A poor mobilizer is defined for purposes of this analysis as a patient who collected < 2 x $10^6$ $CD34^+$ cells with one mobilization regimen. This group includes all patients in studies 2102 and 2112, and subsets from studies 2101, 2103, 3101, and 3102. All of these studies used G-CSF/plerixafor at the 240 µg/kg dose level for plerixafor, with two patients in 2101 receiving 160 µg/kg. Because of differences in study conduct and patient population, this group does not include patients from the CUP, although by definition all patients in the CUP were poor mobilizers.

Other patient subgroups of potential interest include those with lymphoma or MM treated with plerixafor monotherapy (n = 9), those who received plerixafor by compassionate use (n = 368), non-oncology patients with renal impairment (n = 17), pediatric patients (n = 8), patients treated with G-CSF/plerixafor (240 µg/kg) plus rituximab (n = 15), and patients receiving G-CSF/plerixafor as rescue therapy after failed mobilization (n = 69). However, because of limited sample sizes, these subgroups were not analyzed separately.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### 7.2.1.1 Exposure of patients with NHL and MM in randomized placebo-controlled studies

Mean (± SD) cumulative doses of plerixafor and placebo were 543.8 µg/kg (± 263.0) and 743.5 µg/kg (± 232.9), respectively. The average daily dose of study drug for all but one patient was 240 µg/kg (Table 49). Extents of exposure by gender, age (< 65 vs. ≥ 65) and race were similar to those described for the entire patient population (data not shown).

**Table 49. Exposure to G-CSF and plerixafor in randomized studies 3101 and 3102**

| | G-CSF/plerixafor (n = 298) | G-CSF/placebo (n = 295) |
|---|---|---|
| **Cumulative dose of G-CSF (µg/kg)[a]** | | |
| N | 298 | 294 |
| Mean (SD) | 59.9 (13.2) | 68.1 (14.1) |
| Median | 59.7 | 70.0 |
| Range | 10 – 86 | 20 – 107 |
| Missing | 0 | 1 |
| **Number of G-CSF doses administered[b]** | | |
| N | 298 | 294 |
| Mean (SD) | 6.1 (1.2) | 7.0 (1.1) |
| Median | 6.0 | 7.0 |

| | | |
|---|---|---|
| Range | 1 – 8 | 2 – 8 |
| Missing | 0 | 1 |
| **Cumulative dose of plerixafor or placebo (μg/kg)[c]** | | |
| N | 291 | 290 |
| Mean | 543.8 (263.0) | 743.5 (232.9) |
| Median | 481.1 | 742.7 |
| Range | 225 – 1061 | 236 – 1116 |
| Missing | 7 | 5 |
| **Number of plerixafor/placebo doses administered[d]** | | |
| N | 291 | 290 |
| Mean (SD) | 2.3 (1.1) | 3.1 (1.0) |
| Median | 2.0 | 3.0 |
| Range | 1 – 4 | 1 – 4 |
| Missing | 7 | 5 |

[a] (EX2.xpt where P3POP = 1 and RESCUE = 0) by (TRTGRPR and GDOSWT)
[b] (EX2.xpt where P3POP = 1 and RESCUE = 0) by (TRTGRPR and GCSFNUM)
[c] (EX2.xpt where P3POP = 1 and RESCUE = 0) by (TRTGRPR and SDOSWT)
[d] (EX2.xpt where P3POP = 1 and RESCUE = 0) by (TRTGRPR and SDDGNUM)

7.2.1.2 Exposure of all patients with lymphoma or MM treated with G-CSF/plerixafor

Mean (± SD) cumulative doses of plerixafor and placebo were 603.9 μg/kg (± 366.5) and 743.5 μg/kg (± 232.9), respectively. Exposure was similar between disease subgroups (Table 50).

**Table 50. Exposure of all patients with NHL and MM treated with G-CSF/plerixafor**

| | G-CSF/plerixafor | | | | G-CSF/placebo | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **NHL (n = 244)** | **MM (n = 255)** | **HD (n = 39)** | **Total (n = 540)** | **NHL (n = 145)** | **MM (n = 150)** | **Total (n = 295)** |
| **Cumulative G-CSF dose (μg/kg)[a]** | | | | | | | |
| N | 242 | 255 | 38 | 537 | 144 | 150 | 294 |
| Mean (SD) | 66.5 (19.7) | 63.4 (31.3) | 70.1 (25.0) | 65.3 (26.2) | 66.3 (14.4) | 69.9 (13.7) | 68.1 (14.1) |
| Median | 63.5 | 59.6 | 60.5 | 60.1 | 69.3 | 72.0 | 70.0 |
| Range | 10 – 176 | 14 – 402 | 48 – 159 | 10 – 402 | 20 – 90 | 22 – 107 | 20 - 107 |
| Missing | 2 | 0 | 1 | 3 | 1 | 0 | 1 |
| **G-CSF doses administered[b]** | | | | | | | |
| N | 244 | 255 | 39 | 540 | 144 | 150 | 294 |
| Mean (SD) | 6.7 (1.8) | 6.4 (2.8) | 6.6 ( 2.6) | 6.5 (2.4) | 6.9 (1.2) | 7.1 (1.0) | 7.0 (1.1) |
| Median | 6.0 | 6.0 | 6.0 | 6.0 | 7.0 | 7.0 | 7.0 |
| Range | 1 – 19 | 3 – 35 | 4 – 16 | 1 – 35 | 2 – 8 | 4 – 8 | 2 – 8 |
| Missing | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| **Cumulative plerixafor/placebo dose (μg/kg)[c]** | | | | | | | |
| N | 239 | 251 | 37 | 529 | 142 | 148 | 290 |
| Mean (SD) | 655.4 (333.3) | 551 (385.7) | 619.3 (402.9) | 603.9 (366.5) | 738.7 (231.7) | 748.1 (234.7) | 743.5 (232.9) |
| Median | 507.1 | 478.5 | 484.9 | 483.9 | 744.9 | 740.5 | 742.7 |
| Range | 156 – 2057 | 225 – 2345 | 210 – 1746 | 156 – 2345 | 236 – 1014 | 236 – 1116 | 236 – 1116 |
| Missing | 5 | 4 | 2 | 11 | 3 | 2 | 5 |
| **Number of plerixafor/ placebo doses administered[d]** | | | | | | | |
| N | 241 | 251 | 38 | 532 | 142 | 148 | 290 |
| Mean (SD) | 2.8 (1.5) | 2.3 (1.6) | 2.6 (1.7) | 2.5 (1.6) | 3.1 (1.0) | 3.1 (1.0) | 3.1 (1.0) |
| Median | 2.0 | 2.0 | 2.0 | 2.0 | 3.0 | 3.0 | 3.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Range | 1 – 11 | 1 – 10 | 1 – 8 | 1 – 11 | 1 – 4 | 1 – 4 | 1 – 4 |
| Missing | 3 | 4 | 1 | 8 | 3 | 2 | 5 |

[a] (EX2.xpt where ONCPOP = 1 and RESCUE = 0) by (TRTGRPR and GDOSWT)
[b] (EX2.xpt where ONCPOP = 1 and RESCUE = 0) by (TRTGRPR and GCSFNUM)
[c] (EX2.xpt where ONCPOP = 1 and RESCUE = 0) by (TRTGRPR and SDOSWT)
[d] (EX2.xpt where ONCPOP = 1 and RESCUE = 0) by (TRTGRPR and SDDGNUM)
Note: Two patients with cancers other than lymphoma or MM are included in the total column. Patient 2112-01-102 was a 17 year old male with desmoplastic small round cell tumor and Patient 2112-01-103 was a 66 year old female with AML; both were in the G-CSF/plerixafor group.

### 7.2.1.3 Exposure of poor mobilizers

The mean (± SD) cumulative dose of plerixafor was 906.0 µg/kg (± 441.7) with an average of 3.8 doses per patient. All but two patients were assigned to plerixafor doses of 240 µg/kg/day (Table 51). The cumulative dose of plerixafor among poor mobilizers was higher than the cumulative dose in the phase 3 studies because there were more days of dosing in the Phase 2 studies (mean 3.8 vs. 2.3 doses, respectively).

**Table 51. Exposure of poor mobilizers to plerixafor/G-CSF**

| | **G-CSF[a] (n = 131)** | **Plerixafor[b] (n = 131)** |
|---|---|---|
| **Cumulative dose (µg/kg)** | | |
| N | 130 | 130 |
| Mean (SD) | 82.6 (41.7) | 906.0 (441.7) |
| Median | 77.2 | 927.3 |
| Range | 27 – 402 | 232 – 2345 |
| Missing | 1 | 1 |
| **Number of doses administered** | | |
| N | 2131 | 131 |
| Mean (SD) | 8.3 (3.8) | 3.8 (1.9) |
| Median | 8.0 | 4.0 |
| Range | 3 – 35 | 1 – 11 |
| Missing | 0 | 0 |

[a] (EX2.xpt where PMPOP = 1 and RESCUE = 0) by (TRTGRPR and [GDOSWT or GCSFNUM])
[b] (EX2.xpt where PMPOP = 1 and RESCUE = 0) by (TRTGRPR and [SDOSWT or SDDGNUM])

## 7.2.2 Explorations for Dose Response

None of the four clinical trials submitted to demonstrate efficacy in patients with lymphoma or MM were designed to evaluate exposure-response relationships. The chief sources of clinical information in this regard are three earlier phase I open-label dose-escalation studies in healthy volunteers (1002, 1003, and 1005) and one patients with NHL and MM (1004), which enrolled a total of 84 individuals. All dose-toxicity information from those studies pertains to single doses of plerixafor; no clear dose-toxicity relationship was seen at plerixafor doses up to 320 µg/kg.

A population PK analysis conducted by Clinical Pharmacology review team found a decreased response rate in NHL patients weighing < 85 kg. This analysis also found that the proposed

weight-based dose calculation leads to an increased plerixafor exposure in patients weighing > 160 kg and a decreased plerixafor exposure in patients weighing < 85 kg, when compared to patients in the weight range of 85 kg to 160 kg. The decreased exposure in patients less than 85 kg was associated with decreased efficacy. A logistic regression analysis conducted by the Clinical Pharmacology review team showed that both low body weight (i.e. low exposure) and low $CD34^+$ baseline cell counts were predictors of poor response to G-CSF/plerixafor$CD34^+$.

The Office of Clinical Pharmacology and the clinical review team are requesting that the Applicant conduct a post-approval study to consider predictors of poor response such as low exposure and baseline CD34+ count, and explore alternative dosing regimens (e.g. flat dosing) to optimize treatment in this population of poor responders. To limit toxicity in patients weighing > 160 kg due to increased exposure, OCP further recommends a maximum dose of 40 mg in patients weighing > 160 kg.

### 7.2.3 Special Animal and/or In Vitro Testing

None

### 7.2.4 Routine Clinical Testing

See section 5.3 of this review.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4.3 of this review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Class

Plerixafor is the first CXCR4 inhibitor, so there are no other approved drugs in this class. G-CSF and GM-CSF are approved for this indication, and the adverse effects are discussed in Section 7.1.3 of this review.

## 7.3 Major Safety Results

### 7.3.1 Deaths

The safety database contained 974 patients enrolled and treated 16 clinical studies (Table 52). In addition, the Applicant provided listings of deaths for the other five clinical studies and the CUP. Of the 974 patients in the safety database, 599 received G-CSF/plerixafor, 303 received G-

CSF/placebo, and 72 received plerixafor alone. As of the respective study data cut-off dates, a total of 66 (7%) patients in the safety database had died: 38/599 (6%) who received G-CSF/plerixafor, 26/303 (9%) who received G-CSF/placebo, and 2/72 (3%) who received plerixafor alone. An additional 42 patients died in the CUP.

The most common cause of death overall in the pooled safety population was disease progression post-transplantation, accounting for 37 of the 69 deaths (54%). This was followed by pneumonia or respiratory failure with eleven deaths (16%). Although more deaths due to disease progression and pneumonia/respiratory failure occurred in the G-GSF/plerixafor group than with G-CSF/placebo, these deaths seem unlikely related to plerixafor, given the favorable rates of transplantation, times to engraftment, and graft durability in that group. No consistent pattern was observed for other causes of death (Table 52).

**Table 52. Causes of death by treatment (safety pop.; n = 974)**

| Cause of death | G-CSF/plerixafor (n = 599) | G-CSF/placebo (n = 303) | Plerixafor alone (n = 72) |
|---|---|---|---|
| Disease progression or relapse | 20 | 15 | 2 |
| Pneumonia, ARDS, resp. failure, or cardioresp. failure, | 8 | 3 | 0 |
| Arrhythmia, myocardial infarction, or cardiac arrest | 3 | 1 | 0 |
| Multiple organ failure/sepsis | 4 | 4 | 0 |
| Intracranial hemorrhage | 0 | 1 | 0 |
| Perforated colon | 0 | 1 | 0 |
| Stroke | 2 | 0 | 0 |
| AML | 1 | 0 | 0 |
| Missing, unknown, or "natural" | 4 | 0 | 0 |
| **Total** | **42 (7%)** | **25 (9%)** | **2 (3%)** |

Source: ADSL.xpt by TRTGRPR and DTHSP

Fifty-five (83%) of the 69 deaths in the pooled safety population occurred during Period 3 (Table 53), the post-engraftment interval when patients are at risk of late infections, graft failure, and long-term complications of the myeloablative regimen (infertility, cataracts, myelodysplasia, secondary cancers, etc.).

