

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-311**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review Amendment

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|---|--|
| <b>NDA</b>                              | 22-311   |
| <b>Submission Date:</b>                 | 16 June 2008   |
| <b>Brand Name:</b>                      | Mozobil™   |
| <b>Generic Name:</b>                    | Plerixafor   |
| <b>Formulation:</b>                     | 20 mg/mL solution for injection  |
| <b>OCP Reviewer:</b>                    | Jeanne Fourie, Ph.D.   |
| <b>Pharmacometrics Reviewer:</b>        | Christoffer Tornoe, Ph.D   |
| <b>OCP Team Leader:</b>                 | Brian Booth, Ph.D.   |
| <b>Pharmacometrics Team<br/>Leader:</b> | Yaning Wang, Ph.D.   |
| <b>OCP Division:</b>                    | Division of Clinical Pharmacology V  |
| <b>ORM Division:</b>                    | Division of Drug Oncology Products   |
| <b>Sponsor:</b>                         | Genzyme Corporation  |
| <b>Submission Type; Code:</b>           | Original NDA; 000  |
| <b>Dosing regimen:</b>                  | 240 µg/kg SC injection 11 hours prior to initiation of<br>apheresis, repeat dose up to 7 consecutive days  |
| <b>Indication:</b>                      | Enhance mobilization of hematopoietic stem cells to<br>the peripheral blood for collection and subsequent<br>autologous transplantation in patients with lymphoma<br>and multiple myeloma. |

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The following amendment addresses Section 2.3 (Intrinsic Factors) in the original OCP review for NDA 22-311.

- The sentence (b) (4) [redacted] needs to be revised as follows: (b) (4) [redacted] (b) (4) [redacted]
- The sentence (b) (4) [redacted] needs to be removed from the original review. This statement needs to be replaced by the following results from an additional analyses conducted by OCP.
- These new data described below were also included in the plerixafor label (Section 12.3) as follows:

**Race**

Clinical (b) show (b) similar plerixafor pharmacokinetics for Caucasians and African-Americans, and the effect of other racial/ethnic groups has not been studied.

**Gender**

Clinical (b) show (b) no effect of gender on plerixafor pharmacokinetics.

**Age**

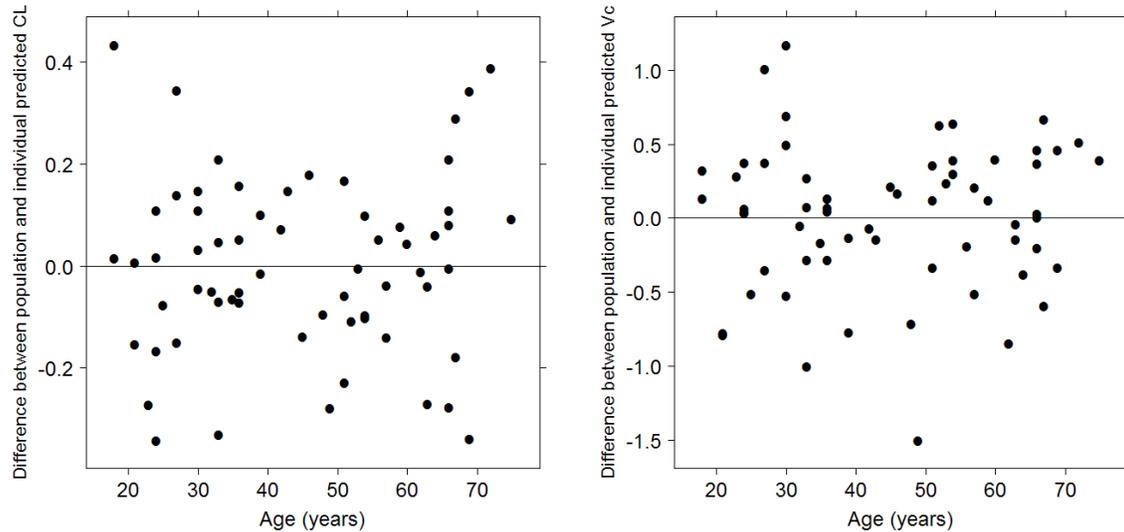
Clinical (b) show (b) no effect of age on plerixafor pharmacokinetics

The analyses in the current revision address the effects of age, disease (multiple myeloma (MM), non-Hodgkin's disease (NHL) or Hodgkin's disease (HD)), gender and race on the exposure to plerixafor. Pharmacokinetic parameters from the population pharmacokinetic analysis conducted in the original NDA submission were used in all of the following analyses. This population consisted of healthy volunteers with varying degrees of renal function and patients with HD, MM and NHL.

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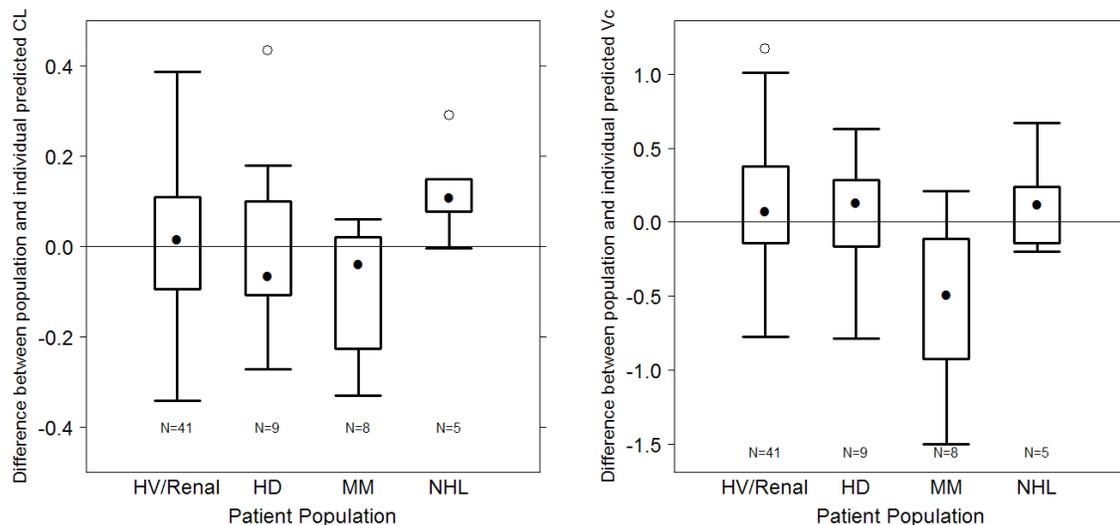
**Is there an effect of age on plerixafor exposure?** There appeared to be no effect of age on plerixafor pharmacokinetics after correcting for both  $CL_{CR}$  (which has age as a covariate) and body weight on clearance and volume of distribution parameters (Figure 1).

**Figure 1** Scatter plots of age versus the difference between population and individual predicted volume of distribution and clearance parameters.



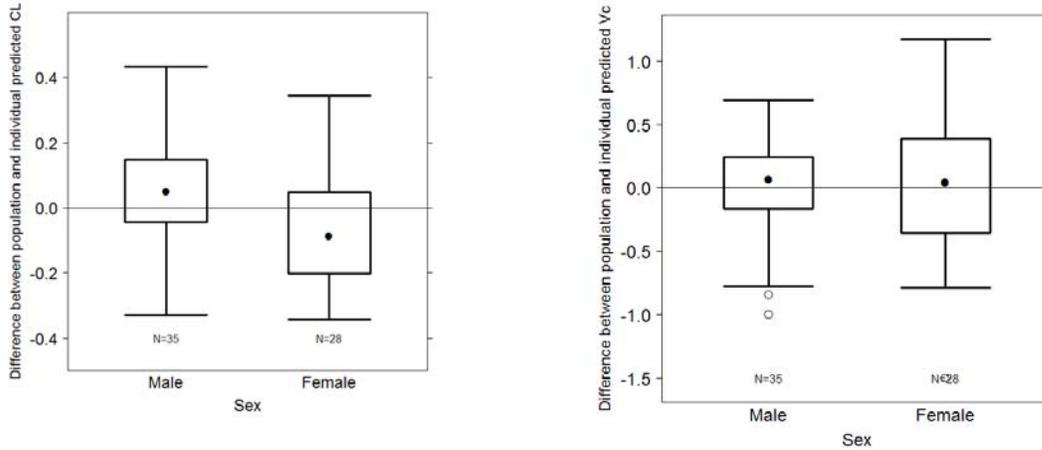
**Is there an effect of disease (HD, MM or NHL) on plerixafor exposure?** There appeared to be no effect of disease status on plerixafor pharmacokinetics after correcting for both  $CL_{CR}$  (which has age as a covariate) and body weight on clearance and volume of distribution parameters (Figure 2).

**Figure 2** The distribution of the difference between population and individual predicted volume of distribution and clearance parameters in healthy subjects with varying degrees of renal function (HV/Renal) and patients with HD, MM and NHL.



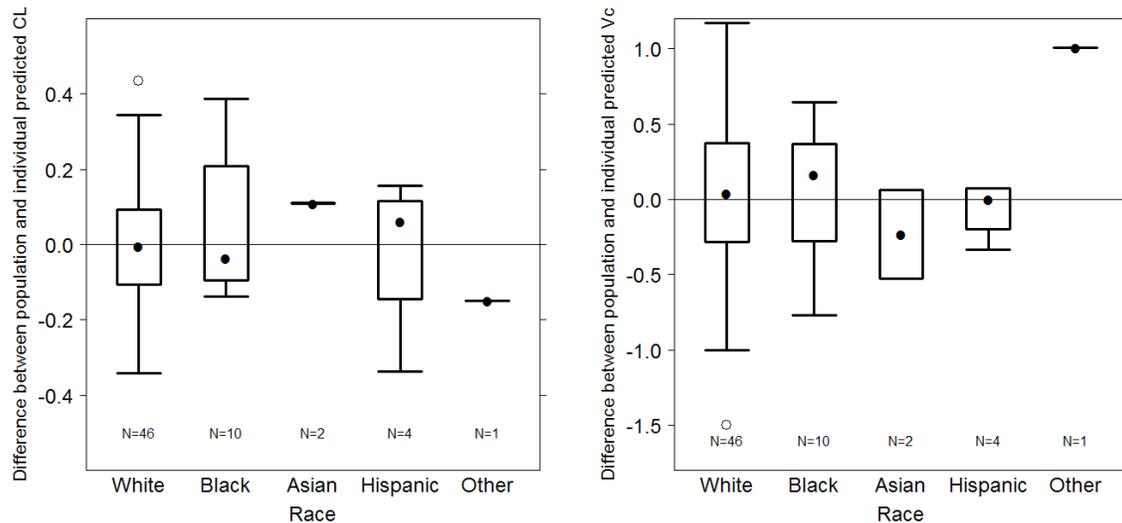
**Is there an effect of gender on plerixafor exposure?** There appeared to be no effect of gender on plerixafor pharmacokinetics after correcting for both  $CL_{CR}$  (which has age as a covariate) and body weight on clearance and volume of distribution parameters (Figure 3).

**Figure 3** The distributions of the difference between population and individual predicted volume of distribution and clearance parameters in male and female subjects.



**Is there an effect of race on plerixafor exposure?** Plerixafor pharmacokinetics were similar for Caucasians and African-Americans after correcting for both  $CL_{CR}$  (which has age as a covariate) and body weight on clearance and volume of distribution parameters. Small numbers of patients from other racial/ethnic groups were enrolled in the clinical trials. Therefore, conclusions regarding the effect of other racial/ethnic groups on plerixafor exposure cannot be made based on the limited data submitted (Figure 4).

**Figure 4** The distributions of the difference between population and individual predicted volume of distribution and clearance parameters in subjects with different racial/ethnic backgrounds.



**Signatures:**

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Reviewer: Jeanne Fourie, Ph.D.  
Division of Clinical Pharmacology 5

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Deputy Director & Acting Team Leader: Brian Booth,  
Ph.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - S Jenney; MTL - R Justice, A Farrell; MO - M Brave,  
DCP- Reviewers - J Fourie, C Torno  
5: Acting TL & DDD - B Booth  
PM TL - Y Wang  
DD - A Rahman

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/s/

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Jeanne Fourie  
12/4/2008 04:09:12 PM  
PHARMACOLOGIST

Brian Booth  
12/5/2008 07:48:16 AM  
BIOPHARMACEUTICS

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## Clinical Pharmacology Review

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|-------------------------------------|---|
| <b>NDA</b>                          | 22-311  |
| <b>Submission Date:</b>             | 16 June 2008  |
| <b>Brand Name:</b>                  | Mozobil™  |
| <b>Generic Name:</b>                | Plerixafor  |
| <b>Formulation:</b>                 | 20 mg/mL solution for injection   |
| <b>OCP Reviewer:</b>                | Jeanne Fourie, Ph.D.  |
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| <b>OCP Division:</b>                | Division of Clinical Pharmacology V   |
| <b>ORM Division:</b>                | Division of Drug Oncology Products  |
| <b>Sponsor:</b>                     | Genzyme Corporation   |
| <b>Submission Type; Code:</b>       | Original NDA; 000   |
| <b>Dosing regimen:</b>              | 240 µg/kg SC injection 11 hours prior to initiation of apheresis, repeat dose up to 7 consecutive days  |
| <b>Indication:</b>                  | Enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma. |

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OCP Briefing held on November 5, 2008 attended by: OCP staff

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## 1 EXECUTIVE SUMMARY

Plerixafor (Mozobil®, AMD3100) is a small-molecule bicyclam derivative CXCR4 antagonist. The current submission is the original NDA for plerixafor, in conjunction with granulocyte-colony stimulating factor (G-CSF or G), to enhance the mobilization of hematopoietic stem cells (CD34+ cells) to the peripheral blood for collection and subsequent autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

A population pharmacokinetic (PK) analysis conducted by OCP indicated a decreased response rate in NHL patients weighing < 85 kg. The population PK analysis also indicated that the proposed mcg/kg-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 significantly decreased efficacy. A logistic regression analysis conducted by OCP also showed that both low body weight (i.e. low exposure) and low CD34+ baseline cell counts, were predictors of poor response to CD34+ mobilization therapy with plerixafor + G-CSF. Based on these data the dose of plerixafor needs to be optimized in patients with low exposure and low CD34+ baseline values, as these are predictors of poor response. The OCP phase 4 commitments include a study to address optimization of the plerixafor dose in patients with low body weight and those who are predicted to be poor responders to plerixafor based CD34+ baseline cell count. This study will consider predictors of poor response such as low exposure and baseline CD34+ count, and will 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.

Results from the dedicated renal impairment study showed an increase in plerixafor exposure with increasing severity of renal impairment. The population PK analysis also indicated an increased exposure in patients with moderate and severe renal impairment compared to patients with mild and normal renal function. OCP recommends a dose reduction of one-third (160 mcg/kg) across all body weights for patients with moderate to severe renal impairment ( $CL_{CR} \leq 50$  mL/min). OCP also recommends a maximum dose of 27 mg in patients with  $CL_{CR} \leq 50$  mL/min.

Plerixafor was not screened *in vitro* to assess whether it is a substrate or inhibitor of P-glycoprotein. The OCP phase 4 commitments include a request that the applicant conducts an *in vitro* screen to assess this. Based on the results submitted, the use of plerixafor in combination with P-glycoprotein substrates and/or inhibitors will be addressed in the label.

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-311. This NDA is considered acceptable from a clinical pharmacology perspective.

## Phase IV Commitments

1. You should screen plerixafor *in vitro* assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an *in vivo* drug-drug interaction study may be needed.
2. You should submit the study report and data from your thorough QT/QTc study report upon its completion.
3. The currently proposed body weight adjusted dosing of plerixafor (240 mcg/kg) results in a lower exposure to plerixafor in patients with low body weight compared to patients with higher body weights. This decreased exposure was associated with significantly decreased efficacy in patients with low body weight. Based on the logistic regression analysis, both low body weight (i.e. low exposure) and low CD34+ baseline cell counts, were predictors of poor response to CD34+ mobilization therapy with plerixafor + G-CSF. The applicant agrees to design, conduct and submit a clinical study to optimize dosing in NHL patients by matching exposure in lower weights to that in patients over 85 kg. The applicant should also compare this result 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+ cell counts at baseline and time points prior to G-CSF administration and prior to apheresis as was done in protocol AMD3100-3101. 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.

## Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

1. The following should be added under the Dosage and Administration section:
  - (b) (4)

## Comments:

1. Since patients predicted to be poor responders to plerixafor may have low exposure to plerixafor and also appear to take longer to respond to the mobilization/apheresis treatment it may be useful to further characterize the exposure/response relationships in terms of efficacy and toxicity in this subpopulation.

## Signatures:

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Reviewer: Jeanne Fourie, Ph.D.  
Division of Clinical Pharmacology 5

Deputy Director & Acting Team Leader: Brian Booth, Ph.D.  
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - S Jenney; MTL - R Justice; MO - M Brave,  
DCP- Reviewers - J Fourie, C Tornoe  
5: Acting TL & DDD - B Booth  
PM TL - Y Wang  
DD - A Rahman

## 1.2 CLINICAL PHARMACOLOGY SUMMARY

Plerixafor (Mozobil®, AMD3100) is a small-molecule reversible antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ , also known as CXCL12). The proposed indication is for plerixafor, administered in conjunction with a G-CSF, to enhance the mobilization of hematopoietic stem cells (CD34+ cells) to the peripheral blood for collection and subsequent autologous transplantation in adult patients with NHL and MM. The applicant conducted several phase 1, phase 2 and phase 3 clinical studies in healthy subjects, subjects with renal impairment and oncology patients (patients with MM, NHL and Hodgkin's lymphoma (HD)) to characterize the pharmacodynamics (peripheral blood CD34+ cell mobilization), pharmacokinetics (PK) efficacy and safety of plerixafor.

In both phase 3 studies, patients participated in a mobilization period (G-CSF administration) followed by a treatment period (plerixafor or placebo administration). The primary efficacy endpoint in the pivotal phase 3 trial in patients with NHL was the proportion of patients that was able to mobilize at least  $5 \times 10^6$  CD34+ cells/kg in four or fewer apheresis days. The primary efficacy endpoint in the pivotal phase 3 trial in patients with MM was the proportion of patients that was able to mobilize at least  $6 \times 10^6$  CD34+ cells/kg in two or fewer apheresis days.

In all clinical studies, plerixafor produced a significant increase in absolute peripheral blood (PB) CD34+ cell counts from baseline. A dose-response relationship was demonstrated for the 40 to 240 mcg/kg dose range, and supported selection of the 240 mcg/kg/day SC dose in phase 2 and 3 trials. The pharmacodynamic response of plerixafor occurred between 6 to 10 hours after dosing when administered alone in healthy volunteers. Administration of plerixafor, following a 4 day mobilizing regimen with G-CSF (10 mcg/kg, QD) produced higher PB CD34+ cell counts than either plerixafor or G-CSF alone. In lymphoma and MM patients the pharmacodynamic response to plerixafor, following a 4 day mobilizing regimen of G-CSF (10 mcg/kg, QD), occurred over a broad peak, with maximum PB CD34+ levels occurring between 10 to 14 hours after dosing. These data supported the proposed phase 3 dosing regimen in which plerixafor is administered following a 4 day mobilization regimen with G-CSF as well as the time frame that separates plerixafor administration and the subsequent apheresis (11 hours).

Following a single 240 mcg/kg subcutaneous (SC) dose of plerixafor in subjects with normal renal function, approximately 71% of the parent drug was recovered in the urine within 24 hours. Results from the dedicated renal impairment study showed an increase in plerixafor exposure,

with increasing severity of renal impairment following a single 240 mcg/kg SC dose. Compared to subjects with normal renal function, subjects with mild, moderate, or severe renal impairment had average respective increases in systemic exposure ( $AUC_{0-24h}$ ) of 7%, 32%, and 39%.

Plerixafor has limited oral bioavailability, which led to selection of the SC injection route of administration for clinical development. The PK profile of plerixafor was similar between healthy volunteers given a SC dose of plerixafor alone (240 mcg/kg) and oncology patients given a SC dose of plerixafor (240 mcg/kg) following a 4 day mobilizing regimen of G-CSF (10 mcg/kg, QD). Plerixafor was rapidly absorbed with peak concentrations at 0.5 to 1 hour after SC injection and the mean elimination half-life ranged from 3.1 to 5.3 hours across the dose range of 40 to 240 mcg/kg. The apparent volume of distribution of plerixafor in humans is 0.3 L/kg demonstrating that plerixafor is largely confined to, but not limited to, the extravascular fluid space. Plerixafor PK parameters were dose-proportional, and the  $C_{max}$  and exposure of plerixafor were linear within the dose range of 40 mcg/kg to 240 mcg/kg. *In vivo* drug-drug interactions studies were not warranted, as *in vitro* studies indicated that plerixafor is not metabolized significantly by human liver microsomes or hepatocytes, and that plerixafor is neither an inducer nor an inhibitor of the cytochrome P450 isozymes. An *in vitro* study to assess the potential for plerixafor to act as a P-glycoprotein substrate and inhibitor was not conducted, and will be a phase 4 commitment.

A population PK analysis conducted by OCP indicated a decreased response rate in NHL patients weighing < 85 kg. The population PK analysis also indicated that the proposed mcg/kg-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 significantly decreased efficacy. A logistic regression analysis conducted by OCP also showed that both low body weight (i.e. low exposure) and low CD34+ baseline cell counts, were predictors of poor response to CD34+ mobilization therapy with plerixafor + G-CSF. Based on these data the dose of plerixafor needs to be optimized in patients with low exposure and low CD34+ baseline values, as these are predictors of poor response. The OCP phase 4 commitments include a study to address optimization of the plerixafor dose in patients with low exposure and those who are predicted to be poor responders to plerixafor based CD34+ baseline cell count. This study will consider predictors of poor response such as low exposure and baseline CD34+ count, and will 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.

The population PK analysis conducted by OCP also showed an increased exposure in patients with moderate and severe renal impairment, as compared to patients with normal renal function and mild renal impairment. OCP further included a dose reduction of one-third (160 mcg/kg) in patients with moderate to severe renal impairment ( $CL_{CR} \leq 50$  mL/min, estimated using the Cockcroft-Gault formula) such that the exposure of plerixafor is matched to that in individuals with normal renal function. OCP further recommends a maximum dose of 27 mg in patients with  $CL_{CR} \leq 50$  mL/min.

The applicant's population PK analysis led to identification of a 2-compartment model with a

first order input and first order elimination to describe the PK of plerixafor. This model was parameterized in terms of apparent clearance (CL/F), the central volume of distribution (Vc/F), the peripheral volume of distribution (Vp/F) and inter-compartmental clearance (Q/F). The primary covariate identified as the most important in influencing plerixafor PK was creatinine clearance (CL<sub>CR</sub>), where total body weight, gender and age covariates were incorporated in the Cockcroft and Gault equation. The CL<sub>CR</sub> covariate described some of the inter-individual variability in clearance (CL/F). The second most important covariate was total body weight (WT) which described some of the inter-individual variability in central volume of distribution (Vc/F). When CL<sub>CR</sub> and WT covariates were included in the final covariate model, the inter-individual variability of CL/F and Vc/F reduced from 40.6% and 71.7% to 21.8% and 58.3%, respectively. The applicant suggested a weight-based dosing strategy due to the influence of weight, and a dose reduction in patients with severe renal impairment based on the influence of CL<sub>CR</sub>.

In studies with a single dose of plerixafor, that included the 160 and 240 mcg/kg does groups, the safety profiles of the two doses were similar and 100% of adverse events (AEs) were mild in intensity. The integrated safety analysis showed that the majority of reported AEs were mild to moderate in severity.

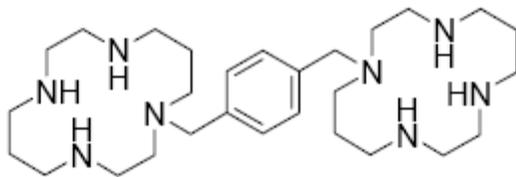
## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

##### Physical-chemical properties

1. Structural formula:



2. Established name: plerixafor
3. Molecular Weight: 502.79 g/mol (anhydrous)
4. Molecular Formula: C<sub>28</sub>H<sub>54</sub>N<sub>8</sub>
5. Chemical Name: 1,1'-[1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane
6. What are the proposed mechanisms of action and therapeutic indications?

Plerixafor is a reversible antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ , also known as CXCL12). CXCR4 is

expressed on hematopoietic stem cells. SDF-1 is expressed in the bone marrow, and through its interaction with CXCR4 it acts to localize hematopoietic stem cells to the bone marrow. Interruption of the CXCR4-SDF-1 interaction by plerixafor results in the mobilization of hematopoietic stem cells from the bone marrow to the peripheral blood where they can be collected by apheresis for subsequent transplantation. There is a potential for tumor cell mobilization in NHL and MM patients treated with plerixafor in conjunction with G-CSF. Details are provided in the Pharmacogenomics Review (Section 4.5) by Rosane Charlab Orbach.

### **2.1.2 What are the proposed dosage and route of administration?**

The applicant's recommended dosing regimen for plerixafor is a once-daily 240 mcg/kg SC injection in conjunction with daily dosing of G-CSF to enhance mobilization of hematopoietic stem cells prior to apheresis for autologous transplantation in patients with lymphoma and MM. The recommended mobilization/apheresis cycle involves a single daily morning dose of G-CSF 10 mcg/kg administered for 4 days prior to the first single daily evening dose of plerixafor 240 mcg/kg, followed by a subsequent single daily morning dose of G-CSF. It is recommended that the timing of G-CSF and plerixafor dosing be such that administration of the evening dose of plerixafor occurs (b) (4) to 11 hours prior to apheresis, and such that administration of the fifth dose of G-CSF occurs in the morning, 1 hour prior to the initiation of apheresis. In patients with NHL, plerixafor administration followed by G-CSF and apheresis was continued for up to four consecutive days until  $\geq 5 \times 10^6$  CD34+ cells/kg were collected. In patients with MM, plerixafor administration followed by G-CSF and apheresis was continued for up to two consecutive days until  $\geq 6 \times 10^6$  CD34+ cells/kg were collected.

## **2.2 GENERAL CLINICAL PHARMACOLOGY**

### **2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

A total of ten completed studies in healthy subjects and oncology patients were used to support the clinical pharmacology and biopharmaceutics section of the NDA (Table 1 and Table 2). Note that all studies will only be referred to based on the last 4 digits of the study/protocol number. These include phase 1 and phase 2 studies in healthy subjects and NHL, HD and MM patients, and include studies in which plerixafor was administered with and without G-CSF. The PK results from Studies 1002, C201, 2106, and 1101 were used to support pharmacokinetic claims. The applicant also provided pharmacokinetic information from the United States (US) compassionate use programme (CUP) (CUP001) and an Investigator-sponsored study (06-H-0156) at the National Institutes of Health, Bethesda, MD, US (United States). Three additional studies (98-01, 2001, and 1005) included pharmacokinetic analyses. However, audits of (b) (4) (b) (4) that were undertaken by Genzyme and a third party (b) (4) identified deficiencies in the conduct and reporting of their results. The findings from these audits are consistent with those identified by FDA in the 31 August 2006 warning letter to (b) (4). In recognition of these deficiencies, results from these three studies are not used by the applicant to support statements concerning the PK of plerixafor.

**Table 1** Studies supporting the clinical pharmacology and biopharmaceutics of plerixafor in healthy subjects

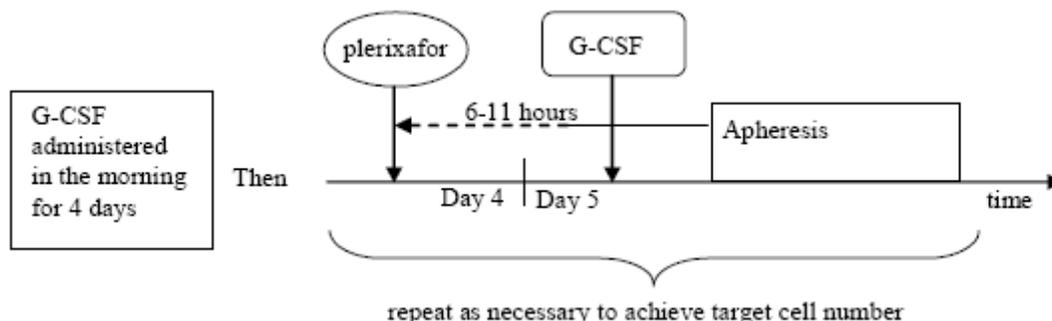
| Study Description  | Plerixafor Dose Range (SC injection)   | Subjects with PK/PD data | G Dose   |
|--|--|--------------------------|--|
| Phase 1 Study of the Safety, Pharmacokinetic and Hematological Activity of One Dose of AMD3100 Administered by Subcutaneous Injection to Healthy Volunteers (Protocol No. AMD3100-1002) <sup>A</sup>       | 40, 80, 160, and 240 µg/kg   | PK: 18<br>PD: 23         | None   |
| Analysis of the Effect of AMD3100 When Given Alone or With G to Mobilize Progenitor Cells after Pre-Treatment with G in Healthy Subjects (Protocol No. AMD3100-1003)                                       | Group A: 160 µg/kg + 5th day of G<br>Group B: 160 µg/kg<br>Group C: 5th day of G (no plerixafor)<br><br>Groups D and E: 240 µg/kg + 5 <sup>th</sup> day of G | PD: 25                   | All Groups: 10 µg/kg for 4 days prior to any plerixafor<br>For all except Group B: 10 µg/kg on 5 <sup>th</sup> day |
| Phase 1 Study of the Safety and Hematological Activity of One Dose of AMD3100 Administered by Subcutaneous Injection at a Dose of 240 µg/kg or 320 µg/kg to Healthy Volunteers (Protocol No. AMD3100-1005) | 320 µg/kg or 240-µg/kg   | PK/PD: 6                 | None   |
| A Pilot Study of the Safety and Activity of Escalating Doses of AMD3100 to Mobilize CD34+ Cells in Healthy Volunteers (Protocol No. 06-H-0156)   | 400 µg/kg  | PK/PD: 6                 | None   |
| A Phase 1 Study of the Safety, Pharmacokinetics, and Hematological Activity of AMD3100 (240 µg/kg) in Healthy Subjects With Renal Impairment (Protocol No. AMD3100-1101) <sup>A</sup>                      | 240 µg/kg  | PK/PD: 23                | None   |
| Phase 1 Study: Safety, Pharmacokinetics, Bioavailability and Tolerability of AMD3100 in Normal, Healthy Subjects (Protocol No. AMD3100-98-01)  | 10, 20, 40, and 80 µg/kg IV; 40 and 80 µg/kg SC; 80 and 160 µg/kg PO (31288; 10 mg/mL)   | 13                       | None   |
| A: Studies used to support PK claims   |  |                          |  |

**Table 2** Studies supporting the clinical pharmacology and biopharmaceutics of plerixafor in cancer patients.

| Study Description  | Plerixafor Dose Range (SC injection) | Subjects/Patients with PK/PD data             | G Dose  |
|--|--------------------------------------|---|---|
| Phase I Study of the Safety and Effect on Circulating CD34+ Cells of a Single Dose of 160, 240, or 320 µg/kg of AMD3100 Administered by Subcutaneous Injection to Patients With Non-Hodgkin's Lymphoma or Multiple Myeloma (Protocol No. AMD3100-1004) | 160, 240, or 320 µg/kg               | 160 µg/kg : 6<br>240 µg/kg: 7<br>320 µg/kg: 7 | 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 (Protocol No. AMD3100-C201) <sup>A</sup>                                     | 240 µg/kg                            | PK: 13<br>PD: 4                               | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |
| Phase II Treatment with AMD3100 Added to a Mobilizing Regimen of G to Increase the Number of Peripheral Blood Stem Cells in Patients With Hodgkin's Disease (Protocol No. AMD3100-2106) <sup>A</sup>   | 240 µg/kg                            | PK: 9<br>PD: 4                                | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |
| Compassionate Use Protocol for the Use of AMD3100 to Mobilize Peripheral Blood Stem Cells for Collection and Transplantation (Protocols No. AMD3100-CUP001)  | 160 or 240 µg/kg                     | PK: 5   | 10 µg/kg  |
| A: Studies used to support PK claims   |                                      |   |   |

Four studies in patients with lymphoma and MM were conducted to support the efficacy claim. These studies are summarized below in Table 3. A generalized schematic of plerixafor administration and apheresis in these studies is shown in Figure 1.