**Table 53. Deaths by study periods (safety pop.)**

| | G-CSF/plerixafor | | | | | | G-CSF/placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment period** | 1 | 2 | **3** | **4** | **5** | **All** | **1** | **2** | **3** | **4** | **5** | **All** |
| **Entire safety database** | 1 (2%) | 2 (5%) | 37 (88%) | 0 (0%) | 2 (5%) | **42 (100%)** | 3 (12%) | 0 (0%) | 22 (88%) | 0 (0%) | 0 (0%) | **25 (100%)** |
| **Subpopulations** | | | | | | | | | | | | |
| Patients in randomized trials | 1 (4%) | 1 (4%) | 21 (88%) | 0 (0%) | 1 (4%) | **24 (100%)** | 3 (15%) | 0 (0%) | 21 (85%) | 0 (0%) | 0 (0%) | **24 (100%)** |
| All oncology patients | 1 (2%) | 2 (5%) | 36 (88%) | 0 (0%) | 2 (5%) | **41 (100%)** | 3 (15%) | 0 (0%) | 21 (85%) | 0 (0%) | 0 (0%) | **24 (100%)** |
| Poor mobilizers | 0 (0%) | 1 (11%) | 7 (78%) | 0 (0%) | 1 (11%) | **9 (100%)** | 1 (14%) | 0 (0%) | 6 (86%) | 0 (0%) | 0 (0%) | **7 (100%)** |

Source: ADSL.xpt by TRTGRPR, DTHSP, and DHTPER

In the randomized trials, there were no notable differences in incidences of death between treatment groups or by disease category. Overall mortality was numerically slightly higher in the poor mobilizer population compared to all patients in the randomized trials or all oncology patients (Table 54). Not shown in Table 54 are two deaths in the plerixafor monotherapy population and one each in the rituximab and chemotherapy populations.

**Table 54. Deaths on study by treatment group (safety pop.)**

| | G-CSF/plerixafor | | | | G-CSF/placebo | | |
|---|---|---|---|---|---|---|---|
| **Population** | **NHL** | **MM** | **HD** | **Total** | **NHL** | **MM** | **Total** |
| **Entire safety database** | 30/270 (11%) | 12/284 (4%) | 0/43 (0%) | **42/599* (6%)** | 20/152 (13%) | 5/151 (3%) | **25/303 (8%)** |
| **Subpopulations** | | | | | | | |
| Patients in randomized trials | 18/150 (12%) | 6/148 (4%) | 0/0 (0%) | **24/298 (8%)** | 19/145 (13%) | 5/150 (3%) | **24/295 (8%)** |
| All oncology patients | 29/244 (12%) | 12/255 (5%) | 0/39 (0%) | **41/538 (8%)** | 19/145 (13%) | 5/150 (3%) | **24/295 (8%)** |
| Poor mobilizers | 5/38 (13%) | 4/26 (15%) | 0/6 (0%) | **7/72* (12%)** | 7/52 (13%) | 0/7 (0%) | **7/59 (12%)** |

* Denominators include Patient 2112-01-102 (a 17 year old male with desmoplastic small round cell tumor) and Patient 2112-01-103 (a 66 year old female with AML), both in the G-CSF/plerixafor group.
Source: ADSL.xpt by TRTGRP, P3POP, ONCPOP, PMPOP, and CANCER

Only one patient in the randomized studies died during administration of plerixafor (i.e. Period 1). The cause of death in that patient was progressive disease (Table 55).

**Table 55. Causes of and timing of deaths in phase 3 study population**

| | G-CSF/plerixafor | | | | | | G-CSF/placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment period** | **1** | **2** | **3** | **4** | **5** | **All** | **1** | **2** | **3** | **4** | **5** | **All** |
| **N** | **298** | **278** | **277** | **32** | **32** | **298** | **295** | **217** | **217** | **24** | **24** | **295** |
| **Cause of death** | | | | | | | | | | | | |
| Disease prog. or relapse | 1 (<1%) | 0 (0%) | 11 (3%) | 0 (0%) | 0 (0%) | **12 (3%)** | 3 (1%) | 0 (0%) | 12 (5%) | 0 (0%) | 0 (0%) | **15 (5%)** |
| Pneumonia or respiratory failure, | 0 (0%) | 0 (0%) | 4 (1%) | 0 (0%) | 0 (0%) | **4 (1%)** | 0 (0%) | 0 (0%) | 3 (1%) | 0 (0%) | 0 (0%) | **3 (1%)** |
| Myocardial infarction | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | **1 (<1%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | **0 (0%)** |
| Multiple organ failure/sepsis | 0 (0%) | 1 (<1%) | 3 (1%) | 0 (0%) | 0 (0%) | **4 (1%)** | 0 (0%) | 0 (0%) | 4 (1%) | 0 (0%) | 0 (0%) | **4 (1%)** |
| Intracranial hemorrhage | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | **0 (0%)** | 0 (0%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | **1 (<1%)** |
| Perforated colon | 0 (0%) | 0 (0%) | 0 (1%) | 0 (0%) | 0 (0%) | **0 (0%)** | 0 (0%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | **1 (<1%)** |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | **1 (<1%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | **0 (0%)** |
| AML | 0 (0%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | **1 (<1%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | **0 (0%)** |
| Missing, unknown, or "natural" | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (0%) | **1 (0%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | **0 (0%)** |
| **Total** | **1 (<1%)** | **1 (<1%)** | **21 (6%)** | **0 (0%)** | **1 (0%)** | **24 (6%)** | **3 (2%)** | **0 (0%)** | **21 (9%)** | **0 (0%)** | **0 (0%)** | **24 (8%)** |

Source: (ADSL.xpt where P3POP = 1) by (TRTGRPR, DTHSP, and DTHPER)

## 7.3.2 Nonfatal Serious Adverse Events

Tables 56-58 summarize overall incidences of all-grade and grade 3-4 AEs by treatment period for the safety populations of the randomized trials, oncology patients, and the poor mobilizer subsets of oncology patients. All AEs were recorded during Period 1, but only those grade ≥ 3 were recorded during Periods 2 through 5. These data must be interpreted with caution because patient numbers changed considerably over the course of the studies, primarily due to those who failed mobilization entering rescue treatment.

### 7.3.2.1 Patients in randomized trials 3101 and 3102

Overall incidences of all-grade and Grade 3-4 AEs were numerically slightly higher among patients randomized to G-CSF/plerixafor compared to G-CSF/placebo. Most AEs occurred in Periods 2 and 3, when patients were no longer receiving study drug (Table 56). Periods 4 and 5 must be interpreted with particular caution because of small patient numbers and exposure to tandem transplantation. Less than 1% of all AEs were reported between the initial NDA submission and the 4-month safety update (data not shown).

**Table 56. AE Summary of randomized trials 3101 and 3102 (safety population)**

| | **G-CSF/plerixafor** | | | | | | **G-CSF/placebo** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **1** | **2** | **3** | **4** | **5** | **All** | **1** | **2** | **3** | **4** | **5** | **All** |
| Patients (n)[a] | 298 | 278 | 277 | 32 | 32 | **298** | 295 | 217 | 217 | 24 | 24 | **295** |
| Any AE[b] | 287 (96%) | 129 (46%) | 55 (20%) | 13 (41%) | 4 (12%) | **291 (98%)** | 277 (94%) | 95 (44%) | 36 (17%) | 4 (17%) | 1 (4%) | **285 (97%)** |
| Grade 3-4 AEs[c] | 23 (8%) | 81 (29%) | 37 (13%) | 11 (34%) | 3 (9%) | **124 (42%)** | 25 (8%) | 58 (27%) | 25 (12%) | 3 (12%) | 1 (4%) | **96 (33%)** |

[a] (EX2 where P3POP = 1 and RESCUE = 0) by PATID and TRTGRPR
[b] (AE1.xpt where P3POP = 1) by (PATID, TRTGRPR, and maxAESEV) by (TRTGRPR and AEPER)
[c] (AE1.xpt where P3POP = 1 and AESEV ≥ 3) by (PATID, TRTGRPR, and maxAESEV) by (TRTGRPR and AEPER)

7.3.2.2. All oncology patients

Approximately three quarters of NHL and MM patients treated with both G-CSF/plerixafor and G-CSF/placebo had at least one Grade 3-4 event at some time (Table 57). However, only about 10% of NHL and MM patients had Grade 3-4 events during Period 1 (Table 58). Patients with HD generally had less toxicity than those with NHL or MM.

**Table 57. AE summary for all oncology patients (safety pop.)**

| Population | G-CSF/plerixafor | | | | G-CSF/placebo | | |
|---|---|---|---|---|---|---|---|
| | **NHL (n = 244)** | **MM (n = 255)** | **HD (n = 39)** | **Total (n = 540*)** | **NHL (n = 145)** | **MM (n = 150)** | **Total (n = 295)** |
| **Patients with any AE** | 242 (99%) | 238 (93%) | 29 (74%) | **511 (95%)** | 143 (99%) | 144 (96%) | **287 (97%)** |
| **Patients with Gr. ≥ 3 AEs** | 179 (73%) | 209 (82%) | 5 (13%) | **394 (73%)** | 122 (84%) | 98 (65%) | **220 (75%)** |

***** Denominators include Patient 2112-01-102 (a 17 year old male with desmoplastic small round cell tumor) and Patient 2112-01-103 (a 66 year old female with AML), both in the G-CSF/plerixafor group.
[a] (AE1.xpt where ONCPOP = 1) by (USUBJID, TRTGRPR, CANCER, AEPT, and maxAESEV) by (TRTGRPR and CANCER)
[b] (AE1.xpt where ONCPOP = 1 and AESEV ≥ 3) by (USUBJID, TRTGRPR, CANCER, AEPT, and maxAESEV) by (TRTGRPR and CANCER)

**Table 58. AE summary for all oncology patients during Period 1 (safety pop.)**

| Population | G-CSF/plerixafor | | | | G-CSF/placebo | | |
|---|---|---|---|---|---|---|---|
| | **NHL (n = 244)** | **MM (n = 255)** | **HD (n = 39)** | **Total (n = 540*)** | **NHL (n = 145)** | **MM (n = 150)** | **Total (n = 295)** |
| **Patients with any AE** | 238 (98%) | 235 (92%) | 29 (74%) | **504 (93%)** | 138 (95%) | 139 (93%) | **277 (94%)** |
| **Patients with Gr. ≥ 3 AEs** | 24 (10%) | 25 (10%) | 2 (5%) | **52 (10%)** | 14 (10%) | 11 (7%) | **25 (8%)** |

***** Denominators include Patient 2112-01-102 (a 17 year old male with desmoplastic small round cell tumor) and Patient 2112-01-103 (a 66 year old female with AML), both in the G-CSF/plerixafor group.
[a] (AE1.xpt where ONCPOP = 1 and AEPER = 1) by (USUBJID, TRTGRPR, and CANCER) by (TRTGRPR and CANCER)
[b] (AE1.xpt where ONCPOP = 1, AEPER = 1, and AESEV ≥ 3) by (USUBJID, TRTGRPR, and CANCER) by (TRTGRPR and CANCER)

7.3.2.3. Poor mobilizer population

Almost most poor mobilizers treated with both G-CSF/plerixafor and G-CSF/placebo had at least one Grade 3-4 event at some point in time, only 15 of 131 (11%) had Grade 3-4 events during Period 1 (Table 59). Patient numbers were too small to make definitive comparisons with the phase 3 and all-oncology study populations.

**Table 59. AE summary for poor mobilizers during Period 1 (safety pop.)**

| | G-CSF/plerixafor | G-CSF/placebo |
|---|---|---|

| Population | NHL (n = 38) | MM (n = 26) | HD (n = 6) | Total (n = 72*) | NHL (n = 52) | MM (n = 7) | Total (n = 59) |
|---|---|---|---|---|---|---|---|
| **Patients with any AE** | 38 (100%) | 24 (92%) | 6 (74%) | **70 (97%)** | 50 (96%) | 7 (100%) | **57 (97%)** |
| **Patients with Gr. ≥ 3 AEs** | 4 (11%) | 7 (27%) | 1 (17%) | **13 (18%)** | 2 (4%) | 0 (0%) | **2 (3%)** |

***** Denominators include Patient 2112-01-102 (a 17 year old male with desmoplastic small round cell tumor) and Patient 2112-01-103 (a 66 year old female with AML), both in the G-CSF/plerixafor group.
[a] (AE1.xpt where PMCPOP = 1 and AEPER = 1) by (USUBJID, TRTGRPR, CANCER, AEPT, and maxAESEV) by (TRTGRPR and CANCER)
[b] (AE1.xpt where PMPOP = 1, AEPER = 1, and AESEV ≥ 3) by (USUBJID, TRTGRPR, CANCER, AEPT, and maxAESEV) by (TRTGRPR and CANCER)

## 7.3.3 Dropouts and/or Discontinuations

Of the 974 patients in the safety population, 18 permanently discontinued study treatment, five required treatment interruption, and one required treatment modification because of AEs (not including rescue treatment). These events were relatively evenly distributed across treatment groups (Table 60) and the phase 3, all oncology, poor mobilizer, and other (HIV and chemotherapy) subpopulations (data not shown). Each Preferred Term category accounted for less than one percent of treatment discontinuations, treatment interruptions, or treatment modifications.