**Figure 1:** Schematic of Plerixafor Administration and Apheresis:



**Table 3** Studies supporting the efficacy of plerixafor in cancer patients.

| Study Description   | Plerixafor Dose Range (SC injection) | G-CSF (G) Dose  |
|---|--------------------------------------|---|
| Phase 3 Multicentre, randomized, double-blind, placebo controlled, comparative trial of G + plerixafor (N=150) and G (N=148) in Patients with Non-Hodgkin's Lymphoma (Protocol No AMD3100-3101) | 240 µg/kg                            | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |
| Phase 3 Multicentre, randomized, double-blind, placebo controlled, comparative trial of G + plerixafor (N=148) and G (N=154) in patients with Multiple Myeloma (Protocol No AMD3100-3102)       | 240 µg/kg                            | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |
| Phase 2 Open-label cross-over study in patients with non-Hodgkin's lymphoma (N=15) or multiple myeloma (N=10) (Protocol No AMD3100-2101)  | 160 or 240 µg/kg                     | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |
| Phase 2 Treatment with AMD3100 Added to a Mobilizing Regimen of G to Increase the Number of Peripheral Blood Stem Cells in Patients With Hodgkin's Disease (Protocol No. AMD3100-2106)          | 240 µg/kg                            | 10 µg/kg for 4 days prior to initiating Plerixafor 10 µg/kg with plerixafor |

**Phase 2 Study in Patients with MM or NHL:**

Study 2101 was a Phase 2, multicenter, open-label, crossover study in patients with NHL or MM who were eligible for autologous stem cell transplantation. Patients received both G-CSF + plerixafor and G-CSF alone mobilization regimens, with a Rest Interval in between. In the G-CSF + plerixafor mobilization regimen, patients received 4 days of G-CSF run-in, followed by G-CSF + plerixafor and apheresis (6 hours after) daily for up to 4 days, or until the target of  $\geq 5 \times 10^6$  CD34+ cells/kg was achieved. In the G-CSF alone mobilization regimen, patients received 4 days of G-CSF run-in, followed by G-CSF only and apheresis (6 hours after) daily for up to 4 days, or until the target of  $\geq 5 \times 10^6$  CD34+ cells/kg was achieved. After the completion of Crossover Treatment, patients then underwent myeloablative chemotherapy and transplantation

with G-CSF + plerixafor mobilized apheresis product. The primary objective was to evaluate the difference in the number of CD34+ cells/kg collected after mobilization with a G-CSF + plerixafor regimen compared with that collected after mobilization with a G-CSF alone regimen. Overall, 20/25 patients (80.0%) achieved the target of  $\geq 5 \times 10^6$  CD34+ cells/kg when mobilized with G-CSF + plerixafor, while 8/25 patients (32.0%) achieved this target when mobilized with G-CSF alone. After 2 days of apheresis, 15/25 patients (60.0%) in the G-CSF + plerixafor regimen versus 4/25 patients (16.0%) in the G-CSF alone regimen reached the target cell dose (Table 4).

**Table 4** Number of patients reaching the primary end point (protocol 2101)

|   | Number of NHL patients (%) |             | Number of MM Patients (%) |             |
|---|----------------------------|-------------|---------------------------|-------------|
|   | Plerixafor + G-CSF         | G-CSF alone | Plerixafor + G-CSF        | G-CSF alone |
| Number of patients that reached target ( $\geq 5 \times 10^6$ CD34+ cells/kg) after 4 days of apheresis | 10/15 (66.7)               | 3/15 (20.0) | 10/10 (100)               | 5/10 (50)   |
| Number of patients that reached target ( $\geq 5 \times 10^6$ CD34+ cells/kg) after 2 days of apheresis | 8/15 (53.5)                | 1/15 (6.7)  | 7/10 (70)                 | 3/10 (30)   |

**Phase 2 Study in Patients with HD:**

Study 2106 was a single center, open-label study of 22 patients with Hodgkin’s disease (HD). Patients underwent G-CSF mobilization for 4 days. On the evening of the 4th day, plerixafor (240 µg/kg) was administered, then followed 10 to 11 hours later by G-CSF (10 µg/kg/day) and apheresis. Patients continued to receive G-CSF 10 µg/kg in the morning and plerixafor 240 µg/kg in the evening for up to a total of 5 days, or until  $\geq 5 \times 10^6$  CD34+ cells/kg were collected. Patients underwent pre-transplant ablative chemotherapy and autologous transplantation with cells obtained from the G-CSF + plerixafor mobilization regimen. The primary objective was to determine the proportion of patients with HD who collected  $\geq 5 \times 10^6$  CD34+ cells/kg after stem cell mobilization with G-CSF + plerixafor. The observed failure rate was 4.5% (1/22) compared to 26% (n=130) and 22% (n=98) in the historical controls for patients collecting the minimum transplantable cell dose of  $\geq 2 \times 10^6$  CD34+ cells/kg. Intensive PK sampling was obtained in this study.

**Phase 3 Study in Patients with NHL:**

Study 3101 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, study in patients with NHL eligible for autologous stem cell transplantation. Patients were randomized to receive the study treatment: G-CSF + plerixafor (n = 150 patients in the Primary Intent-to-Treat

[ITT] population) or G-CSF + placebo (n = 148 patients). Patients underwent mobilization with G-CSF 10 µg/kg/day for four days, and starting on Day 4 received an evening dose of plerixafor 240 µg/kg or placebo. On Day 5, patients received a morning dose of G-CSF 10 mcg/kg and underwent apheresis. Apheresis occurred approximately 10-11 hours after the dose of study treatment and within 60 minutes after administration of the morning dose of G-CSF). Patients continued to receive an evening dose of study treatment followed the next day by a morning dose of G-CSF and apheresis until  $\geq 5 \times 10^6$  CD34+ cells/kg were collected. The maximum number of apheresis sessions allowed in order to reach the target CD34+ cell number (primary endpoint) was four sessions for the NHL patients. In the Primary ITT population, the proportion of patients in the G-CSF + plerixafor group who achieved a target number of cells ( $\geq 5 \times 10^6$  CD34+ cells/kg) in four days or less of apheresis was approximately 3 times higher than in the G-CSF + placebo group (59.3% versus 19.6%, respectively; estimated treatment effect [TE] 39.7%,  $p < 0.001$ ). For the primary European Agency for the Evaluation of Medicinal Products [EMA] composite endpoint a greater proportion of G-CSF + plerixafor patients achieved (compared with G-CSF + placebo)  $\geq 2 \times 10^6$  CD34+ cells/kg within 4 apheresis days and successful polymorphonuclear cell (PMN) and platelet (PLT) engraftment (84.0% versus 43.2%, respectively; estimated TE 40.8%;  $p < 0.001$ ); and  $\geq 5 \times 10^6$  CD34+ cells/kg in 4 or fewer days of apheresis and successful PMN and PLT engraftment (57.3% versus 18.9%, respectively; estimated TE 38.4%,  $p < 0.001$ ). Ten patients treated with G-CSF + plerixafor, compared with 52 patient treated with G-CSF + placebo, failed to collect a sufficient number of CD34+ cells and entered the rescue procedure. Among the Rescue patients, 37/62 (59.7%) achieved  $\geq 2 \times 10^6$  CD34+ cells/kg in four or fewer days of apheresis in the rescue procedure: 4/10 (40.0%) of the rescue patients from the G-CSF + plerixafor group and 33/52 (63.5%) from the G-CSF + placebo group.

### **Phase 3 Study in Patients with MM:**

Study 3102 was a Phase 3, multicentre, randomized, double-blind, placebo-controlled, study in patients with MM eligible for autologous stem cell transplant. Patients were randomized to receive the study treatment: G-CSF + plerixafor (n = 148 patients in the Primary Intent-to-Treat [ITT] population) or G + placebo (n = 154 patients). Patients underwent mobilization with G-CSF 10 µg/kg/day for 4 days, and starting on Day 4 received an evening dose of plerixafor 240 µg/kg or placebo. On Day 5, patients received a morning dose of G-CSF 10 mcg/kg and underwent apheresis. Apheresis occurred approximately 10-11 hours after the dose of study treatment and within 60 minutes after administration of the morning dose of G-CSF). Patients continued to receive an evening dose of study treatment followed the next day by a morning dose of G-CSF and apheresis until  $\geq 6 \times 10^6$  CD34+ cells/kg were collected. The maximum number of apheresis sessions allowed in order to reach the target CD34+ cell number (primary endpoint) was two sessions for the MM patients. Fifty-six patients in the Primary ITT population received a tandem transplant: 32/148 (21.6%) in the G-CSF + plerixafor group, 24/147 (16.3%) in the G-CSF + placebo group. Patients were followed for up to 12 months following stem cell transplant. Patients who failed to collect specified target numbers of CD34+ cells had the option of entering an open-label rescue procedure where they received another 4-day mobilization regimen of G-CSF followed by G-CSF + plerixafor. In the Primary ITT population, a significantly greater proportion of patients in the G-CSF + plerixafor group achieved  $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or fewer days of apheresis than MM patients who received G-CSF + placebo (71.6% versus 34.4%, respectively; estimated treatment effect [TE] 37.2%,  $p < 0.001$ ). For the primary European

Agency for the Evaluation of Medicinal Products (EMA) composite endpoint a greater proportion of G-CSF + plerixafor patients achieved (compared with G-CSF + placebo)  $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or fewer days of apheresis and had successful polymorphonuclear cell (PMN) and platelet (PLT) engraftment (70.3% versus 34.4%, respectively; estimated TE 35.9%,  $p < 0.001$ ). Seven patients, all initially treated with G-CSF + placebo, enrolled in the rescue procedure. During this procedure, 2/7 (29%) achieved  $\geq 6 \times 10^6$  cells/kg in 2 or fewer days of apheresis.

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

The interruption of the CXCR4/SDF-1 $\alpha$  interaction by plerixafor results in the mobilization of bone marrow hematopoietic stem cells (HSCs) to the peripheral blood. The cell surface marker CD34 is a well-established surrogate marker for HSCs. A close correlation exists between the number of CD34+ cells and the colony forming units (which indicate functional HSCs) in peripheral blood HSC collections. Based on all these, the pharmacodynamic activity of plerixafor was assessed by measuring the number of PB CD34+ cells using fluorescence activated cell sorting (FACS) analysis. In Studies 1002, 1003 and 1005, the pharmacodynamics of plerixafor were also assessed by colony forming units (CFUs), as a confirmation that CD34+ cell count by FACS analysis was an adequate proxy measure of functional HSCs. Other secondary efficacy endpoints included precursor cell functionality (SCID mouse engraftment), complete blood count (CBC) and differential as well as cell cycle status.

For the proof of principle phase 2 study (protocol 2106), the primary objective was to evaluate the difference in the number of CD34+ cells/kg collected after mobilization with G-CSF + plerixafor vs. that collected after mobilization with G-CSF alone. The primary objective of the study was to determine the proportion of HD patients who had  $\geq 5 \times 10^6$  CD34+ cells/kg after mobilization with G-CSF + plerixafor vs. that collected after mobilization with G-CSF alone in historical controls.

The two primary efficacy endpoints in the phase 3 protocols (3101 and 3102) were: 1) the proportion of patients achieving the target number of CD34+ cells (*Apheresis yield*) within a specified number of apheresis days, and 2) the composite endpoints (referred to as EMA [European Medicines Agency] primary endpoints) of the proportion of patients achieving the target number of cells with successful engraftment. The respective endpoint definitions were based on advice from the US Food and Drug Administration (FDA) and from the Committee for Medicinal Products for Human Use (CHMP)/Committee for Orphan Medicinal Products (COMP) in the EU.

*Apheresis yield* refers to the number of CD34+ cells/kg collected during the apheresis phase of each mobilization (G-CSF + plerixafor and G-CSF -alone), and was calculated as follows:

$$\text{Apheresis yield (CD34+ cells/kg)} = \frac{\% \text{CD34+} \times \text{WBC count} \times \text{volume of apheresis product}}{\text{Patient's weight in kg}}$$

**Definitions of primary endpoints in the phase 3 Study (protocol 3101):**

1) The target number =  $\geq 5 \times 10^6$  CD34+ cells/kg in 4 or fewer days of apheresis. Data used to determine the endpoint were taken from Days 5 to 8 of the Mobilization/Treatment/ Apheresis period.

2) EMEA Composite Primary Endpoint:

- Target number of cells:  
 $\geq 2 \times 10^6$  CD34+ cells/kg in 4 or fewer days of apheresis  
 $\geq 5 \times 10^6$  CD34+ cells/kg in 4 or fewer days of apheresis.
- Successful Engraftment:  
Polymorphonuclear cell (PMN) values  $\geq 0.5 \times 10^9$ /L for 3 consecutive days or  $\geq 1.0 \times 10^9$ /L for 1 day, and platelet (PLT) values  $\geq 20 \times 10^9$ /L for 7 consecutive days without patient receiving a transfusion in the prior 7 days.

**Definitions of primary endpoints in the phase 3 Study (3102):**

1) The target number =  $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or fewer days of apheresis. Data used to determine the endpoint were taken from Days 5 and 6 of the Mobilization / Treatment/ Apheresis period.

2) EMEA Composite Primary Endpoint:

- Target number of cells:  
 $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or fewer days of apheresis.
- Successful Engraftment:  
PMN values  $\geq 0.5 \times 10^9$ /L for 3 consecutive days or  $\geq 1.0 \times 10^9$ /L for 1 day, and PLT values  $\geq 20 \times 10^9$ /L for 7 consecutive days without patient receiving a transfusion in the prior 7 days.

In both studies, the cell product was collected after apheresis and was subjected to fluorescence activated cell sorting (FACS). FACS analysis was used to count CD34+ cells in venous samples and apheresis product. For venous samples, duplicate samples of 4-mL whole blood were collected. For apheresis product, duplicate 1-mL samples were collected. Local laboratories and a central laboratory were used in these studies. Samples were collected, processed, and shipped to the central laboratory (b) (4) according to instructions provided by the laboratory. The local laboratory values were used for all clinical decisions. Efficacy endpoints were calculated using the percentage of CD34+ cells determined by the central laboratory applied to the absolute WBC count from the local laboratory. When the central laboratory value was missing, the corresponding local laboratory value was used.

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

*In vitro* and *in vivo* studies did not identify any major metabolites of plerixafor and all pharmacokinetic determinations have been based on concentrations of the plerixafor parent molecule only. Two validated bioanalytical methods were used for the determination of plasma plerixafor concentrations: high performance liquid chromatography with electrochemical

detection (HPLC-ECD) (b) (4) and liquid chromatography with tandem mass spectrometry (LCMS/MS) (b) (4)

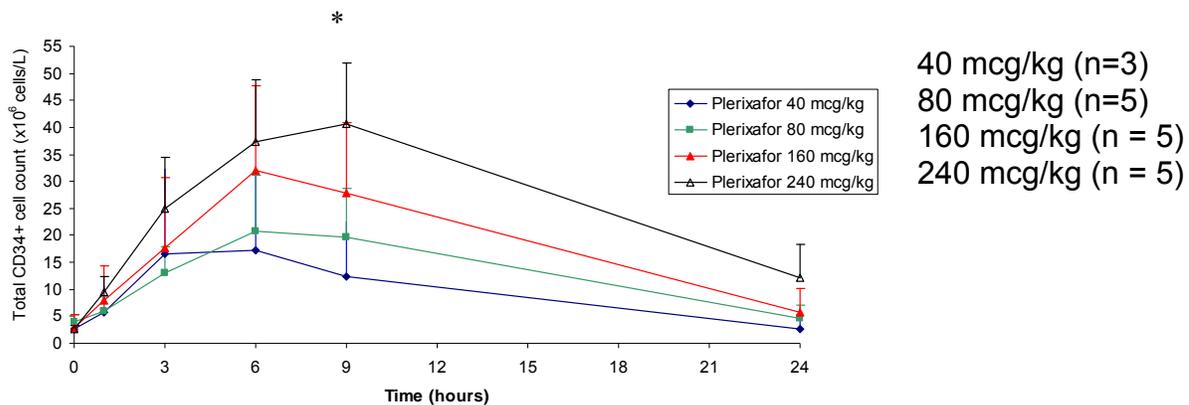
Due to concerns raised in audits of the testing laboratory (b) (4) some of the data obtained with the HPLC-ECD method (studies 98-01, 2001, and 1005) are not used by the applicant to support statements concerning the bioavailability or pharmacokinetics of plerixafor, and were provided by the applicant for informational use only. Audit deficiencies were not identified in the bioanalytical data for study 1002 which also utilized the HPLC-ECD bioanalytical method.