**Table 60. Treatment discontinuation, dose interruption or dose modification (safety pop.)**

| | Treatment group | | | |
|---|---|---|---|---|
| **Action and Preferred Term** | **Plerix. alone (n = 72)** | **G-CSF/plerix. (n = 599)** | **G-CSF/placebo (n = 303)** | **Total (n = 974*)** |
| **Treatment discontinued** | | | | |
| Abdominal pain | 0 | 1 | 1 | 2 |
| Anxiety | 1 | 2 | 0 | 3 |
| Arrhythmia (bradycardia, or bundle branch block, or ventricular extra-systoles) | 1 | 2 | 0 | 3 |
| Pain (back pain, bone pain, or non-cardiac chest pain) | 0 | 1 | 3 | 3 |
| Bacteremia | 0 | 1 | 0 | 1 |
| Blood stem cell harvest failure | 0 | 1 | 0 | 1 |
| Venous access (Central line infection or injection site infection) | 1 | 1 | 0 | 2 |
| Chest pain | 0 | 1 | 0 | 1 |
| Chills or pyrexia | 0 | 0 | 2 | 2 |
| Cough | 0 | 1 | 0 | 1 |
| Depression | 0 | 1 | 0 | 1 |
| Diarrhea | 0 | 2 | 0 | 2 |
| Disease progression | 0 | 0 | 1 | 1 |
| Dyspnea | 0 | 1 | 0 | 1 |
| Erythema | 1 | 0 | 0 | 1 |
| Eye swelling | 0 | 1 | 0 | 1 |

| | | | | |
|---|---|---|---|---|
| Fatigue | 0 | 1 | 0 | 1 |
| Headache | 0 | 0 | 1 | 1 |
| Hyperhydrosis | 0 | 2 | 0 | 2 |
| Nausea or vomiting | 2 | 2 | 2 | 6 |
| Paresthesia | 0 | 1 | 1 | 2 |
| Pharyngeal erythema | 0 | 1 | 0 | 1 |
| Splenomegaly | 0 | 0 | 1 | 1 |
| Thrombocytopenia | 1 | 1 | 0 | 2 |
| Tremor | 0 | 1 | 0 | 1 |
| **Total** | **7 (10%)** | **25 (4%)** | **12 (4%)** | **43 (4%)** |
| **Treatment interrupted** | | | | |
| Appetite decreased | 1 | 0 | 0 | 1 |
| Eructation | 1 | 0 | 0 | 1 |
| Liver function test abnormal | 1 | 0 | 0 | 1 |
| Nausea or vomiting | 2 | 0 | 0 | 2 |
| Postural hypotension | 2 | 0 | 0 | 2 |
| Pulsus bigeminus | 1 | 0 | 0 | 1 |
| Sinus tachycardia | 1 | 0 | 0 | 1 |
| Staphylococcal bacteremia | 1 | 0 | 0 | 1 |
| **Total** | **10 (14%)** | **0 (0%)** | **0 (%)** | **10 (1%)** |
| **Treatment modified** | | | | |
| Insomnia | 1 | 0 | 0 | **1** |

Source: AE1.xpt where RESPOP = 0 by AEACNC, AEPT, and TRTGRPR

## 7.3.4 Significant Adverse Events

See Section 7.4.1 of this review.

## 7.3.5 Submission Specific Primary Safety Concerns

### 7.3.5.1 Hypersensitivity

The reviewer queried the safety database for the following MedDRA Preferred Terms during Period 1: dyspnea, hypersensitivity, hypotension, hypoxia, throat tightness, and wheezing. Their combined incidence was numerically slightly higher among patients receiving G-CSF/plerixafor compared to G-CSF/placebo (Table 61). Their combined incidence was 8% among patients receiving G-CSF/plerixfor and 6% with G-CSF/placebo (45/599 vs. 17/303). Two of these events were Grade 3 (hypotension in Patient 3101-13-008 receiving G-CSF/plerixafor and dyspnea in Patient 3101-47-001 receiving G-CSF/placebo); none were Grade 4. Patient 3101-13-008) was found the following day to have Gram negative bacteremia.

**Table 61. AEs potentially related to acute systemic hypersensitivity (safety pop.)**

| | G-CSF/plerixafor | | | | G-CSF/placebo | | |
|---|---|---|---|---|---|---|---|
| **Population** | **NHL** | **MM** | **HD** | **Total*** | **NHL** | **MM** | **Total** |
| **Entire safety database** | 25/270 (9%) | 18/284 (6%) | 2/43 (5%) | **45/599 (8%)** | 8/152 (5%) | 9/151 (6%) | **17/303 (6%)** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Subpopulations** | | | | | | | |
| Patients in randomized trials | 15/150 (10%) | 5/148 (3%) | 0/0 (0%) | **20/298 (7%)** | 7/145 (5%) | 9/150 (6%) | **16/295 (5%)** |
| All oncology patients | 23/244 (9%) | 17/255 (7%) | 2/39 (5%) | **42/538 (8%)** | 7/145 (5%) | 9/150 (6%) | **16/295 (5%)** |
| Poor mobilizers | 3/38 (8%) | 4/26 (15%) | 0/6 (0%) | **7/72 (10%)** | 4/52 (8%) | 0/7 (0%) | **4/59 (7%)** |

* G-CSF/plerixafor group includes two patients from Study 2112 with other cancers (Patient 2112-01-102 with desmoplastic small round cell tumor and Patient 2112-01-103 with AML).
Source: ADSL.xpt by TRTGRP, P3POP, ONCPOP, PMPOP, and CANCER

***Reviewer's comment:*** *It appears doubtful that plerixafor causes clinically significant hypersensitivity.*

7.3.5.2 Neurological

Plerixafor administered subcutaneously to mice, rats, and dogs at doses 7.7 to 9-fold above the recommended human dose rapidly (between 30 minutes and four hours) induced neurological signs, including apparent sedation, followed by tremors, convulsions, and possible cardio-depression. In addition, respiratory depression was seen in a safety pharmacology study at doses 6.7-fold above the recommended human dose. These effects were dose-limiting and the timing of their onset and recovery suggests a relation to plasma $C_{max}$. Similar signs were not seen clinically.

Frequent neurological symptoms reported clinically were paresthesias, dizziness and headache. In Phase 1 studies of healthy volunteers (n = 77), the incidence of paresthesias varied: 0% in Study 98-01, 8% in Study 1002, 22% in Study 1003 and 70% in Study 1005 (data not shown).

Pre-existing paresthesias was an exclusion criterion for some Phase 2 studies (EU21 and C201). Peripheral nerve function testing at baseline was not required for any of the clinical studies. Data from the Phase 2 and 3 studies are unadjusted for prior neurotoxic chemotherapy.

Incidences of paresthesias, dizziness, headache, and neuropathy in the overall safety database appeared similar among patients receiving G-CSF/plerixafor, G-CSF/placebo, and plerixafor alone (Table 62). There were no reports of grade 3 or peripheral neuropathy.

**Table 62. AEs potentially related to neurotoxicity (safety pop.)**

| | G-CSF/plerixafor (n = 599) | | G-CSF/placebo (N = 303) | | Plerixafor alone (N = 72) | |
|---|---|---|---|---|---|---|
| **Neurological AE** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** |
| Paresthesias[a] | 127 (21%) | 0 (0%) | 73 (24%) | 0 (0%) | 16 (22%) | 0 (0%) |
| Dizziness[b] | 52 (9%) | 0 (0%) | 25 (8%) | 0 (0%) | 13 (18%) | 1 (1%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Headache[c] | 129 (22%) | 2 (%) | 75 (25%) | 3 (1%) | 19 (26%) | 0 (%) |
| Peripheral neuropathy[d] | 8 (1%) | 0 (%) | 1 (<1%) | 0 (0%) | 0 (%) | 0 (%) |
| **Total** | **241 (40%)** | **2 (<1%)** | **136 (45%)** | **3 (1%)** | **37 (51%)** | **1 (1%)** |

Source: (AE1 select AEPTs) by (USUBJID, TRTGRPR, and maxAESEV) by (TRTGRPR, and maxAESEV)
[a] Preferred Terms, "paresthesia" and "paresthesia NEC
[b] Preferred Terms, "dizziness", "dizziness (exc vertigo)", and "dizziness postural"
[c] Preferred Terms "headache" and "headache NOS"
[d] Preferred Terms, "neuropathy" and "peripheral sensory neuropathy"

***Reviewer's Comment:*** *Although these data are suggestive, a causal relationship between plerixafor and neurologic symptoms remains uncertain.*

7.3.5.3 Hematological

7.3.5.3.1 Thrombocytopenia

Thrombocytopenia has been reported in approximately 6% of normal donors receiving G-CSF for stem cell mobilization, and in 50 to 75% of donors undergoing multiple aphereses; grade 3 or 4 thrombocytopenia is uncommon.[54,55]

In the phase 3 plerixafor studies, 3% of patients in both treatment groups had thrombocytopenia during Period 1. Among the subset of all oncology patients, incidences of all-grade and Grade 3-4 thrombocytopenia during Period 1 were numerically higher in the G-CSF/plerixafor compared to G-CSF/placebo (Table 70)

Two patients in the phase 3 studies of plerixafor had thrombocytopenia reported as an SAE. One of these events occurred 235 days post-transplant and was not suspected as related to study drug. The other occurred at the 24-hour post apheresis visit, was Grade 4, lasted approximately two weeks, and was suspected to be study drug related.

One patient in the HIV study (Study 2001) experienced an SAE of thrombocytopenia assessed as probably related to study drug. That patient received an IV infusion of plerixafor at 5 g/kg/h for 7 days.

***Reviewer's comment:*** *The addition of plerixafor to G-CSF may slightly increase the risk of thrombocytopenia during Period 1.*

7.3.5.3.2 Splenomegaly

Increased spleen weight was observed in rats (but not dogs) following 2 to 4 weeks exposure to plerixafor ~4-fold above the recommended human dose. G-CSF can cause splenic enlargement

as well, and rare instances of spontaneous splenic rupture have been reported in normal donors following G-CSF administration.[28,29]

Only two patients in the safety database – one who received G-CSF/plerixafor and one who received G-CSF/placebo had physical findings reported consistent with splenomegaly beyond the screening period (Table 63)

**Table 63. Physical examination findings related to the spleen (safety pop.)**

| Patient | Study | Treatment group | Treatment period | Verbal description |
|---|---|---|---|---|
| 03-043 | 3101 | G-CSF/plerixafor | Mobilization | Tip of spleen palpable |
| 12-018 | 3101 | G-CSF/plerixafor | Screening | Splenomegaly |
| 28-012 | 3101 | G-CSF/placebo | Screening | Spleen tip slightly palpable |
| 20-903 | 3102 | G-CSF/placebo | Mobilization | Positive splenomegaly |

Sources: PE1.xpt where PETESTC = ["Abdomen" or "Lymph nodes"]) by PECOM
AE1 where AESOC = "Blood and lymphatic system disorder" by AETERM

***Reviewer's comment:*** *These data suggest that neither hypersplenism nor splenic rupture are likely to be common toxicities of plerixafor.*

7.3.5.4 Cardiovascular

7.3.5.4.1 Cardiac rhythm

Transient dose-dependent increases in heart rate up to ~100% above baseline were seen in dogs in a 4-week study (once daily SC) at a dose ~2.2 fold higher than the recommended human dose and with high-dose continual IV infusion of plerixafor. No effects on cardiac output, stroke volume, total peripheral resistance, or ECG wave forms were noted in dogs at single doses up to 9-fold above the recommended human dose or during continual IV infusion for 8 hours at steady state blood levels up to 7.4 times the peak plerixafor plasma level in humans at the recommended dose.

7.3.5.4.2 Myocardial infarction

The proposed patient population for plerixafor will often have risk factors for coronary artery disease. Atherosclerotic plaque expresses cytokines and chemokines that could theoretically attract pro-inflammatory subsets of plerixafor-mobilized cells.

Incidences of all-grade and Grade 3-4 cardiac disorders among all patients in the safety database appeared independent of treatment assignment. Seven patients – five (1%) patients treated with G-CSF/plerixafor and two (1%) treated with G-CSF/placebo – had myocardial infarctions. All five of the plerixafor-treated patients had at least one cardiac risk factor; five had received prior anthracycline chemotherapy (Table 64). In addition to these five patients, myocardial infarction was listed the cause of death for one plerixafor-treated patient ten months after the last dose. That patient also had a cardiac risk factor plus prior anthracycline exposure.

**Table 64. Cardiovascular AEs reported (safety pop.)**

| | G-CSF/plerixafor (n = 599) | | G-CSF/placebo (N = 303) | | Plerixafor alone (N = 72) | |
|---|---|---|---|---|---|---|
| **Event** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** |
| Arrhythmia[a] | 12 (2%) | 27 (5%) | 15 (5%) | 11 (4%) | 28 (39%) | 10 (14%) |
| Conduction block[b] | 4 (1%) | 0 (0%) | 2 (1%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Congest. heart failure[c] | 74 (12%) | 5 (0%) | 41 (14%) | 3 (1%) | 1 (1%) | 0 (0%) |
| Hypertension[d] | 1 (<1%) | 0 (0%) | 2 (1%) | 0 (0%) | 2 (2%) | 0 (0%) |
| Hypotension[e] | 5 (1%) | 24 (4%) | 3 (1%) | 15 (5%) | 1 (1%) | 0 (0%) |
| Miscellaneous[f] | 4 (1%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Myocard. infarction[g] | 0 (0%) | 5 (1%) | 1 (<1%) | 2 (1%) | 0 (0%) | 0 (0%) |
| Myocardial ischemia[h] | 10 (2%) | 9 (2%) | 17 (6%) | 3 (1%) | 0 (0%) | 0 (0%) |
| Stroke[i] | 0 (0%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Syncope[j] | 0 (0%) | 6 (1%) | 0 (0%) | 2 (1%) | 1 (1%) | 0 (0%) |
| Thrombosis[k] | 8 (1%) | 9 (2%) | 1 (<1%) | 6 (3%) | 0 (0%) | 0 (0%) |
| **Total** | **141 (24%)** | **37 (6%)** | **98 (32%)** | **23 (8%)** | **8 (11%)** | **1 (1%)** |

Source AE1 where AEPT =
[a] atrial fibrillation, atrial flutter, heart rate increased, heart rate irregular, pulsus bigeminus, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachyarrhythmia, tachycardia, tachycardia NOS, ventricular extrasystoles, ventricular tachyarrhythmia, ventricular tachycardia
[b] atrioventricular block first degree, bradycardia, bradycardia NOS
[c] cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, fluid overload, fluid retention, edema, edema peripheral, pitting edema, pulmonary congestion, pulmonary edema, rales
[d] blood pressure increased
[e] blood pressure decreased, hypotension, hypotension NOS
[f] cardiac murmur, cardiovascular insufficiency, cardio-respiratory arrest, pulmonary hypertension
[g] acute myocardial infarction, myocardial infarction
[k] atrial thrombosis, axillary vein thrombosis, or deep vein thrombosis
[h] angina, chest discomfort, chest pain, chest pain NEC, coronary artery disease, electrocardiogram ST segment elevation, electrocardiogram T wave inversion, myocardial ischemia
[i] cerebral infarction, cerebrovascular accident
[j] syncope

Two hundred and six cardiovascular AEs were reported by the total safety population during Period 1 (Table 65). Twelve (6%) of those 206 cardiovascular AEs during Period 1 were Grade 3 or 4. The overall incidence of Grade 3-4 AEs during Period 1 was similar among patients receiving G-CSF/plerixafor compared to G-CSF/placebo (6 vs. 8%)

**Table 65. Cardiovascular AEs reported during Period 1 (safety pop.)**

| | G-CSF/plerixafor (n = 599) | | G-CSF/placebo (N = 303) | | Plerixafor alone (N = 72) | |
|---|---|---|---|---|---|---|
| **Event** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** |
| Arrhythmia[a] | 19 (3%) | 2 (<1%) | 16 (5%) | 1 (1%) | 22 (31%) | 1 (1%) |
| Conduction block[b] | 4 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Congest. heart failure[c] | 52 (8%) | 4 (1%) | 33 (10%) | 3 (1%) | 0 (0%) | 0 (0%) |
| Hypertension[d] | 1 (<1%) | 0 (0%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hypotension[e] | 7 (1%) | 1 (<1%) | 9 (1%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Miscellaneous[f] | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Myocardial ischemia[g] | 15 (3%) | 0 (0%) | 11 (3%) | 0 (0%) | 3 (4%) | 0 (0%) |
| Syncope[h] | 5 (1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Thrombosis[i] | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Total** | **107 (24%)** | **7 (6%)** | **72 (32%)** | **4 (8%)** | **27 (11%)** | **1 (1%)** |

Source AE1 where AEPT =
[a] atrial fibrillation, heart rate increased, heart rate irregular, pulsus bigeminus, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachyarrhythmia, tachycardia, tachycardia NOS, ventricular extrasystoles, ventricular tachyarrhythmia, ventricular tachycardia
[b] atrioventricular block first degree, bradycardia, bradycardia NOS
[c] fluid overload, fluid retention, edema, edema peripheral, pitting edema, rales
[d] blood pressure increased
[e] blood pressure decreased, hypotension, hypotension NOS
[f] cardiac murmur, cardiovascular insufficiency
[g] angina pectoris, chest discomfort, chest pain, chest pain NEC, electrocardiogram T wave inversion, myocardial ischemia
[h] syncope, syncope vasovagal
[i] deep vein thrombosis

***Reviewer's comment:*** *These data do not suggest that plerixafor when used for the proposed indication is likely to cause clinically significant cardiovascular disease.*

7.3.5.5 Electrolyte and bone metabolism

Increased urinary excretion of divalent metals (zinc, copper, calcium, and magnesium) was observed in rats and/or dogs at doses approximately 4- to 8-fold higher than the recommended human dose. A decrease in bone density was observed in a 4-week rat study at a dose approximately 8-fold above the recommended human dose. Serum calcium levels generally remained normal, but hypomagnesemia was occasionally observed in rats and dogs. Heparin and citrate used during apheresis are also associated with electrolyte disturbances including hypokalemia, hypocalcemia, and hypomagnesemia.[56,57]

Incidences of hypocalcemia and hypomagnesemia in the pooled safety population appeared comparable among patients treated with G-CSF/plerixafor, G-CSF alone and plerixafor alone. The incidence of Grade 3 hypophosphatemia was highest (2%) among patients treated with G-CSF/plerixafor (Table 66). In addition, two patients – one treated with G-CSF/plerixafor and one

treated with plerixafor alone – developed nephrolithasis. All but five reports of hypocalcemia, hypomagnesemia, and hypophosphatemia were from Periods 1 and 2 (data not shown)

**Table 66. Cardiovascular AEs reported (safety pop.)**

| | G-CSF/plerixafor (n = 599) | | G-CSF/placebo (N = 303) | | Plerixafor alone (N = 72) | |
|---|---|---|---|---|---|---|
| **Event** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** | **All Grade** | **Grade 3-4** |
| Hypocalcemia[a] | 26 (4%) | 1 (<1%) | 14 (5%) | 0 (0%) | 3 (4%) | 0 (0%) |
| Hypomagnesemia[b] | 70 (12%) | 0 (%) | 33 (11%) | 2 (1%) | 1 (0%) | 0 (0%) |
| Hypophosphatemia[c] | 1 (<1%) | 13 (2%) | 2 (1%) | 0 (0%) | 2 (3%) | 0 (0%) |

[a] AE1.xpt where AEPT = blood calcium decreased, calcium deficiency, or hypocalcemia
[b] AE1.xpt where AEPT = blood magnesium decreased or hypomagnesemia
[c] AE1.xpt where AEPT = blood phosphate decreased, blood phosphorous decreased, or hypophosphatemia

***Reviewer's comment:*** *Plerixafor appears unlikely to cause clinically significant electrolyte disturbances when used as recommended. Electrolyte levels should be monitored in patients receiving plerixafor and replaced as necessary.*

7.3.5.6 Interstitial lung disease

Impaired gas exchange and interstitial lung disease has been reported in healthy donors receiving G-CSF.[58,59,60] Interstitial lung disease was reported in one patient in the CUP within 24 hours of the initial G-CSF/plerixafor dose. This patient was hospitalized with fever and cough, and pulmonary changes on computed tomography consistent with either infection or hypersensitivity pneumonitis.

***Reviewer's comment:*** *These data do not suggest that plerixafor when used for the proposed indication is likely to cause clinically significant interstitial lung disease.*

7.3.5.7 Mobilization of non-target cells

In animal models, plerixafor at pharmacologic doses mobilized not only HPC, but also other CXCR4 cell populations into the blood, including angiogenic cells (endothelial progenitors, monocytes, $CD34^+$ cells), immunomodulatory cells (lymphocytes, neutrophils, monocytes, eosinophils), and tumor cells (ALL, APL, Namalwa B lymphoblastoid cells). The functional capacity of these mobilized cells was demonstrated in respective animal models of transplantation, ischemic hind limb or myocardial tissue injury, asthma or rheumatoid arthritis, and tumor growth.

G-CSF can increase leukemic and other malignant cells in peripheral blood by small amounts.[61] The presence in the apheresis product of malignant cells with self-renewing capacity could carry a risk of reintroducing the malignancy. In the pooled safety population, the addition of plerixafor to G-CSF did not increase the overall incidence of AEs related to malignancy, and no instances of malignancy were reported in patients receiving plerixafor alone (Table 67).

**Table 67. AEs related to malignancy (safety pop.)**

| AE Preferred Term | G-CSF/plerixafor (n = 599) | G-CSF/placebo (n = 303) | Plerixafor alone (n = 72) |
|---|---|---|---|
| Disease progression | 7 (1%) | 3 (1%) | 0 (0%) |
| Disease recurrence | 0 (0%) | 1 (<1%) | 0 (0%) |
| Lymphoma | 1 (<1%) | 0 (0%) | 0 (0%) |
| B-cell unclassifiable lymphoma high-grade | 0 (0%) | 1 (<1%) | 0 (0%) |
| Bone neoplasm malignant | 1 (<1%) | 0 (0%) | 0 (0%) |
| Malignant disease of orbit | 0 (0%) | 1 (<1%) | 0 (0%) |
| Malignant neoplasm progression | 0 (0%) | 1 (<1%) | 0 (0%) |
| Metastases to central nervous system | 0 (0%) | 1 (<1%) | 0 (0%) |
| Metastases to skin | 1 (<1%) | 0 (0%) | 0 (0%) |
| Non-Hodgkin's lymphoma | 0 (0%) | 1 (<1%) | 0 (0%) |
| **Total** | **10 (2%)** | **9 (3%)** | **0 (0%)** |

Source: AE1 by TRTGRPR and AEPT

Two patients in the CUP were thought to have previously undiagnosed plasma cell leukemia. One patient had circulating blasts prior to plerixafor administration, and following plerixafor administration, the number of circulating blasts increased. The second patient had 15% plasma cells in the apheresis product.

***Reviewer's comment:*** *Mobilization of leukemic cells by plerixafor has not been well studied.*

7.3.5.8 Tissue accumulation

In a mass balance study in rats, plerixafor was eliminated from most tissues between 4 and 24 hours. However, drug-derived material was detectable in bone marrow, spleen, liver, kidney and cartilage up to 144 hours after a single SC dose. Concentrations of radioactivity in these tissues were 5- to 10-fold greater following seven daily doses compared to Day 1. The absence of histopathological findings in 4-week repeat-dose toxicity studies in the rat and dog and the short duration of clinical dosing recommended clinical suggest the risk of toxicity from tissue retention is low.

The primary route of excretion of plerixafor is renal, and tissue accumulation in patients with renal impairment has not been studied. Based on the AUC in patients with renal impairment, dose modification is recommended for such patients, and post-marketing surveillance will be planned for patients on dialysis.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### 7.4.1.1 Patients with NHL and MM in randomized placebo-controlled studies

The most frequently reported (> 10% in either treatment group) AEs during Period 1 were diarrhea, nausea, bone pain, fatigue, injection site erythema, headache, paresthesia, back pain, hypokalemia, arthralgia, catheter site pain and dizziness. Common AEs with an incidence ≥ 2% higher in the G-CSF/plerixafor group compared to G-CSF/placebo during Period 1 were diarrhea (38 vs. 17%), nausea (34 vs. 22%), vomiting (10 vs. 6%), flatulence (7 vs. 4%), injection site erythema (26 vs. 5%), injection-site pruritus (6 vs. 1%), and dizziness (10 vs. 6%). Common AEs with an incidence ≥ 2% higher in the G-CSF/placebo group compared to G-CSF/plerixafor during Period 1 were catheter site pain (14 vs. 11%), bone pain (36 vs. 32%), back pain (22 vs. 18%), extremity pain (7 vs. 5%).

AEs reported in ≥ 5% of patients in either treatment group during Period 2 of the randomized studies were mucosal inflammation, febrile neutropenia, nausea, vomiting and diarrhea. Events reported in more than one patient in the G-CSF/plerixafor group were mucosal inflammation, febrile neutropenia, nausea and vomiting. Events reported in more than one patient in the G-CSF/placebo group were neutropenia and pyrexia. These events are typical of the known toxicities of myeloablative chemotherapy.

During Period 3, no AE category was reported in ≥ 5% of patients in either group. During Period 5, the only event that occurred in ≥ 5% of patients in either treatment group was pyrexia in 2/32 (6.3%) patients in the G-CSF/plerixafor group. No AEs in Period 5 were considered serious or related to study treatment (Table 68).

**Table 68. AEs in ≥ 5% of patients in any period in the randomized studies (safety pop.)**

| | G-CSF/plerixafor | | | | | | G-CSF/placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | All | 1 | 2 | 3 | 4 | 5 | All |
| N | 298 | 278 | 277 | 32 | 32 | 298 | 295 | 217 | 217 | 24 | 24 | 295 |
| **Blood and lymphatic system disorders** | | | | | | | | | | | | |
| Febrile neutrop. | 1 (<1%) | 24 (9%) | 2 (1%) | 4 (12%) | 0 (0%) | 30 (10%) | 0 (0%) | 18 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 18 (6%) |
| **Gastrointestinal disorders** | | | | | | | | | | | | |
| Diarrhea | 112 (38%) | 12 (4%) | 2 (1%) | 0 (0%) | 0 (0%) | 119 (40%) | 49 (17%) | 11 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 57 (19%) |
| Nausea | 102 (34%) | 22 (8%) | 1 (<1%) | 3 (9%) | 0 (0%) | 116 (39%) | 64 (22%) | 19 (9%) | 0 (0%) | 0 (%) | 0 (0%) | 77 (26%) |
| Vomiting | 29 (10%) | 14 (5%) | 0 (0%) | 3 (9%) | 0 (0%) | 43 (14%) | 18 (6%) | 10 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| Paresthesias oral | 22 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 22 (7%) | 25 (8%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| Flatulence | 20 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (7%) | 11 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (4%) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdominal pain[a] | 94 (32%) | 8 (3%) | 2 (1%) | 0 (0%) | 0 (0%) | 104 (35%) | 83 (28%) | 7 (2%) | 1 (1%) | 0 (0%) | 0 (0%) | 91 (%) |
| **General disorders and administration site conditions** | | | | | | | | | | | | |
| Fatigue[b] | 82 (28%) | 6 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 88 (30%) | 76 (26%) | 4 (%) | 0 (0%) | 0 (0%) | 0 (0%) | 81 (%) |
| Injection site[c] | 159 (53%) | 6 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 165 (55%) | 97 (33%) | 4 (2%) | 1 (1%) | 0 (0%) | 0 (0%) | 102 (%) |
| Mucositis[d] | 4 (1%) | 44 (%) | 1 (<1%) | 5 (16%) | 0 (0%) | 53 (18%) | 1 (<1%) | 27 (%) | 0 (0%) | 1 (4%) | 0 (0%) | 42 (%) |
| Catheter site pain | 32 (11%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 34 (11%) | 40 (14%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 40 (14%) |
| Pyrexia | 18 (6%) | 5 (2%) | 6 (2%) | 0 (0%) | 2 (6%) | 31 (10%) | 19 (6%) | 8 (4%) | 4 (2%) | 2 (8%) | 0 (0%) | 33 (11%) |
| Edema peripheral | 27 (9%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (9%) | 28 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 28 (10%) |
| Pain | 24 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 24 (8%) | 26 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| **Metabolism and nutrition disorders** | | | | | | | | | | | | |
| Hypokalemia[e] | 45 (15%) | 4 (1%) | 0 (0%) | 1 (3%) | 0 (0%) | 49 (16%) | 49 (16%) | 2 (1%) | 1 (1%) | 0 (0%) | 0 (0%) | 51 (17%) |
| Hypomagnesemia[f] | 28 (9%) | 3 (1%) | 0 (0%) | 1 (3%) | 0 (0%) | 32 (11%) | 29 (10%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 36 (%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | | | | | | | |
| Bone pain | 95 (32%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 96 (32%) | 105 (36%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 105 (36%) |
| Back pain | 54 (18%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 56 (13%) | 64 (21%) | 1 (1%) | 1 (1%) | 0 (0%) | 0 (0%) | 66 (22%) |
| Arthralgia | 39 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 39 (13%) | 36 (12%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 37 (12%) |
| Pain in extremity | 15 (5%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | 16 (5%) | 21 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 21 (7%) |
| **Nervous system disorders** | | | | | | | | | | | | |
| Headache | 67 (22%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 67 (22%) | 62 (21%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 63 (21%) |
| Paresthesia | 60 (20%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 61 (20%) | 64 (22%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 64 (22%) |
| Dizziness | 31 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 31 (10%) | 18 (6%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 19 (6%) |
| **Psychiatric disorders** | | | | | | | | | | | | |
| Insomnia | 21 (7%) | 3 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 24 (8%) | 15 (5%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 16 (5%) |
| Anxiety | 16 (5%) | 4 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (7%) | 13 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 13 (5%) |
| **Skin and subcutaneous tissue disorders** | | | | | | | | | | | | |
| Rash | 9 (3%) | 7 (2%) | 1 (<1%) | 0 (0%) | 0 (0%) | 17 (6%) | 10 (3%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 12 (4%) |

Source: (AE1.xpt where P3POP = 1) by (USUBID, AEPT, TRTGRPR, and AEPER) by (AEPT, TRTGRPR, and AEPER)

[a] includes abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and abdominal tenderness

[b] includes fatigue, asthenia, and lethargy

[c] includes injection site erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, reaction, swelling, and urticaria

[d] includes mucosal inflammation and stomatitis
[e] includes hypokalemia and blood magnesium decreased
[f] includes hypomagnesemia and blood magnesium decreased

One percent of all AEs reported during Period 1 in the two randomized trials were Grade 3 or 4. Grade 3-4 AEs reported by more than one patient receiving G CSF/plerixafor were atrial fibrillation (n = 2), thrombocytopenia (n = 3), nausea (n = 2), and bone pain (n = 3; Table 69).