## 2.2.4 Exposure-response

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

In the phase 1 protocol 1002, a single dose of plerixafor injection administered to healthy volunteers generated a dose-dependent increase in mean CD34+ counts for all doses (range 40 mcg/kg to 240 mcg/kg). Increased plerixafor levels were observed within three hours of dosing for all doses. The peak response was observed at 6 hours post-dose for the 40, 80 and 160 mcg/kg treatment groups and at 9 hours post-dose for the 240 mcg/kg treatment group. CD34+ levels returned to baseline values at 24 hours post-dose for all groups except the 240 mcg/kg group (Figure 2 and Figure 3). Study 1005 was conducted in healthy subjects, administered a single dose of plerixafor (240 mcg/kg (n = 4) or 320 mcg/kg (n = 6)) The CD34+ counts for the 320 mcg/kg dose (protocol 1005) showed a peak response at 8 hours post dose, however the CD34+ values were significantly less than that obtained at the 240 mcg/kg dose ( $p < 0.05$ ), and the reason for this is unclear (Figure 4). In the phase 1 protocol 1004, the effectiveness of 160, 240, and 320  $\mu\text{g}/\text{kg}$  of plerixafor injection administered as a single SC injection to increase circulating CD34+ cells in 21 patients with NHL and MM was assessed (Figure 5). Thirteen patients received a single SC dose of 160 or 240 mcg/kg plerixafor injection and an additional 8 patients received a dose of 320 mcg/kg. Six patients proceeded to receive a mobilization regimen of G-CSF and 320 mcg/kg plerixafor injection. In NHL patients, the exposure for each plerixafor injection dose was: 160 mcg/kg (3 patients), 240 mcg/kg (3 patients), and 320 mcg/kg (5 patients). A greater than 4-fold increase from baseline in PB CD34+ cell counts was observed following all doses of plerixafor injection. Given the small sample sizes, the concentration-response relationship was difficult to evaluate. However, among the NHL patients the 320 mcg/kg dose did not show an increase in absolute counts of PB CD34+ cells over the 160  $\mu\text{g}/\text{kg}$  dose. Among the MM patients there was a trend towards higher doses resulting in increased absolute counts of PB CD34+ cells, but variability was too great to determine a meaningful relationship. In the 320  $\mu\text{g}/\text{kg}$  dose group (NHL and MM) the peak fold increase occurred between 8 and 10 hours post plerixafor injection. Given the conflicting results with the 320 mcg/kg dose, it is difficult to evaluate whether this dose may be more efficacious than the 240 mcg/kg dose. Overall, the limited data with the 320 mcg/kg dose were inconclusive, and suggested that selection of the 240 mcg/kg dose in phase 2 and 3 trials was appropriate.

**Figure 2** Absolute PB CD34+ Cell Count (Mean +/- SD) in Healthy Subjects after a Single SC dose of Plerixafor 40, 80, 160 and 240 mcg/kg (Study 1002).



**Figure 3** Absolute PB CD34+ Cell Count in Healthy Subjects at 9 hours following a single SC dose of Plerixafor (40 – 240 mcg/kg) (study 1002)

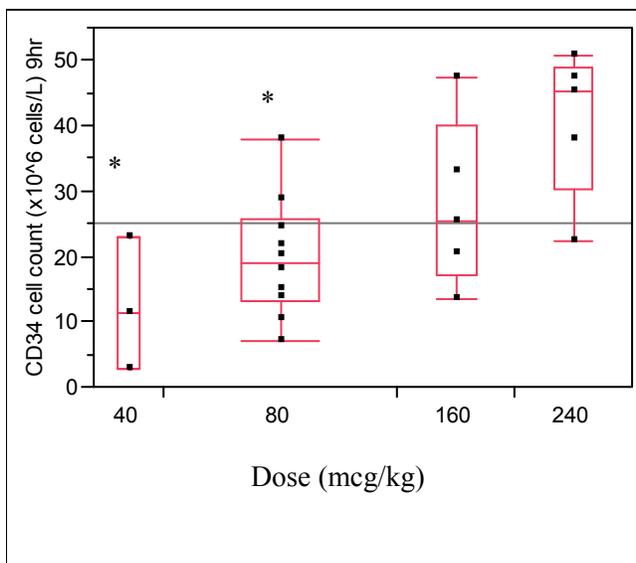
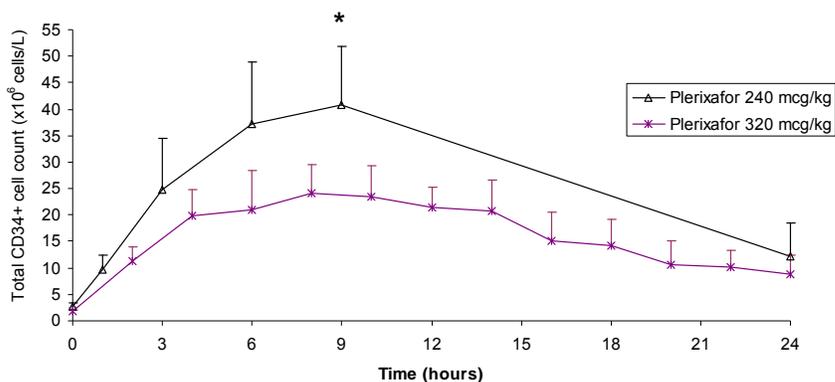


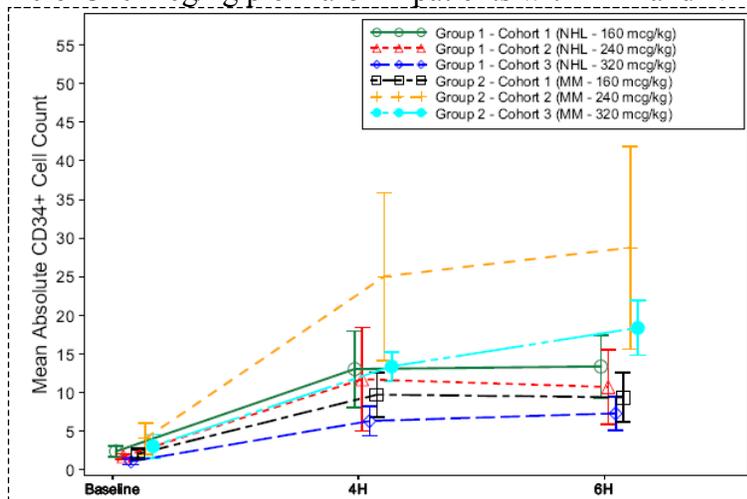
Figure 2 and

Figure 3\*  $p < 0.05$   
 (240 mcg/kg dose significantly different response from the 40 mcg/kg and 80 mcg/kg)

**Figure 4** Absolute PB CD34+ Cell Count (Mean +/- SD) in Healthy Subjects after a Single SC dose of Plerixafor 240 mcg/kg (Study 1002) and 320 mcg/kg (Study 1005).



**Figure 5** Mean absolute PB CD34+ cell count (protocol 1004) following a single dose of 160, 240 or 320 mcg/kg plerixafor in patients with MM and NHL.



Results from protocol 1002 showed that the serial administration of three consecutive daily doses of 80 mcg/kg plerixafor injection produced large increases in mean total CD34+ counts on each of Days 1 to 3 (Table 5). The post-dose mean total CD34+ levels were similar for Days 1, 2 and 3, indicating that cells return to the bone marrow as plerixafor's antagonistic action at its receptor is removed.

**Table 5** Total CD34 + Cell Count in Subjects Who Received Three Consecutive Doses of 80 mcg/kg Plerixafor Injection (N=3) [Values are x 10<sup>6</sup> cells/L]

|       | Timepoint | Parameter | CD34+ Count <sup>1</sup> |
|-------|-----------|-----------|--------------------------|
| Day 1 | Baseline  | Mean (SD) | 2.68 (1.83)              |
|       |           | Median    | 2.42                     |
|       |           | Range     | 0.98–4.62                |
|       | 6 hours   | Mean (SD) | 12.89 (8.08)             |
|       |           | Median    | 12.96                    |
|       |           | Range     | 4.77–20.93               |
| Day 2 | pre-dose  | Mean (SD) | 5.74 (3.17)              |
|       |           | Median    | 6.86                     |
|       |           | Range     | 2.16–8.21                |
|       | 6 hours   | Mean (SD) | 9.97 (5.85)              |
|       |           | Median    | 10.38                    |
|       |           | Range     | 3.93–15.60               |
| Day 3 | pre-dose  | Mean (SD) | 2.88 (2.23)              |
|       |           | Median    | 3.44                     |
|       |           | Range     | 0.42–4.77                |
|       | 6 hours   | Mean (SD) | 10.22 (6.90)             |
|       |           | Median    | 14.00                    |
|       |           | Range     | 2.26–14.40               |
| Day 4 | n/a       | Mean (SD) | 3.17 (2.59)              |
|       |           | Median    | 3.44                     |
|       |           | Range     | 0.46–5.61                |

In protocol 1002, the relative increases in progenitor cell mobilization (mean n-fold increases) following a single SC dose to healthy subjects, was calculated. A dose-dependent increase in fold change was observed for all hematopoietic progenitor cells (colony forming unit–granulocyte and macrophage (CFU-GM), burst forming unit-erythrocyte (BFU-E) and colony forming unit–granulocyte, erythrocyte, monocyte, and megakaryocyte (CFU-GEMM)). The peak mean fold increase for all CFUs occurred at approximately 6 hours post-dose (Table 6).

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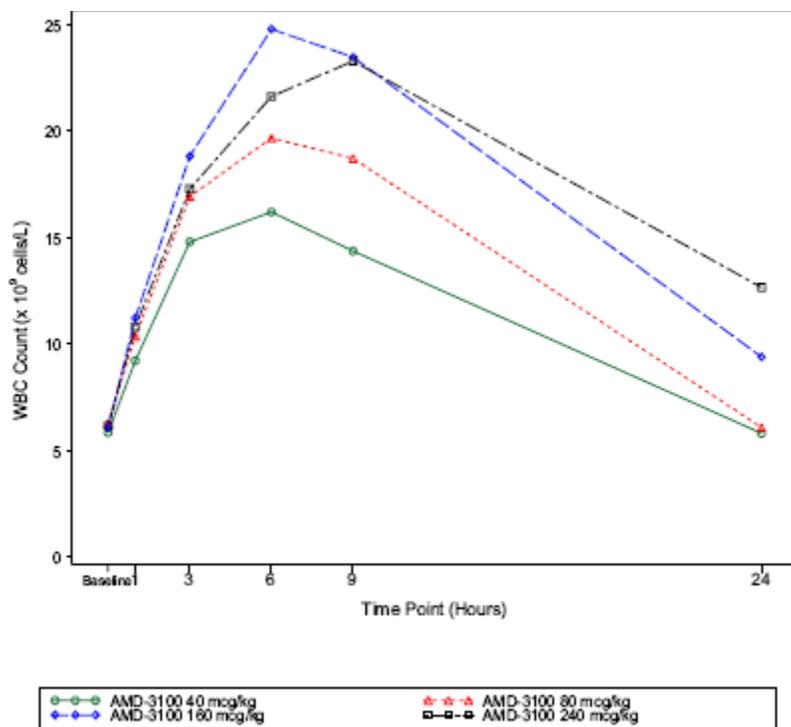
**Table 6** Progenitor cell mobilization effects following a single SC administration of Plerixafor in healthy subjects (study AMD3100-1002). Data are expressed as means (SD).

| Dose Level<br>(µg/kg) | Timepoint | Methylcellulose Assay <sup>1</sup> |             |               |
|-----------------------|-----------|------------------------------------|-------------|---------------|
|                       |           | CFU-GM                             | CFU-GEMM    | BFU-E         |
| 40<br>N=1             | 0 hour    | 224                                | 69          | 455           |
|                       | 1 hour    | 1223                               | 248         | 898           |
|                       | 3 hours   | 2633                               | 858         | 2106          |
|                       | 6 hours   | 3315                               | 545         | 1817          |
|                       | 9 hours   | 3647                               | 938         | 3056          |
|                       | 24 hours  | 516                                | 144         | 897           |
| 80<br>N=10            | 0 hour    | 265 (217.0)                        | 78 (38.1)   | 313 (112.6)   |
|                       | 1 hour    | 1096 (453.0)                       | 186 (71.2)  | 614 (191.0)   |
|                       | 3 hours   | 2392 (927.5)                       | 363 (151.9) | 998 (442.5)   |
|                       | 6 hours   | 4069 (1022.3)                      | 682 (275.2) | 1709 (835.5)  |
|                       | 9 hours   | 1884 (574.4)                       | 305 (141.7) | 1173 (422.5)  |
|                       | 24 hours  | 322 (130.6)                        | 93 (44.7)   | 386 (159.1)   |
| 160<br>N=4            | 0 hour    | 199 (116.8)                        | 47 (19.8)   | 160 (80.8)    |
|                       | 1 hour    | 759 (417.3)                        | 123 (75.1)  | 336 (307.2)   |
|                       | 3 hours   | 2276 (964.5)                       | 335 (273.6) | 714 (656.9)   |
|                       | 6 hours   | 3689 (2061.0)                      | 693 (499.6) | 1684 (1956.1) |
|                       | 9 hours   | 3390 (1885.9)                      | 557 (440.0) | 1310 (1547.5) |
|                       | 24 hours  | 242 (173.0)                        | 56 (48.1)   | 272 (300.6)   |
| 240<br>N=5            | 0 hour    | 89 (56.8)                          | 34 (19.9)   | 160 (62.0)    |
|                       | 1 hour    | 584 (171.6)                        | 103 (43.9)  | 411 (125.1)   |
|                       | 3 hours   | 1719 (699.2)                       | 303 (124.7) | 1169 (477.3)  |
|                       | 6 hours   | 2430 (1135.0)                      | 481 (149.4) | 1936 (947.2)  |
|                       | 9 hours   | 2355 (1118.6)                      | 418 (156.3) | 1901 (604.8)  |
|                       | 24 hours  | 439 (387.1)                        | 121 (75.4)  | 633 (264.4)   |

Data from protocol 1002 showed a single dose of plerixafor injection induced leukocytosis in these healthy subjects in a dose-dependent manner (Figure 6). Peak mean WBC levels occurred at 6 hours post-dose for the 40, 80 and 160 µg/kg treatment groups, and at 9 hours post-dose for the 240 µg/kg treatment group. On Day 2, mean WBC levels had returned to baseline values in the 40 and 80 µg/kg treatment groups. For the 160 and 240 µg/kg treatment groups, mean WBC levels had returned to baseline on Day 3. Three consecutive daily doses of 80 µg/kg plerixafor injection induced leukocytosis in subjects (Table 7). Mean WBC levels increased approximately 2.5 to 3-fold at the 6 hour post-dose timepoint on all 3 days of dosing. Pre-dose mean WBC levels on Days 2, 3 and 4 indicated a return to approximately baseline values.