**Table 69. Period 1 AEs (any grade ≥ 5% or grade 3-4 ≥ 1%) in randomized studies (safety pop.)**

| | G-CSF/plerixafor (n = 298) | | | G-CSF/placebo (n = 295) | | |
|---|---|---|---|---|---|---|
| | **Grade 1-2** | **Grade 3-4** | **All Grade** | **Grade 1-2** | **Grade 3-4** | **All Grade** |
| **Cardiovascular disorders** | | | | | | |
| Atrial fibrillation | 0 (0%) | 2 (1%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Hematologic** | | | | | | |
| Thrombocytopenia | 6 (2%) | 3 (1%) | 9 (3%) | 8 (3%) | 3 (1%) | 9 (3%) |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 113 (38%) | 1 (<1%) | 114 (38%) | 49 (17%) | 0 (0 %) | 49 (17%) |
| Nausea | 102 (34%) | 2 (1%) | 104 (35%) | 64 (22%) | 0 (0%) | 64 (22%) |
| Vomiting | 29 (10%) | 0 (0%) | 29 (10%) | 18 (6%) | 0 (0%) | 18 (6%) |
| Paresthesias oral | 22 (7%) | 0 (0%) | 22 (7%) | 25 (8%) | 0 (0%) | 25 (8%) |
| Flatulence | 20 (7%) | 0 (0%) | 20 (7%) | 11 (4%) | 0 (0%) | 11 (4%) |
| Abdominal pain[a] | 19 (6%) | 0 (0%) | 19 (6%) | 12 (4%) | 0 (0%) | 12 (4%) |
| **General disorders and administration site conditions** | | | | | | |
| Fatigue[b] | 85 (29%) | 0 (0%) | 85 (29%) | 80 (29%) | 0 (0%) | 80 (27%) |
| Injection site[c] | 141 (47%) | 0 (0%) | 141 (47%) | 34 (13%) | 0 (0%) | 34 (12%) |
| Catheter site reactions[d] | 80 (27%) | 0 (0%) | 80 (27%) | 93 (32%) | 0 (0%) | 93 (32%) |
| Pyrexia[e] | 18 (6%) | 1 (<1%) | 19 (6%) | 19 (6%) | 0 (0%) | 19 (6%) |
| Pain | 23 (8%) | 1 (<1%) | 24 (5%) | 26 (9%) | 0 (0%) | 26 (9%) |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypokalemia[e] | 45 (15%) | 1 (<1%) | 46 (15%) | 45 (15%) | 4 (1%) | 49 (16%) |
| Hypomagnesemia[f] | 26 (9%) | 1 (<1%) | 27 (9%) | 26 (0%) | 2 (1%) | 28 (0%) |
| Blood uric acid increased | 8 (3%) | 0 (0%) | 8 (3%) | 12 (40%) | 2 (1%) | 14 (5%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Bone pain | 92 (31%) | 3 (1%) | 95 (32%) | 107 (36%) | 1 (<1%) | 108 (36%) |
| Back pain | 54 (18%) | 1 (<1%) | 55 (18%) | 62 (21%) | 2 (1%) | 64 (22%) |
| Arthralgia | 39 (13%) | 0 (0%) | 39 (13%) | 36 (12%) | 0 (0%) | 36 (12%) |
| Pain in extremity | 15 (5%) | 0 (0%) | 15 (5%) | 20 (7%) | 1 (<1%) | 21 (7%) |
| **Nervous system disorders** | | | | | | |
| Headache | 66 (22%) | 1 (<1%) | 67 (11%) | 49 (20%) | 3 (1%) | 62 (21%) |
| Paresthesia | 60 (20%) | 0 (0%) | 60 (20%) | 64 (21%) | 0 (0%) | 64 (21%) |
| Dizziness | 31 (10%) | 0 (0%) | 31 (10%) | 18 (6%) | 0 (%) | 18 (6%) |
| **Psychiatric disorders** | | | | | | |
| Insomnia | 23 (8%) | 0 (0%) | 23 (8%) | 15 (5%) | 0 (0%) | 15 (5%) |
| Anxiety | 17 (6%) | 0 (0%) | 17 (6%) | 13 (4%) | 0 (0%) | 13 (4%) |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash | 9 (3%) | 0 (0%) | 9 (3%) | 10 (3%) | 0 (0%) | 10 (3%) |

Source: (AE1.xpt where P3POP = 1 and AEPER = 1) by (USUBID, AEPT, TRTGRPR, and maxAEINT) by (AEPT, TRTGRPR, and AEINT)
[a] includes abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and abdominal tenderness
[b] includes fatigue, asthenia, and lethargy

[c] includes injection site erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, reaction, swelling, and urticaria
[d] includes catheter related complication, cellulitis, discharge, erythema, hematoma, hemorrhage, infection, inflammation, edema, pain, pruritus, rash, and related reacton includes mucosal inflammation and stomatitis
[e] includes body temperature increased
[f] includes hypokalemia and blood magnesium decreased
[g] includes hypomagnesemia and blood magnesium decreased

### 7.4.1.2 All patients with lymphoma or MM treated with G-CSF/plerixafor

The most frequently occurring AEs (>10% in either treatment group) in Period 1 were diarrhea, nausea, injection site erythema, fatigue, catheter site pain, hypokalemia, hypomagnesemia, bone pain, back pain, arthralgia, headache, and paresthesia. These were generally similar to those in the pooled randomized studies with the exception of muscles spasms and thrombocytopenia which occurred in 7% and 6% of patients, respectively.

No clinically meaningful differences in AE incidences and types of AEs between the NHL and MM subgroups were apparent. Incidences of AEs were generally lower in patients with HD compared with the NHL and MM subgroups (Table 70).

**Table 70. AEs in ≥ 5% of patients in any period in all oncology studies (safety pop.)**

| | G-CSF/plerixafor | | | | | | G-CSF/placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **1** | **2** | **3** | **4** | **5** | **All** | **1** | **2** | **3** | **4** | **5** | **All** |
| **N** | **540** | **506** | **499** | **63** | **63** | **540** | **295** | **217** | **217** | **24** | **24** | **295** |
| **Any AE** | 504 (93%) | 176 (35%) | 87 (17%) | 21 (33%) | 10 (16%) | 510 (94%) | 277 (94%) | 95 (44%) | 36 (17%) | 4 (17%) | 1 (4%) | 285 (97%) |
| **Blood and lymphatic system disorders** | | | | | | | | | | | | |
| Febrile neutropenia | 1 (<1%) | 31 (6%) | 3 (1%) | 4 (6%) | 0 (0%) | 37 (7%) | 0 (0%) | 18 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 18 (6%) |
| Anemia | 25 (5%) | 2 (<1%) | 1 (<1%) | 0 (0%) | 0 (0%) | 28 (5%) | 9 (3%) | 0 (0%) | 0 (%) | 0 (0%) | 0 (0%) | 9 (3%) |
| Thrombocytopenia | 33 (6%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 35 (6%) | 9 (3%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (3%) |
| **Gastrointestinal disorders** | | | | | | | | | | | | |
| Diarrhea | 178 (33%) | 19 (4%) | 3 (1%) | 0 (0%) | 1 (2%) | 192 (36%) | 49 (17%) | 11 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 57 (20%) |
| Nausea | 180 (33%) | 29 (6%) | 1 (<1%) | 3 (5%) | 0 (0%) | 183 (34%) | 64 (22%) | 19 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 77 (28%) |
| Vomiting | 46 (8%) | 24 (5%) | 0 (0%) | 3 (5%) | 0 (0%) | 69 (13%) | 18 (6%) | 10 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| Paresthesia oral | 42 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 42 (8%) | 25 (8%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| Flatulence | 29 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 29 (5%) | 11 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (4%) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdominal pain[a] | 59 (11%) | 3 (1%) | 2 (<1%) | 0 (0%) | 0 (0%) | 69 (%) | 23 (8%) | 4 (2%) | 2 (1%) | 0 (0%) | 0 (0%) | 28 (10%) |
| **General disorders and administration site conditions** | | | | | | | | | | | | |
| Fatigue[b] | 144 (27%) | 8 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 152 (28%) | 76 (26%) | 4 (2%) | 1 (<1%) | 0 (0%) | 0 (0%) | 81 (28%) |
| Injection site[c] | 184 (25%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 185 (34%) | 34 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 34 (12%) |
| Mucositis[d] | 6 (1%) | 48 (9%) | 1 (<1%) | 9 (14%) | 0 (0%) | 60 (11%) | 1 (<1%) | 28 (%) | 0 (0%) | 1 (4%) | 0 (0%) | 30 (10%) |
| Catheter site pain | 55 (10%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 57 (11%) | 40 (14%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 40 (14%) |
| Pyrexia[e] | 40 (7%) | 7 (1%) | 12 (2%) | 2 (3%) | 3 (14%) | 59 (11%) | 21 (7%) | 8 (4%) | 4 (2%) | 2 (8%) | 0 (0%) | 35 (12%) |
| Edema or edema peripheral | 43 (7%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 43 (8%) | 28 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 28 (10%) |
| Pain | 38 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 38 (7%) | 26 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (9%) |
| **Metabolism and nutrition disorders** | | | | | | | | | | | | |
| Hypokalemia[f] | 86 (16%) | 7 (1%) | 0 (0%) | 1 (2%) | 0 (0%) | 96 (18%) | 50 (17%) | 2 (1%) | 1 (<1%) | 0 (0%) | 0 (0%) | 52 (18%) |
| Hypomagnesemia[g] | 61 (11%) | 5 (1%) | 0 (0%) | 1 (2%) | 0 (0%) | 66 (12%) | 29 (10%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 30 (10%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | | | | | | | |
| Bone pain | 150 (28%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 157 (29%) | 105 (36%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 105 (36%) |
| Back pain | 86 (%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 88 (%) | 64 (22%) | 1 (<1%) | 1 (<%) | 0 (0%) | 0 (0%) | 66 (22%) |
| Arthralgia | 59 (11%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 61 (11%) | 36 (12%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 37 (13%) |
| Musculoskeletal pain[h] | 93 (17%) | 3 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 95 (18%) | 46 (16%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 47 (16%) |
| Muscle spasms | 36 (7%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 37 (7%) | 14 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 14 (<1%) |
| Pain in extremity | 29 (5%) | 1 (<1%) | 1 (<1%) | 0 (0%) | 0 (0%) | 31 (6%) | 21 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 21 (7%) |
| **Nervous system disorders** | | | | | | | | | | | | |
| Headache | 114 (21%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 115 (21%) | 62 (21%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 63 (21%) |
| Paresthesia | 109 | 1 | 0 | 0 | 0 | 110 | 64 | 0 | 0 | 0 | 0 | 64 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (20%) | (<1%) | (0%) | (0%) | (0%) | (20%) | (22%) | (0%) | (0%) | (0%) | (0%) | (22%) |
| Dizziness | 43 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 43 (8%) | 19 (6%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 19 (6%) |
| **Psychiatric disorders** | | | | | | | | | | | | |
| Insomnia | 47 (9%) | 5 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 52 (10%) | 15 (5%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 16 (5%) |
| Anxiety | 35 (6%) | 4 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 39 (7%) | 13 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 13 (4%) |
| **Skin and subcutaneous tissue disorders** | | | | | | | | | | | | |
| Rash[i] | 45 (8%) | 10 (2%) | 1 (<1%) | 0 (0%) | 1 (2%) | 56 (10%) | 25 (8%) | 4 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 28 (10%) |

Source: (AE1.xpt where P3POP = 1) by (USUBID, AEPT, TRTGRPR, and AEPER) by (AEPT, TRTGRPR, and AEPER)
[a] includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal tenderness
[b] includes fatigue, asthenia, and lethargy
[c] includes injection site bruising, discharge, discomfort, erythema, hematoma, hemorrhage, induration, irritation, pain, paresthesia, pruritus, rash, reaction, swelling, and urticaria
[d] includes mucosal inflammation and stomatitis
[e] includes body temperature increased
[f] includes hypokalemia and blood magnesium decreased
[g] includes hypomagnesemia and blood magnesium decreased
[h] includes musculoskeletal stiffness and musculoskeletal discomfort
[i] includes rash macular, rash generalized, rash maculo-papular, rash erythematous, or rash pruritic

One percent of all AEs reported during Period 1 in the two randomized trials were Grade 3 or 4. Eight Grade 3-4 AEs were reported by more than one patient randomized to G CSF/plerixafor: atrial fibrillation (n = 2), anemia (n = 4), thrombocytopenia (n = 12), nausea (n = 3), catheter site reactions (n = 2), hypokalemia (n = 2), bone pain (n = 4), and headache (n = 4). Of those Grade 3-4 AEs, only anemia, thrombocytopenia, and catheter site reactions were reported more frequently in the G-CSF/plerixafor arm compared to G-CSF/placebo (Table 71).

**Table 71. Period 1 AEs (any grade ≥ 5% or grade 3-4 ≥ 1%) in randomized studies (safety pop.)**

| | G-CSF/plerixafor (n = 540) | | | G-CSF/placebo (n = 295) | | |
|---|---|---|---|---|---|---|
| | **Grade 1-2** | **Grade 3-4** | **All Grade** | **Grade 1-2** | **Grade 3-4** | **All Grade** |
| **Cardiovascular disorders** | | | | | | |
| Atrial fibrillation | 0 (0%) | 2 (1%) | 2 (1%) | 2 (0%) | 1 (0%) | 3 (0%) |
| **Hematologic** | | | | | | |
| Anemia | 21 (4%) | 4 (1%) | 25 (5%) | 9 (3%) | 0 (%) | 9 (3%) |
| Thrombocytopenia | 21 (4%) | 12 (2%) | 33 (6%) | 6 (2%) | 3 (1%) | 9 (3%) |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 169 (31%) | 1 (<1%) | 170 (31%) | 49 (17%) | 0 (0%) | 49 (17%) |
| Nausea | 149 (28%) | 3 (1%) | 152 (29%) | 64 (22%) | 0 (0%) | 64 (22%) |
| Vomiting | 44 (8%) | 1 (<1%) | 45 (8%) | 18 (6%) | 0 (0%) | 18 (6%) |
| Paresthesias oral | 41 (8%) | 0 (0%) | 41 (8%) | 25 (8%) | 0 (0%) | 25 (8%) |
| Flatulence | 29 (5%) | 0 (0%) | 29 (5%) | 11 (4%) | 0 (0%) | 11 (4%) |
| Abdominal pain[a] | 33 (6%) | 1 (0%) | 34 (6%) | 5 (4%) | 0 (0%) | 5 (4%) |
| **General disorders and administration site conditions** | | | | | | |
| Fatigue[b] | 106 (19%) | 0 (0%) | 106 (19%) | 80 (27%) | 0 (0%) | 80 (27%) |
| Peripheral edema | 37 (7%) | 0 (0%) | 37 (7%) | 29 (%) | 0 (%) | 29 (%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Injection site[c] | 164 (30%) | 1 (<1%) | 165 (30%) | 34 (12%) | 0 (0%) | 34 (12%) |
| Catheter site reactions[d] | 134 (25%) | 2 (<1%) | 136 (25%) | 93 (32%) | 0 (0%) | 93 (32%) |
| Pyrexia[e] | 36 (7%) | 1 (<1%) | 37 (7%) | 19 (6%) | 0 (0%) | 19 (6%) |
| Pain | 37 (7%) | 1 (<1%) | 38 (7%) | 26 (9%) | 0 (0%) | 26 (9%) |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypokalemia[f] | 80 (15%) | 2 (<1%) | 46 (15%) | 45 (15%) | 4 (1%) | 49 (16%) |
| Hypomagnesemia[g] | 56 (10%) | 0 (0%) | 56 (10%) | 26 (0%) | 2 (1%) | 28 (0%) |
| Blood uric acid increased | 8 (1%) | 0 (0%) | 8 (1%) | 12 (4%) | 2 (1%) | 14 (5%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Bone pain | 146 (27%) | 4 (1%) | 150 (28%) | 104 (36%) | 1 (<1%) | 105 (36%) |
| Back pain | 54 (10%) | 1 (<1%) | 55 (10%) | 62 (21%) | 2 (1%) | 64 (22%) |
| Arthralgia | 59 (11%) | 0 (0%) | 59 (11%) | 36 (13%) | 0 (0%) | 36 (13%) |
| Muscle spasms | 35 (6%) | 1 (<1%) | 36 (6%) | 14 (7%) | 0 (0%) | 21 (7%) |
| **Nervous system disorders** | | | | | | |
| Headache | 106 (20%) | 2 (<1%) | 108 (20%) | 59 (20%) | 3 (1%) | 62 (21%) |
| Paresthesia | 105 (19%) | 0 (0%) | 105 (19%) | 64 (21%) | 0 (0%) | 64 (21%) |
| Dizziness | 43 (8%) | 0 (0%) | 43 (8%) | 18 (6%) | 0 (%) | 18 (6%) |
| **Psychiatric disorders** | | | | | | |
| Insomnia | 47 (9%) | 0 (0%) | 47 (9%) | 15 (5%) | 0 (0%) | 15 (5%) |
| Anxiety | 35 (6%) | 0 (0%) | 35 (6%) | 13 (4%) | 0 (0%) | 13 (4%) |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash | 10 (2%) | 0 (0%) | 10 (2%) | 10 (3%) | 0 (0%) | 10 (3%) |

Source: (AE1.xpt where P3POP = 1 and AEPER = 1) by (USUBID, AEPT, TRTGRPR, and maxAEINT) by (AEPT, TRTGRPR, and AEINT)

[a] includes abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and abdominal tenderness

[b] includes fatigue, asthenia, and lethargy

[c] includes injection site erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, reaction, swelling, and urticaria

[d] includes catheter related complication, cellulitis, discharge, erythema, hematoma, hemorrhage, infection, inflammation, edema, pain, pruritus, rash, and related reacton includes mucosal inflammation and stomatitis

[e] includes body temperature increased

[f] includes hypokalemia and blood magnesium decreased

[g] includes hypomagnesemia and blood magnesium decreased

### 7.4.1.3 Poor mobilizer population

The most common AEs in the poor mobilizers were similar to those reported in the randomized studies. Those reported with a frequency above 10% were diarrhea, injection site erythema, bone pain, fatigue, nausea, hypokalemia, hypomagnesemia, headache, paresthesia, vomiting, arthralgia, back pain, thrombocytopenia, anemia, anxiety, and oral paresthesia. A total of 13.0% of poor mobilizer patients had severe or life-threatening events. Severe or life-threatening events occurring in more than 1 patient were thrombocytopenia and anemia.

**Table 72. AEs in ≥ 5% of patients in any period (poor mobilizer pop.)**

| | G-CSF/plerixafor | | | | | |
|---|---|---|---|---|---|---|
| **Period** | **1** | **2** | **3** | **4** | **5** | **All** |
| **N** | **131** | **116** | **112** | **17** | **17** | **131** |
| **Any AE** | 70 | 2 | 9 | 3 | 2 | 71 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (53%) | (15%) | (8%) | (18%) | (12%) | (54%) |
| **Blood and lymphatic system disorders** | | | | | | |
| Anemia | 10 (8%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (8%) |
| Febrile neutropenia | 0 (0%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (2%) |
| Thrombocytopenia | 14 (11%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 15 (11%) |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 22 (17%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 25 (19%) |
| Anorexia | 8 (6%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 8 (6%) |
| Nausea | 17 (13%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (15%) |
| Vomiting | 10 (8%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 13 (10%) |
| **General disorders and administration site conditions** | | | | | | |
| Fatigue or asthenia | 30 (23%) | 2 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 32 (24%) |
| Mucositis[a] | 4 (3%) | 4 (3%) | 2 (2%) | 0 (0%) | 0 (0%) | 10 (8%) |
| Catheter site pain | 10 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (8%) |
| Pain | 6 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (5%) |
| Injection site[b] | 38 (29%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 39 (30%) |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypokalemia[c] | 21 (16%) | 2 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 23 (17%) |
| Hypocalcemia[d] | 6 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (5%) |
| Hypomagnesemia[e] | 26 (20%) | 2 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 28 (21%) |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Bone pain | 20 (15%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (15%) |
| Back pain | 10 (8%) | 1 (%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (8%) |
| Arthralgia | 9 (7%) | 1 (%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (8%) |
| Pain in extremity | 6 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (5%) |
| **Nervous system disorders** | | | | | | |
| Headache | 14 (11%) | 1 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 15 (11%) |
| Paresthesia | 11 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (8%) |
| Dizziness | 6 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (5%) |
| **Psychiatric disorders** | | | | | | |
| Insomnia | 9 | 1 | 0 | 0 | 0 | 10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (%) | (1%) | (0%) | (0%) | (0%) | (8%) |
| Anxiety | 11 | 0 | 0 | 0 | 0 | 11 |
| | (7%) | (0%) | (0%) | (0%) | (0%) | (8%) |

Source: (AE1.xpt where PMPOP = 1) by (USUBID, AEPT, TRTGRPR, and AEPER) by (AEPT, TRTGRPR, and AEPER)

[a] includes mucosal inflammation and stomatitis

[b] includes injection site bruising, erythema, hemorrhage, irritation, pain, pruritus, reaction, and swelling

[c] includes body temperature increased

[d] includes hypokalemia and blood magnesium decreased

[e] includes hypomagnesemia and blood magnesium decreased

## 7.4.2 Laboratory Findings

The essential laboratory findings are discussed in the main efficacy and safety sections of this review.

## 7.4.3 Vital Signs

The Applicant submitted vital sign data for all 974 patients in the safety database. Vital signs in each of the clinical studies were measured at baseline and followed each day plerixafor (or placebo) was administered.

Both treatment groups in the pooled population of the randomized trials (3101 and 3102) had decreases in median systolic and diastolic blood pressure and increases in heart rate and temperature during administration of study drug. These differences were generally small and of unlikely clinical significance. Their magnitude was similar across treatment arms, suggesting they were due to factors other than plerixafor (e.g. apheresis or G-CSF; Tables 73 and 74).

**Table 73. Blood pressure – treatment phase of 3101 and 3102 (safety pop.; n = 593)**

| | Systolic BP (mmHg) | | | | Diastolic BP (mmHg) | | | |
|---|---|---|---|---|---|---|---|---|
| | G-CSF/plerixafor | | G-CSF/placebo | | G-CSF/plerixafor | | G-CSF/placebo | |
| **Time** | **Value** | **Change*** | **Value** | **Change*** | **Value** | **Change*** | **Value** | **Change*** |
| **Baseline** | | | | | | | | |
| N | 291 | | 290 | | 293 | | 291 | |
| Mean | 128.7 | | 130.5 | | 76.4 | | 77.8 | |
| SD | 18.3 | | 18.3 | | 10.0 | | 10.5 | |
| Median | 127 | | 130 | | 76 | | 78 | |
| Range | 77 - 184 | | 93 – 181 | | 52 – 108 | | 52 – 117 | |
| **Study Day 5** | | | | | | | | |
| N | 199 | 194 | 271 | 266 | 199 | 194 | 271 | 266 |
| Mean | 127.4 | -1.3 | 130.1 | -0.6 | 73.4 | -3.6 | 74.3 | -2.9 |
| SD | 17.1 | 20.2 | 17.6 | 18.4 | 10.6 | 10.8 | 10.3 | 11.4 |
| Median | 128 | -1.5 | 130 | -2.5 | 72 | -4 | 73 | -3 |
| Range | 87 – 186 | -58 – 60 | 82 – 185 | -52 – 60 | 48 – 104 | -33 – 25 | 46 – 105 | -32 – 32 |
| **Study Day 6** | | | | | | | | |
| N | 177 | 170 | 192 | 189 | 176 | 169 | 192 | 189 |
| Mean | 127.9 | -1.4 | 130.5 | -1.4 | 73.3 | -3.2 | 74.9 | -2.9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SD | 16.5 | 19.1 | 18.2 | 19.5 | 10.7 | 11.2 | 10.8 | 11.3 |
| Median | 128 | -2 | 130 | 0 | 72 | -2 | 75 | -5 |
| Range | 90 – 174 | -54 – 41 | 88 – 189 | -70 – 49 | 47 – 98 | -28 – 29 | 48 – 107 | -34 – 30 |
| **Study Day 7** | | | | | | | | |
| N | 149 | 145 | 213 | 210 | 149 | 145 | 213 | 210 |
| Mean | 127.0 | +0.4 | 130.4 | -0.1 | 72.7 | -3.1 | 75.1 | -2.2 |
| SD | 15.3 | 17.1 | 17.7 | 17.3 | 9.6 | 9.8 | 10.4 | 10.6 |
| Median | 128 | 1 | 131 | 1 | 72 | -3 | 75 | -3 |
| Range | 82 – 162 | -54 – 42 | 82 – 181 | -64 – 52 | 52 – 100 | -28 – 24 | 49 – 99 | -33 – 32 |
| **Study Day 8** | | | | | | | | |
| N | 34 | 32 | 51 | 50 | 34 | 32 | 51 | 50 |
| Mean | 129.1 | -0.6 | 127.2 | -2.2 | 72.2 | -3.8 | 77.2 | -1.8 |
| SD | 14.5 | 19.6 | 16.1 | 15.6 | 8.1 | 11.3 | 11.3 | 11.1 |
| Median | 126 | -1 | 124 | -4.5 | 97 | -4 | 105 | -2.5 |
| Range | 109 – 173 | -46 – 48 | 91 – 166 | -26 – 59 | 59 – 97 | -26 – 19 | 58 – 105 | -24 – 32 |

* compared to baseline value
Source: (VITALS1 where SAFETY = 1 and P3POP = 1) by (VTDAY, TRTGRPR, SBP, DBP, [BSBP – SBP], and [BDBP – DBP])