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**Figure 6** Mean WBC Count in Healthy Subjects after a Single SC dose of Plerixafor (Study 1002)



**Table 7** White Blood Cell Count in Healthy Subjects Who Received Three Consecutive Doses of 80 mcg/kg Plerixafor Injection (Study 1002).

| Timepoint |          | Statistic (N=3) | WBC (x 10 <sup>9</sup> µL) |
|-----------|----------|-----------------|----------------------------|
| Screening |          | Mean (SD)       | 4.14 (0.54)                |
|           |          | Median          | 4.16                       |
|           |          | (b) (4)         |                            |
| Day 1     | Baseline | Mean (SD)       | 5.18 (0.52)                |
|           |          | Median          | 4.91                       |
|           |          | (b) (4)         |                            |
|           | 6 hours  | Mean (SD)       | 16.07 (0.15)               |
|           |          | Median          | 16.10                      |
|           |          | (b) (4)         |                            |
| Day 2     | pre-dose | Mean (SD)       | 6.16 (1.26)                |
|           |          | Median          | 5.47                       |
|           |          | (b) (4)         |                            |
|           | 6 hours  | Mean (SD)       | 15.33 (2.11)               |
|           |          | Median          | 15.60                      |
|           |          | (b) (4)         |                            |
| Day 3     | pre-dose | Mean (SD)       | 5.59 (1.31)                |
|           |          | Median          | 5.73                       |
|           |          | (b) (4)         |                            |
|           | 6 hours  | Mean (SD)       | 13.23 (1.69)               |
|           |          | Median          | 14.00                      |
|           |          | (b) (4)         |                            |
| Day 4     | n/a      | Mean (SD)       | 5.77 (1.23)                |
|           |          | Median          | 5.74                       |
|           |          | (b) (4)         |                            |

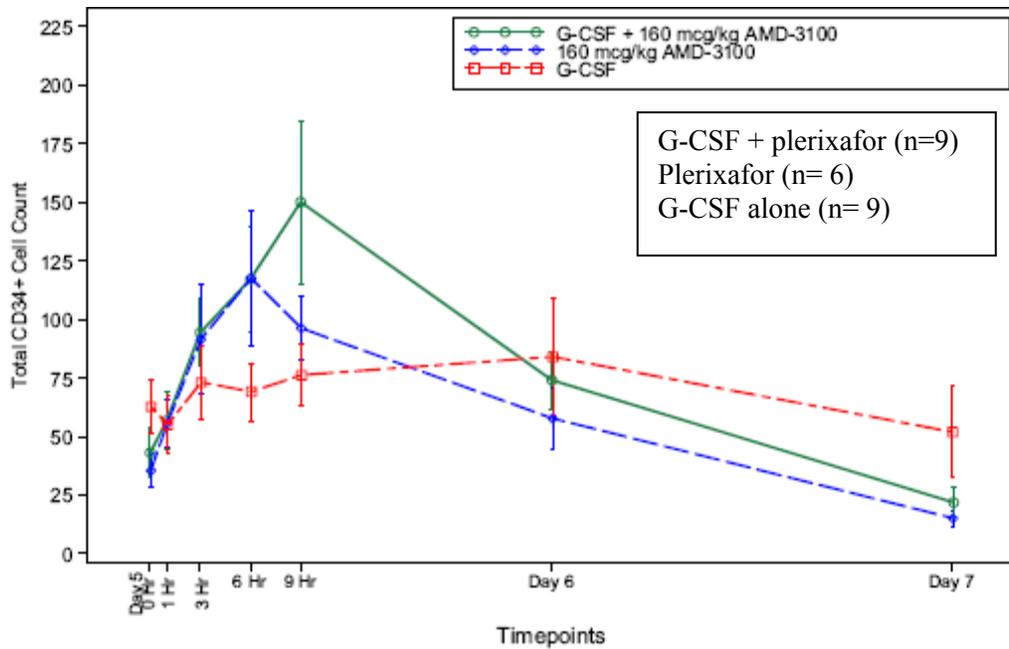
Analysis of the percentage of circulating hematopoietic myeloid progenitor cells in S-phase of the cell cycle before and after administration of a single dose of 80 µg/kg plerixafor injection to healthy subjects in protocol 1002 are shown in Table 8. All cells were in a very slow or non-cycling state before and after plerixafor administration.

**Table 8** Percentage of Circulating Myeloid Progenitors in S-phase of the Cell Cycle Before and After Administration of Plerixafor Injection (study 1002).

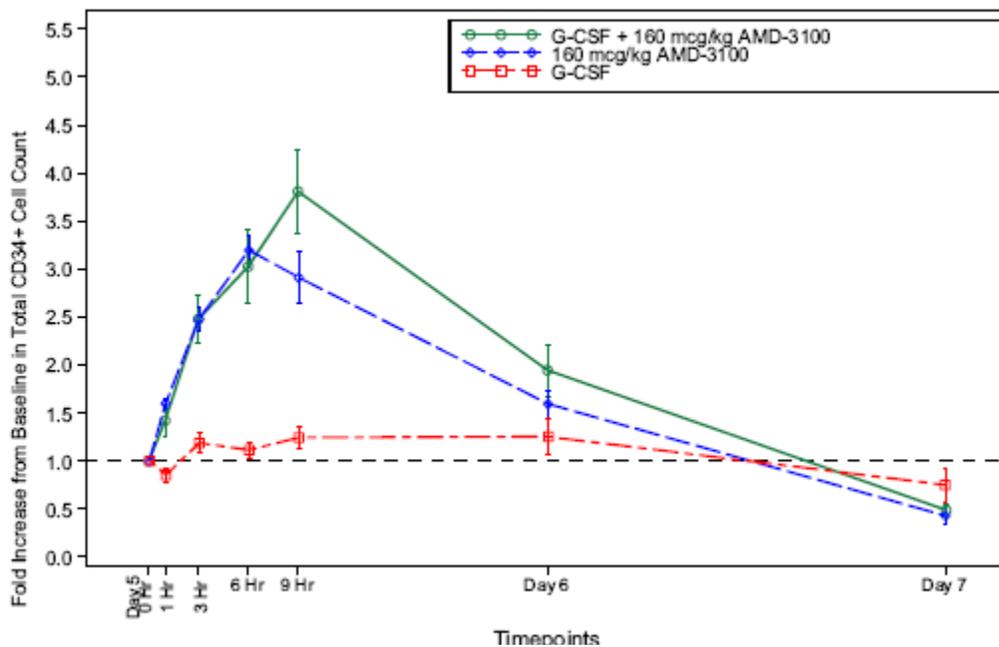
| Progenitor Cell | Predose   | Hours Post-Plerixafor Injection Administration |           |           |           |           |
|-----------------|-----------|--|-----------|-----------|-----------|-----------|
|                 |           | 1  | 3         | 6         | 9         | 24        |
| CFU-GM          | 1.3 ± 0.7 | 0.1 ± 0.1                                      | 0.9 ± 0.5 | 0.2 ± 0.1 | 1.0 ± 0.6 | 0.3 ± 0.3 |
| BFU-E           | 0.7 ± 0.4 | 0.3 ± 0.3                                      | 2.5 ± 1.4 | 0.3 ± 0.2 | 1.6 ± 1.1 | 0.4 ± 0.3 |
| CFU-GEMM        | 0.6 ± 0.6 | 0.6 ± 0.6                                      | 0.7 ± 0.7 | 0.0 ± 0.0 | 0.4 ± 0.4 | 0.0 ± 0.0 |

The phase 1b/2a protocol (1003) showed a significantly higher CD34+ mobilization response when plerixafor was administered in conjunction with G-CSF compared to administration of plerixafor alone or G-CSF alone in healthy subjects (Figure 7 and Figure 8). Following the 4-day G-CSF run-in, 22 subjects were administered a single sc dose of plerixafor injection: 9 subjects received 160 µg/kg plerixafor injection + 10 µg/kg G-CSF, 7 subjects received 240 µg/kg plerixafor injection + 10 µg/kg G-CSF, 6 subjects received 160 µg/kg plerixafor injection alone. In addition, 9 subjects received a single sc dose of 10 µg/kg G-CSF alone. The peak mean relative increases in CD34+ cells were similar for 160 µg/kg plerixafor injection + 10 µg/kg G-CSF (3.8-fold at 9 hours post-dose) and 240 µg/kg plerixafor injection + 10 µg/kg G-CSF (4.0-fold at 10 hours post-dose). When only 160 µg/kg plerixafor injection was given on Day 5, the peak mean relative increase (3.2-fold) occurred at an earlier time-point (6 hours post-dose). The highest CD34+ mobilization responses were observed in Group A (10 µg/kg G-CSF + 160 µg/kg plerixafor injection) with an approximately 4-fold mean relative increase in CD34+ levels at 9 hours post-dose, followed by Group B (160 µg/kg plerixafor injection) with an approximately 3-fold mean relative increase at 6 hours and 9 hours post-dose. Group C (10 µg/kg G-CSF) CD34+ levels were similar to baseline levels at all post-dose timepoints. These data indicate that after 4 days of G-CSF treatment, the combination of plerixafor injection + G-CSF yields the greatest peripheral blood CD34+ mobilization response, and that when only one agent is administered, plerixafor injection is superior to G-CSF. Group D and E (10 µg/kg G-CSF + 240 µg/kg plerixafor injection) produced peak mean relative increases at 10-14 hours post-dose. The Group D peak increase was similar to the Group A peak increase. Mean total CD34+ levels returned to baseline levels between the Day 6 and Day 7 follow-up visits for all treatment groups. These data were used in development of the phase 3 dose regimen in which plerixafor was administered following 4 days of treatment with G-CSF. The data further supported administration of plerixafor at 10-11 hours prior to G-CSF administration and apheresis in the phase 3 trials.

**Figure 7** Peripheral blood: mean total CD34+ cell count x 10<sup>6</sup> cells/L (protocol 1003)



**Figure 8** Peripheral blood: mean total CD34+ fold increase from baseline (protocol 1003)



Protocol 2101 was a phase 2, multicenter, open-label, crossover study in patients with NHL and MM, to compare the number of CD34+ cells/kg collected by apheresis after a mobilization

regimen of G-CSF plus plerixafor and that collected after a mobilization regimen of G-CSF alone (Table 9). Patients were given a daily dose of G-CSF (10 µg/kg) for 4 days, then G-CSF (10 µg/kg) on the following day, followed by apheresis for up to a total of 4 consecutive days or until a target of  $\geq 5 \times 10^6$  CD34+ cells/kg cumulatively were collected, whichever occurred first. After the final apheresis procedure, there was a Rest Interval of 13 to 16 days. After the Rest Interval, patients entered the Crossover Treatment Phase. Patients were given a daily dose of G-CSF (10 µg/kg) for 4 days, then plerixafor (240 µg/kg) plus G-CSF (10 µg/kg) on the following day, followed by apheresis for up to a total of four consecutive days or until a target of  $5 \times 10^6$  CD34+ cells/kg cumulatively were collected, whichever occurred first. In both the MM and NHL disease groups, the G + plerixafor mobilization regimen was more effective than the G-alone mobilization regimen in achieving a higher CD34+ cells/kg total yield and average daily yield in apheresis collections. More patients achieved the target cell dose of  $\geq 5 \times 10^6$  and the minimum transplantable cell dose of  $\geq 2 \times 10^6$  in the G + plerixafor regimen than in the G-alone regimen. These data were supportive of the phase 3 trial design and dosing regimen in which plerixafor daily dosing occurred over 4 and 2 consecutive days for NHL and MM patients.

**Table 9** Daily Number of Patients Reaching CD34+ Cell Doses of  $\geq 5 \times 10^6$  cells/kg and  $\geq 2 \times 10^6$  cells/kg

|   | Summary Statistic | NHL Patients        |                | MM Patients         |                | All Patients        |                |
|---|-------------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|
|   |                   | G+plerixafor (N=15) | G-alone (N=15) | G+plerixafor (N=10) | G-alone (N=10) | G+plerixafor (N=25) | G-alone (N=25) |
| Daily Number of Patients to Reach $5 \times 10^6$ CD34+ cells/kg Target |                   |                     |                |                     |                |                     |                |
| Day 1   | n (%)             | 5 (33.3)            | 0 (0.0)        | 4 (40.0)            | 2 (20.0)       | 9 (36.0)            | 2 (8.0)        |
| Day 2   | n (%)             | 3 (20.0)            | 1 (6.7)        | 3 (30.0)            | 1 (10.0)       | 6 (24.0)            | 2 (8.0)        |
| Day 3   | n (%)             | 1 (6.7)             | 1 (6.7)        | 2 (20.0)            | 2 (20.0)       | 3 (12.0)            | 3 (12.0)       |
| Day 4   | n (%)             | 1 (6.7)             | 1 (6.7)        | 1 (10.0)            | 0 (0.0)        | 2 (8.0)             | 1 (4.0)        |
| Daily Number of Patients to Reach $2 \times 10^6$ CD34+ cells/kg Target |                   |                     |                |                     |                |                     |                |
| Day 1   | n (%)             | 7 (46.7)            | 2 (13.3)       | 7 (70.0)            | 3 (30.0)       | 14 (56.0)           | 5 (20.0)       |
| Day 2   | n (%)             | 8 (53.3)            | 5 (33.3)       | 3 (30.0)            | 6 (60.0)       | 11 (44.0)           | 11 (44.0)      |

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

In phase 1 studies, using a single dose of plerixafor that included the 160 and 240 mcg/kg dose groups (protocol 1002, 1003 and 1004), the safety profiles of the two dose levels were similar. A similar proportion of subjects in each dose group had adverse events (AEs), and the most common event for both the 160 mcg/kg and 240 mcg/kg dose was injection site erythema. In study 1005, conducted in healthy subjects, the intensity of the AEs at the 240 mcg/kg (n = 4) and 320 mcg/kg (n = 6) dose groups appeared dose related. In the 240 mcg/kg dose group, 100% of AEs were mild in intensity compared to the 320 mcg/kg dose group with 61% of AEs mild and 39% moderate in intensity (Table 11). The most common AE in study 1005 was injection site erythema and paresthesia, each experienced by all 6 subjects in the 320 mcg/kg group and 1 of 4 subjects in the 240 mcg/kg group. Chest discomfort was reported in 4 of 6 subjects in the 320 mcg/kg dose group, and was the only AE experienced exclusively in the 320 mcg/kg dose group.

To further determine the safety of plerixafor a 160, 240, and 320 µg/kg dose was administered as a single subcutaneous injection in patients with NHL and MM in protocol 1004 (Table 10). For NHL patients, the exposure for each plerixafor injection dose was: 160 µg/kg (3 patients), 240 µg/kg (3 patients), and 320 µg/kg (5 patients). For MM patients, the exposure for each plerixafor injection dose was: 160 µg/kg (3 patients), 240 µg/kg (4 patients), and 320 µg/kg (3 patients). Overall, the most common AEs reported were injection site erythema (12/21, 57.1 %), fatigue (7/21, 33.3 %), paresthesia (5/21, 23.8 %) and bone pain (5/21, 23.8 %). Injection site erythema was most commonly reported for the 240 µg/kg plerixafor injection treated NHL patients (3/3, 100 %) and the 320 µg/kg plerixafor injection treated MM patients (3/3, 100 %). The incidence of fatigue was highest for the 320 µg/kg plerixafor injection treated NHL patients (3/5, 60.0 %) and the incidence of paresthesia was highest for the 160 µg/kg plerixafor injection treated MM patients (2/3, 66.7 %). Bone pain was only reported for NHL (3/5, 60.0 %) and MM patients (2/3, 66.7 %) treated with 320 µg/kg plerixafor injection. The safety data from phase 1 and 2 trials were used in selection of the 240 mcg/kg dose for the subsequent pivotal trails.