**Table 74. Pulse and temperature – treatment phase of 3101 and 3102 (safety pop.; n = 593)**

| | Pulse (beats/min) | | | | Temperature ($^{O}$C) | | | |
|---|---|---|---|---|---|---|---|---|
| **Time** | **G-CSF/plerixafor** | | **G-CSF/placebo** | | **G-CSF/plerixafor** | | **G-CSF/placebo** | |
| **Baseline** | **Value** | **Change*** | **Value** | **Change*** | **Value** | **Change*** | **Value** | **Change*** |
| N | 288 | | 285 | | 284 | | 285 | |
| Mean | 77.4 | | 79.0 | | 36.5 | | 36.6 | |
| SD | 14.3 | | 13.9 | | 0.41 | | 0.44 | |
| Median | 77 | | 78 | | 36.6 | | 36.6 | |
| Range | 43 – 120 | | 43 – 130 | | 35.1 – 37.6 | | 34.9 – 37.7 | |
| **Study Day 5** | | | | | | | | |
| N | 198 | 191 | 271 | 261 | 198 | 191 | 266 | 259 |
| Mean | 89.1 | 11.9 | 88.7 | 9.7 | 36.8 | 0.2 | 36.8 | 0.2 |
| SD | 14.3 | 14.0 | 13.5 | 13.1 | 0.5 | 0.6 | 0.5 | 0.6 |
| Median | 88 | 13 | 87 | 11 | 36.7 | 0.2 | 36.8 | 0.2 |
| Range | 60 – 128 | -34 – 47 | 46 – 129 | -39 – 44 | 35.4 – 38.2 | -1.2 – 2.0 | 35.2 – 38.2 | -1.3 – 2.1 |
| **Study Day 6** | | | | | | | | |
| N | 198 | 168 | 193 | 185 | 177 | 168 | 190 | 183 |
| Mean | 89.1 | 10.3 | 89.0 | 11.1 | 36.7 | 0.2 | 36.7 | 0.2 |
| SD | 14.3 | 14.9 | 12.7 | 13.3 | 0.4 | 0.5 | 0.6 | 0.8 |
| Median | 88 | 11 | 88 | 10 | 36.8 | 0.2 | 36.7 | 0.1 |
| Range | 60 – 128 | -34 – 55 | 58 – 130 | -39 – 60 | 34.0 – 37.9 | -2.7 – 1.5 | 31.9 – 38.0 | -5.4 – 1.8 |
| **Study Day 7** | | | | | | | | |
| N | 148 | 144 | 212 | 208 | 147 | 145 | 211 | 205 |
| Mean | 87.4 | 9.3 | 87.8 | 9.0 | 36.8 | 0.2 | 36.7 | 0.12 |
| SD | 13.5 | 13.9 | 13.5 | 13.7 | 0.4 | 0.5 | 0.5 | 0.6 |
| Median | 86.5 | 8 | 87 | 9 | 36.8 | 0.2 | 36.7 | 0.1 |
| Range | 53 – 126 | -38 – 45 | 60 – 134 | -46 – 43 | 35.2 – 37.8 | -0.9 – 1.5 | 34.7 – 38.0 | -2.4 – 1.9 |
| **Study Day 8** | | | | | | | | |
| N | 33 | 32 | 50 | 48 | 33 | 32 | 50 | 50 |
| Mean | 85.9 | 11.25 | 85.2 | 5.1 | 36.8 | 0.3 | 36.7 | 0.1 |
| SD | 12.3 | 15.8 | 15.9 | 15.7 | 0.57 | 0.65 | 0.39 | 0.45 |
| Median | 86 | 12.5 | 84 | 1.5 | 36.8 | 0.27 | 36.7 | 0.11 |
| Range | 62 – 109 | -32 – 44 | 53 – 125 | -33 – 45 | 35.2 – 38.5 | -1.4 – 2.0 | 36.0 – 37.5 | -1.2 – 1.0 |

* compared to baseline value
Source: (VITALS1 where P3POP = 1) by (VTDAY, TRTGRPR, PULSE, STTEMP, [STTEMP – baseline temp], and [PULSE – baseline PULSE])
Note: all STTEMP values converted to Centigrade

### 7.4.4 Electrocardiograms (ECGs)

In mice and dogs administered repeat doses of plerixafor higher than the recommended clinical dose, increases in heart rate and blood pressure were seen with no appreciable effect on ECG intervals. In addition, IV infusion of plerixafor was associated with ventricular ectopy in three patients with HIV (Study 2001).

Patients with histories of or risk factors for ventricular arrhythmias were excluded from Phase 2 studies 2102, 2104, 2105, 2106, 2108, 2109, 2113, EU21, and C201. For the Phase 3 studies, patients needed to have cardiac and pulmonary function sufficient to undergo apheresis and transplantation.

ECGs were done at baseline but were not part of the routine interim clinical assessments for any of the clinical studies submitted to support this application. The Applicant submitted no primary ECG data.

This reviewer queried the submitted safety datasets for AEs with the following preferred terms: arrhythmia, atrial fibrillation, atrial flutter, atrioventricular first degree block, supraventricular tachycardia, tachycardia, ventricular extrasystoles, and ventricular tachyarrhythmia. The corresponding CRFs were examined for evidence to support a causal relationship to plerixafor, such as occurrence within 24 hours of dosing and the absence of concomitant risk factors or electrolyte abnormalities. This reviewer did not find evidence of excess risk of heart rate, rhythm or conduction disturbances at the recommended dose of 240 μg/kg (Table 64).

The Applicant is currently conducting a thorough QT study for plerixafor. Results are not yet available.

### 7.4.5 Special Safety Studies

None

### 7.4.6 Immunogenicity

No specific data on immunogenicity were submitted with this application. Plerixafor does not contain a peptide or protein component that would be expected to be immunogenic. See Section 7.3.5.1 of this review for additional details.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Of the 16 clinical studies from which the Applicant submitted primary safety data, only two involved the administration of plerixafor doses other than 240 mg/kg. These were the open-label crossover study 2101 in patients with NHL or MM (n = 25), and the phase 1/2 study in patients with HIV (n = 40). Of the 974 patients in the safety database, 927 were treated at 240 µg/kg only (or placebo). No clinical study allowed plerixafor dose modification for toxicity or intrapatient dose-escalation. Because of these limitations, the safety database did not provide meaningful data regarding the dose-toxicity relationship.

The Applicant did not submit primary safety data from the phase 1 studies in healthy volunteers (98-01, 1002, 1003, 1004, and 1005) or the ongoing thorough QT study 06-H-0156 (n to date = 17) in which other doses of plerixafor were administered (see Table 2 in Section 5.1 of this review). No SAE was reported in any healthy volunteer. The impression of the investigators of those studies was that dose and route of administration had no obvious impact on the type, frequency, or severity of AEs.

### 7.5.2 Time Dependency for Adverse Events

Five hundred and sixty-seven of the 599 (95%) patients in the safety database who received G-CSF/plerixafor had at least one AE, and 355 (59%) had at least one Grade 3 AE. The mean and median times to first AE and to first Grade 3-4 AE were 13.9 and 5 days, and 52.9 and 32 days, respectively. For those AEs considered possibly, probably, or definitely study drug-related, median times to onset were shorter and intra-quartile ranges were smaller, consistent with the temporal administration of study drug (Table 75).

**Table 75. Time to first AE for patients receiving G-CSF/plerixafor (safety pop.; n = 599)**

| Parameter | Value |
|---|---|
| **All AEs[a]** | |
| N | 3982 |
| Mean | 13.9 days |
| Median | 5 days |
| 25% - 75% quartile | 4 – 9 days |
| Missing severity or date | 117 |
| **All AEs possibly, probably, or definitely drug-related[b]** | |
| N | 924 |
| Mean | 6.3 days |
| Median | 5.0 days |
| 25% - 75% quartile | 4 – 6 days |
| Missing attribution | 161 |
| **Grade 3-4 AEs[c]** | |
| N | 404 |
| Mean | 52.9 days |
| Median | 32.0 days |

| | |
|---|---|
| 25% - 75% quartile | 18.3 – 66.0 days |
| Grade 3-4 AEs with missing date | 45 |
| **All Grade 3-4 AEs possibly, probably, or definitely drug-related[d]** | |
| N | 13 |
| Mean | 8.2 |
| Median | 5.0 |
| 25% - 75% quartile | 5.0 – 9.0 |
| Related Grade 3-4 AEs with missing date | 7 |

[a] (AE1.xpt where TRTGRPR = 1) by PATID, AEPT, maxAESEV and AEDAY
[b] (AE1.xpt where TRTGRPR = 1 and AEREL ≥ 3) by PATID, AEPT, maxAESEV, and AEDAY
[c] (AE1.xpt where TRTGRPR = 1 and AESEV ≥ 3) by PATID, AEPT, maxAESEV, and AEDAY)
[c] (AE1.xpt where TRTGRPR = 1, AESEV ≥ 3, and AEREL ≥ 3) by PATID, AEPT, maxAESEV, and AEDAY)

In the pooled safety population of the two randomized trials, the median times to onset of a first AE, Grade 3-4 AE, drug-related AE, and drug-related AE were numerically slightly shorter in the G-CSF/plerixafor group compared to G-CSF/placebo. The clinical significance of this observation is unclear (Table 76).

**Table 76. Time to first AE in trials 3101 and 3102 (safety pop.)**

| Parameter | G-CSF/plerixafor (n = 291) | G-CSF/placebo (n = 292) |
|---|---|---|
| **All AEs[a]** | | |
| N | 2123 | 2095 |
| Mean (days) | 14.2 ± 29.0 | 17.2 ± 27.6 |
| Median (days) | 5.0 | 6.0 |
| 25% - 75% quartile (days) | 4.0 – 9.0 | 5.0 – 20.0 |
| Missing severity or date | 32 (2%) | 20 (1%) |
| **All AEs possibly, probably, or definitely drug-related[b]** | | |
| N | 987 | 719 |
| Mean ± SD (days) | 8.1 ± 13.6 | 11.6 ± 16.4 |
| Median (days) | 5.0 | 6.0 |
| 25% - 75% quartile (days) | 4.0 – 6.0 | 5.0 – 13.0 |
| Missing attribution | 0 | 0 |
| **Grade 3-4 AEs[c]** | | |
| N | 243 | 215 |
| Mean (days) | 50.0 ± 49.9 | 52.4 ± 49.9 |
| Median (days) | 32.0 | 36.0 |
| 25% - 75% quartile (days) | 22.0 – 35.0 | 24.0 – 54.0 |
| Grade 3-4 AEs with missing date | 3 | 5 |
| **All Grade 3-4 AEs possibly, probably, or definitely drug-related[d]** | | |
| N | 38 | 24 |
| Mean (days) | 28.4 ± 27.1 | 38.2 |
| Median (days) | 26 | 27 |
| 25% - 75% quartile (days) | 7.5 – 34.25 | 8.25 – 45.0 |
| Missing attribution | 0 | 0 |

[a] (AE1.xpt where P3POP = 1) by PATID, TRTGRP, AEPT, AESEV, and AEDAY
[b] (AE1.xpt where P3POP = 1 and AEREL≥ 3) by PATID, TRTGRP, AEPT, maxAESEV, and AEDAY
[c] (AE1.xpt where P3POP = 1 and AESEV ≥ 3) by PATID, TRTGRP, AEPT, maxAESEV, and AEDAY
[c] (AE1.xpt where P3POP = 1, AESEV ≥ 3, and AEREL ≥ 3) by PATID, AEPT, TRTGRP, maxAESEV, and AEDAY

7.5.3 Drug-Demographic Interactions

Of the 583 patients in the pooled safety population of the randomized trials 3101 and 3102, 578 (99%) had at least on AE, and 249 (43%) had at least one Grade 3-4 AE. The risk of having at least one Grade 3-4 AE was slightly higher for patients over age 65 in the G-CSF/plerixafor group compared to G-CSF alone, and a higher percentage of females than males experienced at least one Grade 3-4 AE in each treatment group. Cancer type (NHL vs. MM) did not appear to influence the risk of Grade 3-4 toxicity (Table 77).

**Table 77. Toxicity by patient subgroup in Studies 3102 and 3102 (safety pop.; n = 583)**

| | G-CSF/Plerixafor (n = 292) | | G-CSF/Placebo (n = 291) | |
|---|---|---|---|---|
| **Subgroup** | **Any AE** | **Grade 3-4 AEs** | **Any AEs** | **Grade 3-4 AEs** |
| **Age** | | | | |
| 18 – 64 | 224/226 (99%) | 93/226 (41%) | 214/218 (98%) | 94/218 (43%) |
| ≥ 65 | 64/66 (97%) | 35/66 (53%) | 71/73 (97%) | 27/73 (37%) |
| **Gender** | | | | |
| Male | 195/197 (99%) | 76/197 (38%) | 196/201 (98%) | 82/201 (49%) |
| Female | 93/95 (98%) | 52/95 (55%) | 89/90 (99%) | 39/90 (59%) |
| **Race** | | | | |
| Caucasian | 246/249 (99%) | 110/249 (44%) | 253/258 (98%) | 110/258 (43%) |
| African-American | 23/24 (96%) | 9/24 (38%) | 15/15 (100%) | 5/15 (33%) |
| Hispanic | 14/14 (100%) | 7/14 (50%) | 7/7 (100%) | 3/7 (43%) |
| Asian | 3/3 (100%) | 1/3 (33%) | 5/5 (100%) | 2/5 (40%) |
| Other | 2/2 (100%) | 1 (33%) | 5/6 (83%) | 1/6 (17%) |
| **Cancer type** | | | | |
| NHL | 146/147 (99%) | 64/147 (44%) | 141/142 (99%) | 61/142 (43%) |
| MM | 142/145 (98%) | 64/145 (44%) | 144/149 (97%) | 60/149 (40%) |

Source: ([DISP1.xpt of 3101 and 3102] and [AE1.xpt where [RITUX = missing, RANDDT ≠ missing, PATID ≠ 25-401, and ITT1 = 1]) by PATID, TRTGRPR, SEX, ETHNIC, AGE, AEPT, and AESEV

To further explore risks of plerixafor toxicity in individual patient subsets, this reviewer analyzed Periods 1 through 5 of the two randomized clinical trials 3101 and 3102 for incidences of seven key toxicity categories: gastrointestinal symptoms, neurologic or psychiatric, hematological, electrolyte imbalances, fatigue, musculoskeletal pain, and injection-site reactions. These groups were selected because either preclinical data suggested a potential for toxicity or a signal had emerged in the overall safety database. Neither age, gender, nor race appeared to significantly affect patients' risks of any of these toxicities (Table 78). Although no racial or ethnic groups were excluded from the randomized studies, most patients (87%) were Caucasian.

The safety and efficacy of plerixafor in persons under age 18 and in pregnant or breast feeding women has not been established. Because of preclinical teratogenicity findings, plerixafor will be characterized pregnancy Category D.

**Table 78: Risk of select AEs during Studies 3101 and 3102 (Safety pop.; n = 583)**

| | G-CSF/plerixafor (n = 292) | | G-CSF/placebo (n = 291) | |
|---|---|---|---|---|
| | **Age <65** | **Age ≥ 65** | **Age <65** | **Age ≥ 65** |

| Event type | (n = 226) | (n = 66) | (n = 218) | (N = 73) |
|---|---|---|---|---|
| Gastrointestinal upset[a] | 216 (96%) | 64 (97%) | 162 (74%) | 54 (74%) |
| Neurological or psychiatric[b] | 160 (71%) | 38 (58%) | 166 (76%) | 37 (51%) |
| Hematological[c] | 39 (17%) | 11 (17%) | 45 (21%) | 12 (16%) |
| Electrolyte imbalance[d] | 71 (31%) | 21 (32%) | 72 (33%) | 28 (38%) |
| Fatigue[e] | 73 (32%) | 17 (26%) | 72 (33%) | 16 (22%) |
| Musculoskeletal pain[f] | 143 (64%) | 37 (56%) | 159 (73%) | 46 (63%) |
| Injection-site reaction[g] | 79 (35%) | 24 (36%) | 41 (19%) | 15 (21%) |
| | **Male (n = 197)** | **Female (n = 95)** | **Male (n = 201)** | **Female (n = 90)** |
| Gastrointestinal upset[a] | 116 (59%) | 67 (71%) | 96 (48%) | 48 (53%) |
| Neurological/psychiatric[b] | 106 (54%) | 49 (52%) | 93 (46%) | 53 (59%) |
| Hematological[c] | 31 (16%) | 13 (14%) | 33 (16%) | 17 (19%) |
| Electrolyte imbalance[d] | 66 (34%) | 26 (27%) | 70 (35%) | 30 (33%) |
| Fatigue[e] | 57 (30%) | 33 (35%) | 56 (28%) | 32 (36%) |
| Musculoskeletal pain[f] | 116 (59%) | 64 (67%) | 136 (68%) | 69 (77%) |
| Injection-site reaction[g] | 69 (35%) | 34 (36%) | 37 (18%) | 19 (21%) |
| | **Caucasian (n = 249)** | **Non-Caucasian (n = 43)** | **Caucasian (n = 258)** | **Non-Caucasian (n = 33)** |
| Gastrointestinal upset[a] | 162 (65%) | 21 (49%) | 130 (50%) | 14 (42%) |
| Neurological/psychiatric[b] | 115 (46%) | 2 (5%) | 126 (49%) | 20 (61%) |
| Hematological[c] | 47 (19%) | 3 (7%) | 52 (20%) | 5 (15%) |
| Electrolyte imbalance[d] | 62 (25%) | 12 (28%) | 68 (26%) | 9 (27%) |
| Fatigue[e] | 78 (31%) | 12 (28%) | 80 (31%) | 8 (24%) |
| Musculoskeletal pain[f] | 150 (60%) | 30 (70%) | 180 (70%) | 12 (36%) |
| Injection-site reaction[g] | 92 (37%) | 11 (26%) | 48 (19%) | 8 (24%) |

[a] Preferred Terms nausea, vomiting and diarrhea
[b] Preferred Terms anxiety, dizziness, headache, hypoasthesia, and insomnia, paresthesia
[c] Included Preferred Terms anemia, febrile neutropenia, neutropenia, pancytopenia, platelet count decreased, and thrombocytopenia
[d] Preferred Terms blood calcium decreased, blood magnesium decreased, blood potassium decreased, hypokalemia, hypomagnesemia, hypophosphatemia
[e] Preferred Terms asthenia, fatigue, and lethargy
[f] Preferred Terms back pain, bone pain, muscle spasms, musculoskeletal chest pain, musculosketetal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, pain, and pain in extremity
[g] Preferred Terms injection site bruising, discharge, discomfort, erythema, hematoma, hemorrhage, induration, irritation, pain, paresthesia, pruritus, rash, reaction, swelling, and urticaria

### 7.5.4 Drug-Disease Interactions

#### 7.5.4.1. Patients with renal impairment

Patients in the randomized studies 3101 and 3102 were required to have a baseline serum creatinine ≤ 2.3 mg/dL. The Applicant did not submit baseline laboratory data for patients in the randomized trials, so the relationship between baseline renal or hepatic function and subsequent toxicity in those trials could not be explored.

Because the primary route of plerixafor elimination is urinary, the Applicant conducted an open-label study (1101) comparing the PK, PD, and tolerability of a single 240 µg dose of plerixafor

in volunteers with stable renal insufficiency. Subjects were stratified into 4 cohorts based on creatinine clearance measured from a 24-hour urine collection: >90 mL/min (control; n = 6), 51 to 80 mL/min (mild renal impairment; n = 5), 31 to 50 mL/min (moderate renal impairment; n = 6), and <31 mL/min, not requiring dialysis (n = 6). Statistically significant differences in the PK of plerixafor were noted between the moderate renal impairment and control cohorts (see Section 4.4.3 of this review).

No SAEs, discontinuations due to AEs, or withdrawals occurred in Study 1101. All AEs were mild to moderate in severity. The system organ classes with the greatest frequency were gastrointestinal disorders (39%), nervous system disorders (35%), and general disorders and administration site conditions (35%). The most frequent preferred terms were diarrhea (26%), injection site erythema (22%), and paresthesia (17%).

Study 1101 provided limited data because its sample size was small. Nonetheless, the degree of renal insufficiency did not appear to correlate with the overall incidence of AEs.

#### 7.5.4.2 Patients with genetic polymorphisms

Plerixafor is a selective antagonist of the CXCR4 chemokine receptor. Genetic variants in CXCR4 and its ligand SDF-1 (CXCL12) have been described. The SDF-1-3A allele is associated with delayed disease progression among patients infected with HIV,[62] and rare CXCR4 mutations are associated with the warts, hypogammaglobulinemia, infections, and myelokathexis (WHIMS) immunodeficiency syndrome.[63] Since genotyping was not performed as part of the clinical trials of plerixafor, no data are available regarding the potential influences of genetic polymorphisms on safety or efficacy,

### 7.5.5 Drug-Drug Interactions

#### 7.5.5.1 *In vitro* data

Results of *in vitro* studies with rat, dog, and human microsomes and primary hepatocytes showed that plerixafor is not subject to hepatic metabolism and is not a substrate, inhibitor, or inducer of human cytochrome P450. Plerixafor is renally excreted, and the potential for interactions with other renally excreted drugs has not been formally evaluated. Plerixafor is administered parenterally, so food interactions are unlikely.

#### 7.5.5.2 Rituximab

Rituximab may be used in patients with $CD20^+$ lymphoma for its in vivo purging effect during mobilization in order to try to improve relapse-free survival. A total of 15 patients in the safety population of this application received rituximab 375 mg/$m^2$ IV weekly beginning one week

before and continuing until two weeks after the first dose of G-CSF. Nine of the 15 patients were from Study 2113 and six were from one study site in 3101. Eleven had NHL and four had HD.

The mean cumulative dose of G-CSF was 70.5 ± 17.1 μg/kg administered in 5.7 ± 1.3 doses. The mean cumulative dose of plerixafor was 521.7 ± 302.7 μg/kg administered over 2.1 ± 1.2 days. Overall, 14 patients (93%) experienced at least 1 AE during Period 1 (Table 79). In addition, one patient each (7%) also experienced AEs during Periods 2 (peripheral edema) and 3 (staphylococcal bacteremia). The staphylococcal bacteremia during Period 3 was the only Grade 3 event; there were no Grade 4 or 5 events.

**Table 79. AEs during Period 1 in rituximab subpopulation (n = 15)**

| Adverse event | Number of patients experiencing |
|---|---|
| Anal injury | 1 (7%) |
| Anxiety or insomnia | 2 (13%) |
| Musculoskeletal pain[a] | 4 (27%) |
| Catheter site event[b] | 8 (53%) |
| Cough | 1 (7%) |
| Diarrhea | 1 (7%) |
| Dizziness | 1 (7%) |
| Dysgusia | 1 (7%) |
| Dyspnea | 1 (7%) |
| Generalized erythema or hot flush | 2 (13%) |
| Herpes zoster | 1 (7%) |
| Hypocalcemia | 1 (7%) |
| Hypokalemia | 1 (7%) |
| Nausea | 1 (7%) |
| Night sweats | 1 (7%) |
| Edema peripheral | 2 (13%) |
| Oral candidiasis | 1 (7%) |
| Oral herpes | 1 (7%) |
| Oral pain | 1 (7%) |
| Paresthesia oral | 1 (7%) |
| Pharyngolaryngeal pain | 1 (7%) |
| Pyrexia | 1 (7%) |
| Retching or vomiting | 2 (13%) |
| Staphylococcal bacteremia | 1 (7%) |
| Thrombocytopenia | 1 (7%) |
| Visual disturbance | 1 (7%) |

[a] AEPT back pain, bone pain, non-cardiac chest pain, or pain
[b] AEPT catheter/injection site cellulitis, erythema, hematoma, hemorrhage, edema, pain, or urticaria

***Reviewer's comment:*** *The sample size of patients receiving plerixafor and concurrent rituximab was too small to draw conclusions regarding the safety of this combination. Nonetheless, no unique safety signal was apparent.*

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

No direct human data regarding carcinogenicity are available. Plerixafor was not genotoxic in an Applicant-conducted *in vivo* rat micronucleus test, was not mutagenic in a *Salmonella typhimurium* mutation assay, and was not clastogenic in a chromosomal aberration test with V79 Chinese Hamster Cells. See the Pharmacology-Toxicology review of this application for further details.

### 7.6.2 Human Reproduction and Pregnancy Data

An embryo-fetal development study was conducted in rats administered plerixafor SC at 0, 0.5, 3, or 15 mg/kg/day for 12 days from gestation day 6 to 17. At 15 mg/kg/day, there was reduced food consumption, and less body weight gain in dams, as well as an increased incidence of resorption, decreased fetal weights, retarded skeletal development, and an increased incidence of fetal abnormalities. The NOAEL for embryo-fetal development was 3 mg/kg/day, which is approximately twice the recommended human dose. A NOAEL for maternal toxicity was not reported. Because of positive findings in the rat embryo-fetal study, a rabbit study was not conducted.

***Reviewer's comment:*** *Based on these results, plerixafor administration during pregnancy is a potential risk to the fetus.*

The potential effects of plerixafor on male and female fertility or on post-natal development were not evaluated in specific nonclinical studies. However, distribution of drug-derived material to the testes was low in tissue distribution studies, and no histopathological evidence of toxicity to male or female reproductive organs was observed in rats or dogs dosed with plerixafor daily or BID for 28 days.

***Reviewer's comment:*** *The preclinical findings coupled with the recommended short duration of dosing in humans suggest the risk of plerixafor impairing fertility is low.*

### 7.6.3 Pediatrics and Effect on Growth

#### 7.6.3.1 Clinical experience

Plerixafor was granted orphan drug designation (ODA #03-1679) on July 10, 2003 and was therefore exempt from pediatric study requirements. All phase 2 and 3 studies conducted to date were restricted to adult patients.

As of the December 31, 2006 data cutoff, eight patients under 18 years of age had been enrolled in an ongoing CUP which was open to patients who would benefit from an autologous HSCT but could not collect sufficient stem cells. Those eight patients included five males and three females. Their mean and median ages were 13.4 and 14.0 years, respectively. Two had NHL, two had medulloblastoma, and one each had Ewing's sarcoma, a brain tumor, a neuroectodermal tumor, and osteogenic sarcoma.

Of the eight pediatric patients, four experienced a total of 11 AEs. These included nausea (n = 2), and coagulopathy, thrombocytopenia, vomiting, catheter-related complication, injection site pain, leukoencephalopathy, citrate toxicity, headache, and respiratory failure (1 each). The thrombocytopenia event was considered possibly drug-related, and the catheter related complication was considered definitely study drug-related; the remaining AEs were considered not or probably not related.

***Reviewer's comment:*** *The safety and efficacy of plerixafor in pediatric patients has not been established.*

7.6.3.2 Pediatric Written Request

On June 20, 2005, the FDA issued the Applicant a Written Request for the following two pediatric studies:

Study 1 should be an open-label, non-randomized study of G-CSF/plerixafor in pediatric cancer patients eligible for autologous HSCT. The primary endpoint should be determination of the biologically effective dose. Secondary endpoints should be to describe the safety profile, PK, and PD of G-CSF/plerixafor in this population. Descriptive statistics should be used in reporting results.

Study 2, to be conducted after the results of Study 1 are known, should randomize children with pediatric cancers eligible for autologous HSCT to G-CSF/plerixafor versus G-CSF/placebo. Endpoints should include safety, PK, and clinical efficacy (e.g. number of apheresis procedures required to collect a specified minimum target number of $CD34^+$ cells, number of circulating $CD34^+$ cells, total number of $CD34^+$ cells collected, days to neutrophil and platelet engraftment, and graft durability).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The packaging of plerixafor in unit dose vials and the controlled hospital setting in which it will be administered should make accidental overdose rare. In the event of off-label self-administration, overdose will be limited by vial size (one vial contains 24 mg, which is sufficient for a 100 kg individual). Plerixafor has no known attributes that make it a candidate for intentional overdose, abuse, or illegal use.

### 7.7 Additional Submissions

None

# 8 Postmarketing Experience

None

# 9 Appendices

## 9.1 Literature Review/References

See Section 2 of this review.

## 9.2 Labeling Recommendations

The product label was being drafted at the time of this review.

## 9.3 Advisory Committee Meeting

This application was not taken to an advisory committee.

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