**Table 10** AEs considered related (possibly, probably, or definitely) plerixafor injection, experienced by ≥ 2 patients following a single SC injection of plerixafor (protocol 1004).

| System Organ Class, Preferred Term                                   | Treatment Group |                 |                 |                 |                 |                 | All Patients (N=21) |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|---------------------|
|  | NHL             |                 |                 | MM              |                 |                 |                     |
|  | 160 µg/kg (N=3) | 240 µg/kg (N=3) | 320 µg/kg (N=5) | 160 µg/kg (N=3) | 240 µg/kg (N=4) | 320 µg/kg (N=3) |                     |
| <b>Gastrointestinal Disorders [N, (%)]</b>                           |                 |                 |                 |                 |                 |                 |                     |
| Abdominal Distension   | 0               | 0               | 0               | 2 (66.7)        | 0               | 0               | 2 (9.5)             |
| Abdominal Pain   | 1 (33.3)        | 0               | 0               | 1 (33.3)        | 0               | 0               | 2 (9.5)             |
| Diarrhea   | 0               | 1 (33.3)        | 0               | 0               | 0               | 1 (33.3)        | 2 (9.5)             |
| Flatulence   | 1 (33.3)        | 0               | 0               | 1 (33.3)        | 1 (25.0)        | 0               | 3 (14.3)            |
| Loose Stools   | 0               | 0               | 0               | 1 (33.3)        | 1 (25.0)        | 0               | 2 (9.5)             |
| Nausea   | 0               | 1 (33.3)        | 0               | 0               | 1 (25.0)        | 0               | 2 (9.5)             |
| <b>General Disorders And Administration Site Conditions [N, (%)]</b> |                 |                 |                 |                 |                 |                 |                     |
| Injection Site Erythema  | 2 (66.7)        | 3 (100.0)       | 2 (40.0)        | 1 (33.3)        | 1 (25.0)        | 3 (100.0)       | 12 (57.1)           |
| <b>Nervous System Disorders [N, (%)]</b>                             |                 |                 |                 |                 |                 |                 |                     |
| Dizziness  | 1 (33.3)        | 0               | 0               | 0               | 1 (25.0)        | 0               | 2 (9.5)             |
| Paresthesia  | 0               | 0               | 1 (20.0)        | 2 (66.7)        | 0               | 1 (33.3)        | 4 (19.0)            |

**Table 11** AE Profile of Plerixafor in healthy subjects following a single SC dose of plerixafor (1005)

|                                |          | 240 mcg/kg | 320 mcg/kg | All subjects |
|--------------------------------|----------|------------|------------|--------------|
| <b>Number Subjects Treated</b> |          | 4          | 6          | 10           |
| <b>AEs Intensity (%)</b>       | Mild     | 12(100)    | 14(60.9)   | 26 (74.3)    |
|                                | Moderate | 0          | 9 (39.1)   | 9 (25.7)     |
|                                | Severe   | 0          | 0          | 0            |

In the combined safety analyses, AEs observed in the All Oncology studies were similar to those seen in the pooled Phase 3 placebo-controlled studies. When analyzed by cancer type (NHL, MM, and HD), no meaningful differences in the incidences and types of AEs across the cancer types were apparent. For the phase 3 trials (3101 and 3102), the proportion of patients with at least 1 SAE in Period 1 (when placebo or 240 mcg/kg plerixafor are administered) was low and was similar for the 2 treatment groups (3.9% for G + plerixafor compared with 5.8% for G + placebo). The majority of the SAEs occurred in Periods 2 and 3, during which patients received ablative chemotherapy and were no longer receiving study treatment (plerixafor or placebo). In addition, almost all of the AEs in Period 1 were mild or moderate (approximately 88% of patients in the G + plerixafor group and 86% of patients in the G + placebo group had mild or moderate AEs). The types of AEs were similar in patients regardless of treatment group, except for diarrhea, nausea, vomiting and flatulence, injection site erythema and dizziness, which were more common following plerixafor treatment.

#### **2.2.4.3 Does this drug prolong the QT or QTc interval?**

There is not sufficient data in the application to assess this question. A phase 1, healthy volunteer study (protocol 06-H-0156) is being conducted in order to examine the effects of plerixafor on cardiac repolarization (QT/QTc interval), arrhythmogenic potential using telemetry, and the pharmacokinetics (PK) of plerixafor at high doses ( $\geq 400 \mu\text{g}/\text{kg}$ ). A written agreement reached between the applicant and the OCP during the preNDA meeting (dated October 1, 2007) allowed for submission of the full study report after the NDA action date, and thus this study will be reviewed subsequent to the NDA action date.

#### **2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

The phase 2 protocols (C201 and 2106) initially evaluated the effect of plerixafor at 240 mcg/kg administered after 4 days of G-CSF mobilization in patients with NHL, MM and HD. The 240 mcg/kg/day dosing regimen of plerixafor in conjunction with G-CSF mobilization for 4 days prior to plerixafor administration was acceptable based on both efficacy and safety parameter perspectives. Phase 1 and phase 2 data also supported the 10 to 11 hour time frame between the administration of plerixafor and subsequent administration of G-CSF and apheresis, as well as the 4 and 2 consecutive day treatments with plerixafor in lymphoma and MM patients, respectively to obtain maximum efficacy in the phase 3 trials.

### **2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites**

#### **2.2.5.1 What are the single dose and multiple dose PK parameters?**

Plerixafor is not metabolized and therefore major metabolites were not identified via *in vitro*

screens and preclinical studies. The applicant only evaluated the single dose PK parameters of the parent compound, plerixafor.

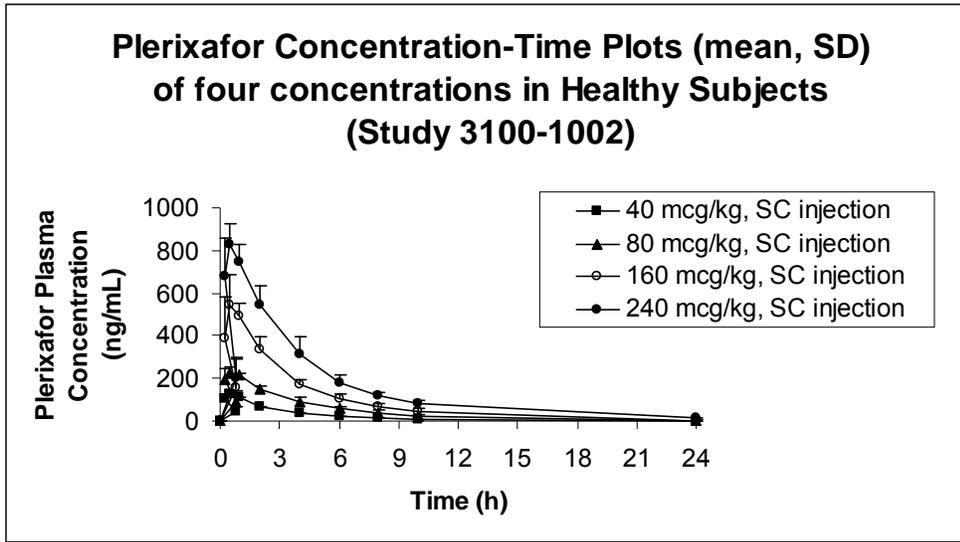
In protocol 1002, healthy subjects were treated with a single SC dose of 40 mcg/kg, 80 mcg/kg, 160 mcg/kg or 240 mcg/kg plerixafor. Figure 9 shows the mean plasma concentration-time profiles of plerixafor in healthy subjects following a single SC dose of plerixafor. PK parameters were calculated using noncompartmental and compartmental PK methodologies. Plasma PK parameters adjusted per kg of individual actual body weight are summarized in Table 12 and Table 13. Inspection of the individual concentration-time plots revealed that most concentrations for the lower dose groups (40 and 80 µg/kg) at the 24 hour PK sampling time-point fall below the limit of quantitation (LOQ), therefore, the noncompartmental estimations of these reported parameters should be interpreted with caution in these dose groups.

PK parameters values were similar for noncompartmental and compartmental analyses. Based on individual subject PK modeling, observed concentrations of the drug were well described with a two-compartment PK model (Figure 10). The average residual variability in plasma concentrations derived from the compartmental PK model was 4.25%. This includes the intra-individual variability, all experimental errors (errors in dosing, errors in analytical analysis, etc.) and errors arising from the PK modeling itself. This value would indicate that the chosen model fitted the data correctly.

The summary of PK parameters from protocol 1002 indicates that plerixafor has linear PK (Table 12 and Table 13). The PK parameters of plerixafor from different studies at different dose ranges are summarized in Table 14, Table 15 and Table 16). Across all clinical PK studies, plerixafor was rapidly absorbed, with a T<sub>max</sub> at approximately 0.5 to 1 hour after SC administration. At the recommended clinical dose of 240 µg/kg, the mean C<sub>max</sub> was 831 ng/mL in Study 2106 (HD, with G-CSF), 847 ng/mL in Study 1002 (healthy subjects, no G-CSF), and 926 ng/mL in Study C201 (NHL and MM, with G-CSF). Mean CL/F was nearly constant after a 240-µg/kg dose, ranging from 4.55 L/hour in Study 1002 to 5.14 L/hour in Study 2106. Furthermore, CL/F does not appear to be dose-dependent. The mean elimination half-life ranged from 3.1 to 5.3 hours across the 10-fold difference in dose (40 to 400 µg/kg, including Study 06-H-156 (healthy subjects, no G-CSF). Exposure to plerixafor was linear with dose; the mean AUC<sub>0-10</sub> ranged from a low of 400 ng\*hour/mL after a 40-µg/kg dose in Study 1002 to a high of 5930 ng\*hour/mL after a 400-µg/kg dose in Study 06-H-156. The mean C<sub>max</sub> of the 400-µg/kg dose was 1368 ng/mL, which is dose-proportional to the 240-µg/kg dose.

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**Figure 9** Mean plerixafor concentrations as a function of time on linear and log-linear scales in healthy subjects (protocol 1002). Data are expressed as means  $\pm$  SD.



**Table 12** Summary of Noncompartmental PK Parameters Calculated for Different Dosing Levels of S.C. plerixafor Administration. (n= 18) (Protocol 1002).

| Dose Level<br>( $\mu\text{g}/\text{kg}$ ) | PK Parameter                |                             |                         |                       |                          |
|---|-----------------------------|-----------------------------|-------------------------|-----------------------|--------------------------|
|   | Cmax<br>(ng/mL)             | CL/f/kg<br>(L/h/kg)         | t <sub>1/2</sub><br>(h) | AUC 0-10<br>(ng•h/mL) | Varea/f/kg<br>(L/kg)     |
| <b>40 (n=3)</b>                           |                             |                             |                         |                       |                          |
| Median<br>(range)                         | 121.20<br>(118.74 – 143.75) | 0.0916<br>(0.0891 – 0.0938) | 3.12<br>(3.00-3.24)     | 397<br>(390 – 412)    | 0.412<br>(0.386 – 0.439) |
| Mean (CV%)                                | 127.897 (10.8)              | 0.09147 (2.6)               | 3.123 (3.8)             | 399.6 (2.8)           | 0.4123 (6.4)             |
| <b>80 (n=5)</b>                           |                             |                             |                         |                       |                          |
| Median<br>(range)                         | 253.39<br>(196.10 – 281.91) | 0.0768<br>(0.0588 – 0.0901) | 3.39<br>(2.81 – 5.24)   | 924<br>(821 – 1047)   | 0.365<br>(0.350 – 0.459) |
| Mean (CV%)                                | 235.796 (13.2)              | 0.07499 (15.1)              | 3.749 (25.8)            | 932.5 (9.7)           | 0.3947 (13.4)            |
| <b>160 (n=5)</b>                          |                             |                             |                         |                       |                          |
| Median<br>(range)                         | 517.48<br>(464.16 – 764.82) | 0.0692<br>(0.0661-0.0893)   | 3.62<br>(2.80-4.61)     | 2032<br>(1664 – 2089) | 0.360<br>(0.301 – 0.461) |
| Mean (CV%)                                | 564.870 (22.5)              | 0.07252 (13.1)              | 3.676 (22.3)            | 1932.1 (10.1)         | 0.3786 (16.4)            |
| <b>240 (n=5)</b>                          |                             |                             |                         |                       |                          |
| Median<br>(range)                         | 854.20<br>(724.36 – 949.52) | 0.0587<br>(0.0574 – 0.0739) | 4.76<br>(3.93 – 5.49)   | 3183<br>(2630 – 3469) | 0.454<br>(0.327-0.508)   |
| Mean (CV%)                                | 847.056 (11.3)              | 0.06206 (11.2)              | 4.826 (13.2)            | 3156.6 (10.9)         | 0.4317 (15.6)            |

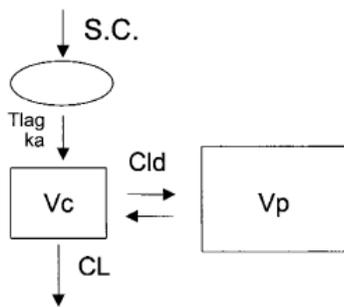
**Table 13** Summary of Compartmental PK Parameters Calculated for Different Dosing Levels of S.C. plerixafor Administration. (n=18). (Protocol 1002).

| Dose Level<br>(µg/kg)                 | PK Parameter                   |                             |                        |                          |                          |
|---------------------------------------|--------------------------------|-----------------------------|------------------------|--------------------------|--------------------------|
|                                       | Vc/f/kg<br>(L/kg)              | CL/f/kg<br>(L/h/kg)         | λz-HL<br>(h)           | ka<br>(1/h)              | Vss/f/kg<br>(L/kg)       |
| <b>40 (n=3)</b><br>Median<br>(range)  | 0.1263<br>(0.0127 – 0.1660)    | 0.0939<br>(0.0655 – 0.0978) | 2.94<br>(2.70-7.03)    | 2.463<br>(0.406 – 2.676) | 0.304<br>(0.216 – 0.331) |
| Mean (CV%)                            | 0.10165 (78.3)                 | 0.09241 (6.8)               | 4.225 (57.5)           | 1.8464 (67.8)            | 0.2837 (21.3)            |
| <b>80 (n=5)</b><br>Median<br>(range)  | 0.01852<br>(0.00987 – 0.17267) | 0.0769<br>(0.0614 – 0.0912) | 3.83<br>(3.10 – 22.55) | 0.602<br>(0.207 – 3.150) | 0.213<br>(0.176 – 0.315) |
| Mean (CV%)                            | 0.053857 (127.9)               | 0.07595 (14.4)              | 7.387 (114.9)          | 1.0056 (120.3)           | 0.2409 (26.2)            |
| <b>160 (n=5)</b><br>Median<br>(range) | 0.0469<br>(0.0262 – 0.0947)    | 0.0725<br>(0.0674 – 0.0909) | 3.95<br>(2.82 – 4.70)  | 0.821<br>(0.641 – 1.384) | 0.228<br>(0.210 – 0.311) |
| Mean (CV%)                            | 0.04931 (54.3)                 | 0.07485 (12.6)              | 3.746 (23.2)           | 0.8872 (34.4)            | 0.2447 (16.1)            |
| <b>240 (n=5)</b><br>Median<br>(range) | 0.0240<br>(0.0106 – 0.0305)    | 0.062<br>(0.0542 – 0.0781)  | 4.79<br>(4.15 – 32.14) | 0.485<br>(0.287 – 0.818) | 0.275<br>(0.164 – 0.532) |
| Mean (CV%)                            | 0.02056 (39.8)                 | 0.06455 (13.6)              | 10.873 (110.5)         | 0.5256 (46.1)            | 0.2891 (50.9)            |

**Table 14** PK data from healthy subjects receiving 400 mcg/kg plerixafor in study 06-H-0156.

| Statistic | C <sub>max</sub><br>(ng/mL) | T <sub>max</sub><br>(hr) | t <sub>1/2</sub> (hr) | CL/F<br>(mL/hr) | Vz/F<br>(mL) | AUC <sub>0-10</sub><br>(hr*ng/<br>mL) | AUC <sub>0-24</sub><br>(hr*ng/<br>mL) |
|-----------|-----------------------------|--------------------------|-----------------------|-----------------|--------------|---------------------------------------|---------------------------------------|
| N         | 6                           | 6                        | 6                     | 6               | 6            | 6                                     | 6                                     |
| Mean      | 1368                        | 0.8                      | 5.3                   | 3773            | 28485        | 5930                                  | 7670                                  |
| SD        | 169                         | 0.3                      | 1.1                   | 452             | 6190         | 726                                   | 1280                                  |
| (b) (4)   |                             |                          |                       |                 |              |                                       |                                       |
| Median    | 1345                        | 0.8                      | 4.9                   | 3697            | 27277        | 5816                                  | 7174                                  |
| (b) (4)   |                             |                          |                       |                 |              |                                       |                                       |
| CV%       | 12.4                        | 36.5                     | 21.7                  | 12.0            | 21.7         | 12.2                                  | 16.7                                  |

**Figure 10** Selected 2-compartment linear model with first-order absorption (Ka) rate input subject to a delay (Tlag). [Note: CLd is the apparent distributional plasma clearance].



### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The single dose PK parameters from healthy subjects and patients with NHL, MM and HD are summarized in Table 15 and Table 16. It is important to note that healthy volunteers received plerixafor only (protocol 1002, 1101, 06-H-0156) while patients (protocol C201 and 2106) received G-CSF in conjunction with plerixafor in these studies. Pharmacokinetic characteristics of plerixafor were notably consistent across healthy subjects and oncology patients (i.e., NHL, MM, and HD). The Population Pharmacokinetic Analysis confirmed these results by finding that a covariate describing patient disease status (i.e., healthy subjects versus oncology patients) did not improve the fit of the model. As PK parameters are similar in the presence and absence of G-CSF, these data also indicate that G-CSF does not alter plerixafor PK.

**Table 15** Comparison of mean pharmacokinetic parameters in healthy subjects and oncology patients treated with 240 µg/kg Plerixafor With or Without G-CSF

| Diagnosis / Study | G-CSF Administered? | N | C <sub>max</sub> (ng/mL) | AUC <sub>0-10</sub> (ng*hr/mL) | AUC <sub>0-24</sub> (ng*hr/mL) | t <sub>1/2</sub> (hr) |
|-------------------|---------------------|---|--------------------------|--------------------------------|--------------------------------|-----------------------|
| MM / C201         | Yes                 | 8 | 1029 ± 242               | 3945 ± 610                     | 5009 ± 737                     | 5.6 ± 2.6             |
| NHL / C201        | Yes                 | 5 | 761 ± 101                | 3035 ± 412                     | 3686 ± 625                     | 4.4 ± 1.1             |
| HD / 2106         | Yes                 | 9 | 831 ± 183                | 3572 ± 772                     | 4072 ± 875                     | 3.5 ± 0.7             |
| Healthy / 1101    | No                  | 6 | 980 ± 196                | 3940 ± 637                     | 5070 ± 979                     | 4.9 ± 0.6             |
| Healthy / 1002    | No                  | 5 | 847 ± 96                 | 3159 ± 344                     | 3823 ± 372                     | 4.9 ± 0.7             |

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**Table 16** Noncompartmental pharmacokinetic parameters from individual clinical Studies of plerixafor in cancer patients and healthy subjects.

| Study   | Dose Level (µg/kg) | C <sub>max</sub> (ng/mL) | CL/F (L/hr)  | V <sub>z</sub> /F (L) | T <sub>max</sub> (hr) | t <sub>1/2</sub> (hr) | AUC <sub>0-10</sub> (ng*hr/mL) | AUC <sub>0-24</sub> (ng*hr/mL) |
|---|--------------------|--------------------------|--------------|-----------------------|-----------------------|-----------------------|--------------------------------|--------------------------------|
| <b>1002 (n=18)</b><br>Without G-CSF                       | 40                 | 128 ± 13.8               | 5.71 ± 0.900 | 25.6 ± 3.10           | 0.50 (0.50, 0.50)     | 3.1 ± 0.12            | 400 ± 11.2                     | ND                             |
|   | 80                 | 236 ± 31.1               | 5.46 ± 0.439 | 29.1 ± 6.29           | 0.55 (0.25, 1.02)     | 3.7 ± 0.90            | 933 ± 90.8                     | ND                             |
|   | 160                | 565 ± 127.3              | 4.72 ± 1.049 | 24.9 ± 9.25           | 0.50 (0.50, 1.00)     | 3.6 ± 0.77            | 1932 ± 194.4                   | ND                             |
|   | 240                | 847 ± 95.6               | 4.53 ± 0.830 | 32.3 ± 9.11           | 0.50 (0.25, 1.00)     | 4.9 ± 0.71            | 3159 ± 343.6                   | 3817 ± 384.2                   |
| <b>C201 (n=13)</b><br>With G-CSF                          | 240                | 926 ± 236.8              | 4.77 ± 1.063 | 33.7 ± 10.53          | 0.5 (0.3, 1.0)        | 5.1 ± 2.2             | 3595 ± 697.1                   | 4500 ± 946.3                   |
| <b>2106 (n=9)</b><br>With G-CSF                           | 240                | 831 ± 183                | 5.14 ± 2.03  | 25.5 ± 9.00           | 0.5 (0.3, 1.3)        | 3.5 ± 0.7             | 3572 ± 772                     | 4072 ± 875                     |
| <b>1101 (Normal renal function, n=6)</b><br>Without G-CSF | 240                | 980 ± 196                | 4.38 ± 0.821 | 30.3 ± 3.62           | 0.56 (0.50, 1.02)     | 4.9 ± 0.56            | 3940 ± 637                     | 5070 ± 979                     |
| <b>06-H-0156 (n=6)</b><br>Without G-CSF                   | 400                | 1368 ± 169               | 3.77 ± 0.452 | 28.5 ± 6.19           | 0.8 (0.5, 1.0)        | 5.3 ± 1.1             | 5930 ± 726                     | 7670 ± 1280                    |

Values are reported as mean ± standard deviation, except T<sub>max</sub> is reported as median (min, max). ND= Not done

### 2.2.5.3 What are the characteristics of drug absorption?

Protocol AMD3100-98 was designed to determine the bioavailability of escalating doses of plerixafor in normal healthy subjects. Deficiencies in the conduct and reporting of the bioanalytical component of this study have been identified as discussed in the BIOANALYTICAL Section), and therefore, these data are provided in the NDA for informational purposes only. A total of 12 subjects received an IV dose and 5 subjects received an SC dose (total of 17 doses) of plerixafor (10, 20, 40 and 80 mcg/kg). Plerixafor was rapidly absorbed following SC injection with approximately 81% bioavailability in the 40 mg/kg groups (n=2) and 91% bioavailability in the 80 mg/kg groups (n=3), data from the 10 and 20 mcg/kg dose groups were below the LLOQ and could not be analyzed. Peak plasma concentrations occurred at approximately 30 to 60 minutes after dosing. As the applicant does not indicate what the deficiencies were in the bioanalytical method, these data should not be used in the labeling of plerixafor.

#### 2.2.5.4 What are the characteristics of drug distribution?

##### Protein Binding

Plerixafor was investigated for its ability to bind proteins from human plasma using (b) (4) analysis (report GT-249-PK-3). This method uses (b) (4) to separate protein bound plerixafor from unbound plerixafor, and LC-MS to quantify plerixafor in the plasma (b) (4) and thus to estimate drug binding to plasma proteins. Quantitation was based on peak area by LC-MS. The percentage of plerixafor protein bound in human plasma ranged from 37% to 58% (Table 17). The known low binding protein standard, (b) (4), was not protein bound in plasma, while the high binding protein standard, (b) (4), was found to be almost entirely protein bound in plasma (97% to 100%). There was a decrease in the percentage of protein bound plerixafor at the highest plerixafor concentration of 10 mcg/mL.

**Table 17** Amount of Plerixafor bound in human plasma

| Species | Conc. Plerixafor (mcg/mL) | %NSB <sub>PBS</sub> (mean) | % Bound (mean) |
|---------|---------------------------|----------------------------|----------------|
| Human   | 1.0                       | 10.8 ± 3.3                 | 53.5 ± 2.5     |
|         | 3.0                       | 9.4 ± 4.7                  | 58.0 ± 0.0     |
|         | 10.0                      | 1.0 ± 1.0                  | 37.0 ± 0.8     |

Errors represent SEM., NSB: non specific binding

(b) (4)



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

A human mass balance study was not conducted by the applicant. Following a single 240 mcg/kg SC dose of plerixafor in subjects with normal renal function, approximately 71% of the parent drug is recovered in the urine within 24 hours (protocol 1101). This result is consistent with a pre-clinical mass balance study in rats which indicated that renal elimination is predominant. Following administration of a single SC dose (1.23 mg/kg) of <sup>14</sup>C-plerixafor to

male and female Wistar Han rats, the predominant route of elimination of radioactivity was via urine (means of 66.4% and 71.8% of the administered dose, respectively) (Study report 7686-108 MS811280A). Elimination in feces accounted for less than 12% of the dose, and elimination in expired air accounted for a mean of less than 1% of the dose. At 168 hours post-dose, the carcasses contained means of 19.0 and 16.1% of the dose in males and females, respectively. The mean overall recoveries of radioactivity were 99.1 and 99.0% in males and females, respectively.

#### **2.2.5.6 What are the characteristics of drug metabolism?**

The metabolite profile of plerixafor in plasma and urine and feces from humans following SC administration was not investigated by the applicant. Preclinical studies and *in vitro* screening assays using human liver microsomes and hepatocytes indicate that plerixafor does not undergo metabolism.

Plerixafor was evaluated for metabolic stability in human hepatocytes (Study report GT-249-PK-2). In these studies, plerixafor (0.1, 1.0 and 10  $\mu$ M final concentrations) was incubated with human hepatocytes from a mixed gender pool of three donors, and the concentration of plerixafor was quantified using LC-MS/MS. Results indicated no loss of plerixafor, indicating that plerixafor is metabolically stable at all concentrations tested in human hepatocytes. The intrinsic clearance value was estimated as  $< 1.7 \mu\text{L}/\text{min}/10^6$  cells).

Plerixafor was evaluated for metabolic stability at concentrations of 0.1  $\mu$ M and 1.0  $\mu$ M in human whole blood. Plerixafor depletion was monitored over time at 0, 1 and 4 hours at 37<sup>0</sup>C, and blood samples were assayed for plerixafor and the internal standard using LC/MS/MS methodology. Results indicated no loss of plerixafor, indicating that plerixafor is metabolically stable at 37<sup>0</sup>C after 4 hours at the concentrations tested in human whole blood.

#### **2.2.5.7 What are the characteristics of drug excretion?**

##### **Route of Elimination**

A human mass-balance study was not conducted by the sponsor. Following a single 240 mcg/kg SC dose of plerixafor in subjects with normal renal function, approximately 71% of the parent drug is recovered in the urine within 24 hours (protocol 1101). These limited data would suggest that the majority of the plerixafor parent structure is eliminated renally.

##### **Clearance**

The clearance of plerixafor after a single 240 mcg/kg dose was similar in all studies including healthy subjects (protocol 1101 (healthy subjects) and 1002) AND oncology patients (2106). The mean CL/F was nearly constant after a 240- $\mu$ g/kg dose, ranging from 4.55 L/hour in Study 1002 to 5.14 L/hour in Study 2106. Furthermore, a study in healthy subjects (protocol 1002) shows that the CL/F does not appear to be dose dependent (Table 13 and Table 16).

##### **Half-life**

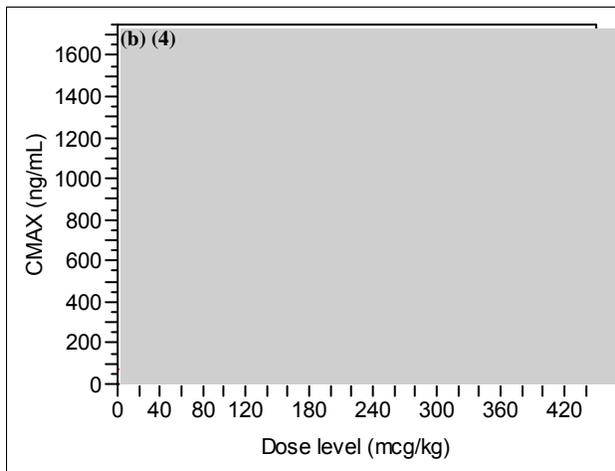
The plerixafor terminal elimination half-life was comparable with and without the co-administration of plerixafor in healthy volunteers and oncology patients. The mean terminal elimination half-life ( $\pm$  SD) ranged from  $3.1 \pm 0.12$  to  $5.3 \pm 1.1$  hours across the 40 to 240

mcg/kg dose range (Table 16).

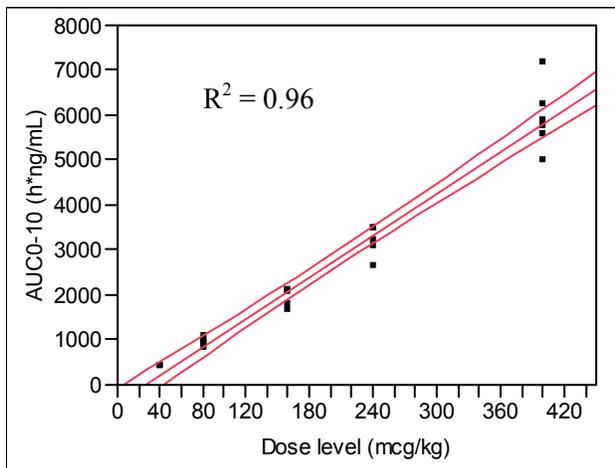
### 2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Mean values of  $AUC_{0-10}$  and  $C_{max}$  observed in protocol 1002; indicate that plerixafor concentrations increased in a dose-proportional manner over the dosing range of 40 to 240  $\mu\text{g}/\text{kg}$  after a single SC administration in normal healthy subjects. These relationships appeared to hold within the dose range of 40 to 400 mcg/kg plerixafor when results from protocol 1002 and 06-H-0156, in which plerixafor was administered as a SC dose to healthy volunteers, were combined (.

**Figure 11** Relationship between individual maximal concentrations of plerixafor ( $C_{max}$ ) and dose level after a single SC injection (dose range 40 to 240 mcg/kg, Study 1002) and (400 mcg/kg dose, study 06-H-0156) in healthy subjects.



**Figure 12** Relationship between individual Exposure to plerixafor ( $AUC_{0-10}$ ) and dose level after a single SC injection (dose range 40 to 240 mcg/kg, Study 1002) and (400 mcg/kg dose, study 06-H-0156) in healthy subjects.



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

There were no clinical studies submitted which evaluated the multiple dose PK of plerixafor. Trough concentrations or sparse PK sampling following multiple dosing of plerixafor were not obtained in any of the clinical studies.

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

Variability between patients with different cancer types ranged between 14-24% for PK measures of exposure (Table 17 and Table 18 and Figure 13). For healthy volunteers the CV% for C<sub>max</sub> and AUC ranged from 11-16% (Table 12). The increase in variability seen in patients may be due to the difference in dosing regimens (G-CSF in conjunction with plerixafor in patients vs. plerixafor alone in healthy subjects), underlying disease status and HSC mobilization capacity in patients compared to healthy volunteers.

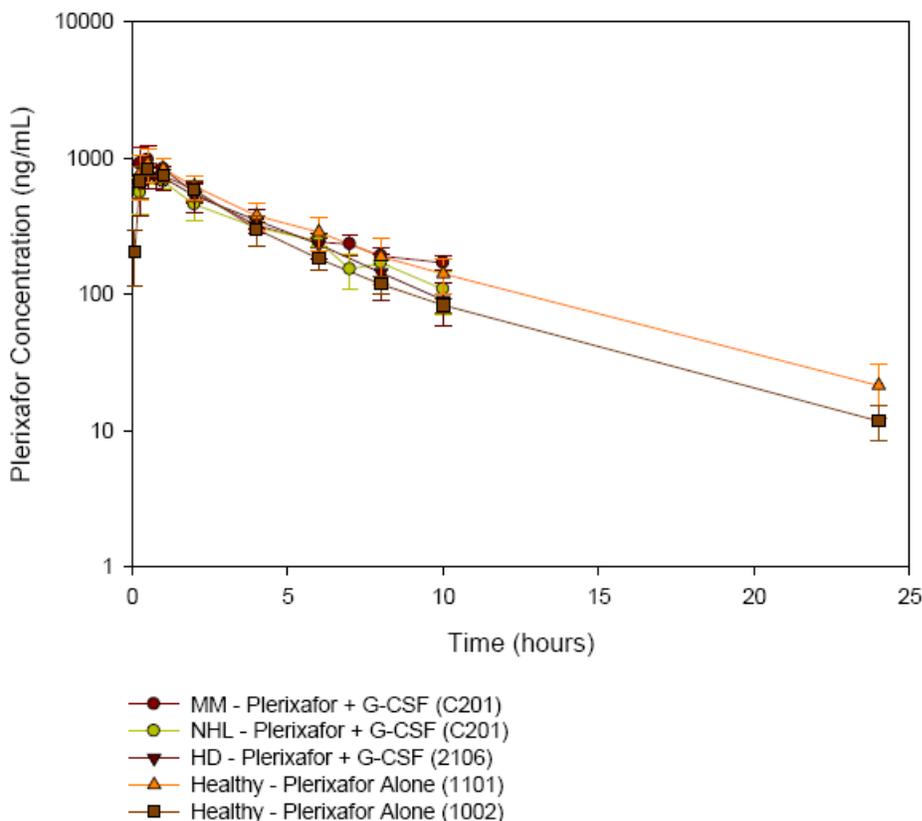
**Table 18** Summary of Select PK parameters in study 2106

|        | C <sub>max</sub><br>(ng/mL) | T <sub>max</sub><br>(hr) | t <sub>1/2</sub><br>(hr) | AUC <sub>0-10</sub><br>(ng*hr/mL) | AUC <sub>0-24</sub><br>(ng*hr/mL) | AUC <sub>0-inf</sub><br>(ng*hr/mL) | CL/F<br>(L/hr) | V <sub>p</sub> /F<br>(L) |
|--------|-----------------------------|--------------------------|--------------------------|-----------------------------------|-----------------------------------|------------------------------------|----------------|--------------------------|
| N      | 9                           | 9                        | 8                        | 9                                 | 8                                 | 8                                  | 8              | 8                        |
| Mean   | 831                         | 0.6                      | 3.5                      | 3572                              | 4072                              | 4108                               | 5.13           | 25.5                     |
| SD     | 183                         | 0.4                      | 0.7                      | 772                               | 875                               | 875                                | 2.029          | 9.00                     |
| Min    | (b) (4)                     |                          |                          |                                   |                                   |                                    |                |                          |
| Median | 750                         | 0.5                      | 3.6                      | 3501                              | 3884                              | 3929                               | 4.93           | 25.87                    |
| Max    | (b) (4)                     |                          |                          |                                   |                                   |                                    |                |                          |
| %CV    | 22.0                        | 61.3                     | 19.8                     | 21.6                              | 21.5                              | 21.3                               | 39.5           | 35.4                     |

**Table 19** Summary of Select PK parameters in study C201

| Diagnosis | Statistic | C <sub>max</sub> (ng/mL) | AUC <sub>0-10</sub><br>(ng*hr/mL) | AUC <sub>0-24</sub><br>(ng*hr/mL) | t <sub>1/2</sub> (hr) |
|-----------|-----------|--------------------------|-----------------------------------|-----------------------------------|-----------------------|
| NHL       | N         | 5                        | 5                                 | 5                                 | 5                     |
|           | Mean      | 761                      | 3035                              | 3686                              | 4.4                   |
|           | SD        | 101                      | 412                               | 625                               | 1.1                   |
|           | Min       | (b) (4)                  |                                   |                                   |                       |
|           | Median    | 799                      | 3012                              | 3907                              | 4.5                   |
|           | Max       | (b) (4)                  |                                   |                                   |                       |
|           | CV%       | 13.3                     | 13.6                              | 17.0                              | 25.5                  |
| MM        | N         | 8                        | 8                                 | 8                                 | 8                     |
|           | Mean      | 1029                     | 3945                              | 5009                              | 5.6                   |
|           | SD        | 242                      | 610                               | 737                               | 2.6                   |
|           | Min       | (b) (4)                  |                                   |                                   |                       |
|           | Median    | 995                      | 3866                              | 4976                              | 4.7                   |
|           | Max       | (b) (4)                  |                                   |                                   |                       |
|           | CV%       | 23.6                     | 15.5                              | 14.7                              | 46.6                  |

**Figure 13** Semi-Logarithmic Comparison of Mean Plasma Plerixafor Concentrations After Treatment With 240 mcg/kg Plerixafor in Healthy Subjects Without G-CSF (1002, 1101) and Oncology Patients With G-CSF (2106, C201) (mean  $\pm$  SD).



## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of race, age and gender on the exposure to plerixafor have not been studied. The populations studied in the phase 3 trials were primarily of Caucasian origin. In protocol 3101, (289/311 (92.9%)) patients were Caucasian and 7/311 (2.3%) were African-American. In protocol 3102, (245/302 (81.1%)) patients were Caucasian and 32/302 (10.5%) were African-American. The small number of non-Caucasian patients enrolled did not allow for meaningful statistical comparisons with race as a covariate.

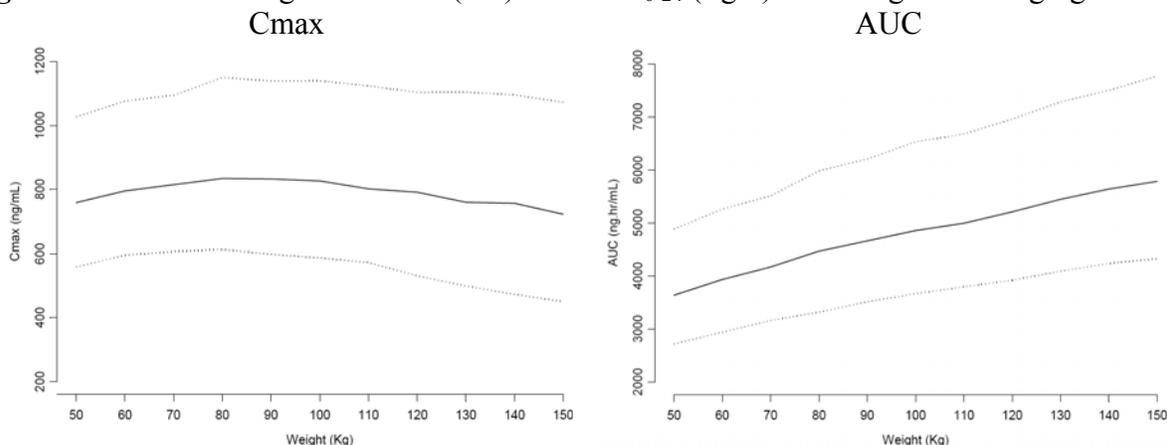
A population PK analysis was performed by the applicant using the pooled PK data from a total of 63 subjects, and included patients with NHL and MM (C201), patients with HD (2106) and

subjects with various degrees of renal impairment (1101) and healthy subjects (1101 and 1002). Covariates assessed in the population PK analysis were: patient age at baseline, patient weight, patient height at baseline, body surface area, patient gender, patient race, renal function (creatinine clearance determined by the Cockcroft and Gault formula), hepatic function (albumin, AST, ALT and total bilirubin).

The best structural model to describe the PK of plerixafor was a 2-compartment model with a first order input and first order elimination. This model was parameterized in terms of apparent clearance (CL/F), the central volume of distribution (Vc/F), the peripheral volume of distribution (Vp/F) and inter-compartmental clearance (Q/F). The primary covariate identified as the most important in influencing plerixafor PK was CL<sub>CR</sub>. The CL<sub>CR</sub> covariate as determined by the Cockcroft and Gault equation incorporates additional covariates, total body weight, gender and age. The CL<sub>CR</sub> covariate described some of the inter-individual variability in clearance (CL/F). The second most important covariate was total body weight (WT) which described some of the inter-individual variability in the central volume of distribution (Vc/F) (Figure 14). The only additional covariate retained in the model was age which described some of the inter-individual variability in peripheral volume of distribution (Vp/F). When CL<sub>CR</sub> and WT and age covariates were included in the final covariate model, the inter-individual variability of CL/F, Vc/F and Vp/F reduced from 40.6%, 71.7% and 31.9% to 21.8%, 58.3% and 22.4%, respectively. The applicant suggested a weight-based dosing strategy (mcg/kg) due to the influence of weight, and a dose reduction in patients with severe renal impairment based on the influence of CL<sub>CR</sub>.

The applicant showed that C<sub>max</sub> does not vary significantly as body weight increases, primarily as weight was the covariate included on Vc, and that AUC<sub>0-24</sub> following a 240 mcg/kg dose increases with weight from 3600 ng\*hr/mL for a 50 kg (110 lbs) patient to 5800 ng\*hr/mL for a 150 kg (330 lbs) patient, which is a 61% increase in AUC over a 300% increase in weight (Figure 14).

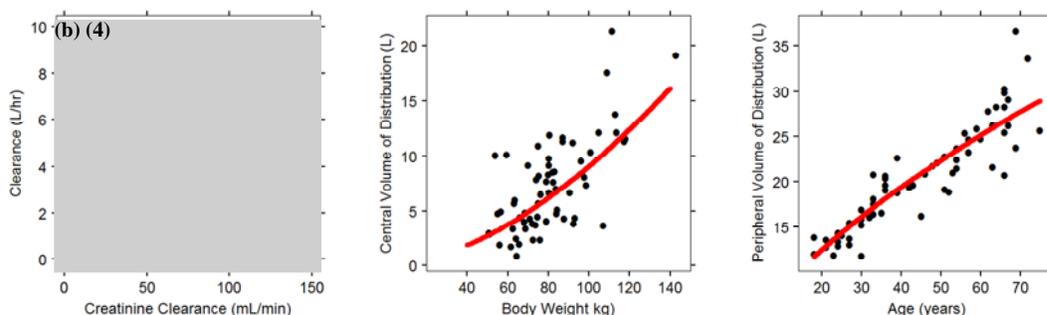
**Figure 14** Effect of weight on C<sub>max</sub> (left) and AUC<sub>0-24</sub> (right) following a 240 mcg/kg dose.



The Clinical Pharmacology Pharmacometrics Reviewer conducted a similar population PK analysis upon which the dosing recommendations for plerixafor are based. For a detailed description of the analysis, please refer to the Pharmacometrics Review for the current NDA

(attached below). Similar to sponsor’s population PK findings, a two-compartment disposition model with first-order absorption and elimination was found adequate to describe the plerixafor concentration-time profile following a subcutaneous dose of 40-240 mcg/kg.  $CL_{CR}$ , body weight, and age were found to be significant PK covariates (Figure 15) similar to sponsor’s findings Figure 14). The estimated distribution half-life ( $t_{1/2,\alpha}$ ) is 0.3 hr and the terminal population half-life ( $t_{1/2,\beta}$ ) is 5.3 h with a steady-state volume of distribution ( $V_{ss}$ ) estimate of 27.7 L.

**Figure 15** Pharmacometrics Reviewer Population PK analysis



Identified demographic covariate – PK parameter relationships for plerixafor. (Left) Clearance vs. CrCL, (Middle) Central volume of distribution vs. body weight, and (Right) Peripheral volume of distribution vs. age. Individual (black dots) and population (red line) predictions.

The applicant’s dedicated renal impairment study assessed the effects of impaired renal function on the PK of a single 240 mcg/kg dose of plerixafor (protocol 1101). The results showed no effect of renal function on the PK parameters related to absorption (e.g.,  $t_{max}$ , maximum plasma concentration [ $C_{max}$ ]) but a decrease in drug clearance with renal impairment was observed.

The mean  $C_{max}$  and area under the curve ( $AUC_{0-24hr}$ ) in subjects with normal, mild, moderate, and severe renal impairment in study (1101) are shown in Table 20.

**Table 20** PK parameter estimates across renal function (protocol 1101)

$C_{max}$   $AUC_{0-24}$  estimates across renal function in study AMD3100-1101.

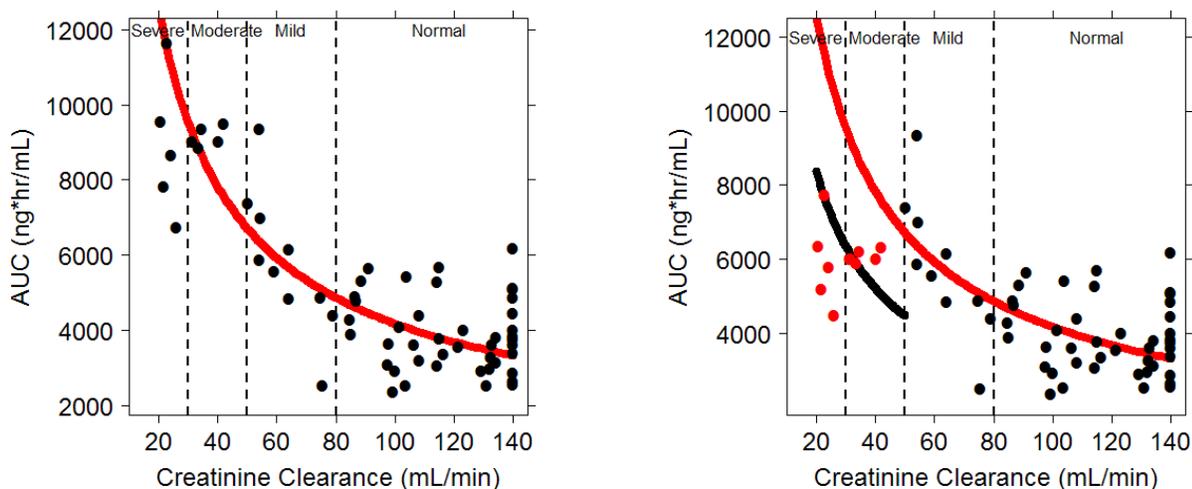
|                         | Renal Impairment | Control (N=6)  | Mild (N=5)      | Moderate (N=6)  | Severe (N=6)    |
|-------------------------|------------------|----------------|-----------------|-----------------|-----------------|
| $C_{max}$ (ng/mL)       | Mean $\pm$ SD    | 980 $\pm$ 196  | 739 $\pm$ 76.1  | 936 $\pm$ 280   | 861 $\pm$ 193   |
|                         | Min, Max         | 812, 1260      | 640, 845        | 559, 1270       | 609, 1140       |
| $AUC_{0-24}$ (ng*hr/mL) | Mean $\pm$ SD    | 5070 $\pm$ 979 | 5410 $\pm$ 1070 | 6780 $\pm$ 1660 | 6990 $\pm$ 1010 |
|                         | Min, Max         | 3900, 6240     | 3970, 6540      | 4680, 8410      | 5700, 8050      |

Source: Table 11-5 in sponsor’s CSR for study AMD3100-1101 on page 55.

The Pharmacometrics Reviewer’s population PK analysis and the mean  $AUC_{0-24h}$  estimates from the table above obtained in the renal impairment study (1101) suggest that the plerixafor dosage

should be reduced by one-third (160 mcg/kg) in patients with moderate or severe renal impairment ( $CL_{CR} \leq 50$  mL/min) in order to bring down the exposure in these patients to a level that was studied and known not to cause unacceptable adverse events in the pivotal trials (Figure 16).

**Figure 16** Pharmacometrics Reviewer analysis: Individual predicted AUC (black dot) vs.  $CL_{CR}$  following a dose of (Left) 240 mcg/kg and (Right) a dose reduction to 160 mcg/kg in patients with moderate and severe renal impairment (red dots). The population predicted  $AUC_{0-24h}$  following 240 mcg/kg is shown as a red line and 160 mcg/kg is shown as a black line.



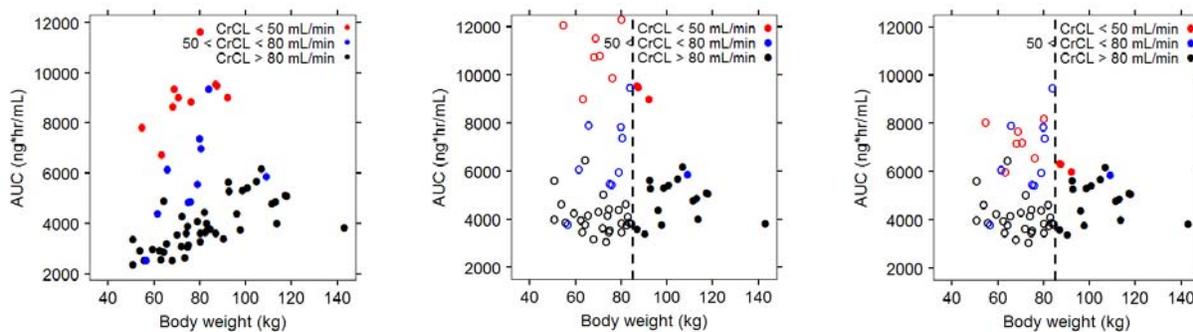
Furthermore, there is a clear trend towards lower  $AUC_{0-24h}$ s with lower body weight when plerixafor is being dosed on a body weight basis as seen in Figure 17 below (Left) and shown by the sponsor in Figure 14 above.

The Pharmacometrics Reviewer's pharmacokinetic-pharmacodynamic modeling using response data from study 3101 also showed a decreased response in NHL patients weighing  $< 85$  kg, compared to those weighing  $\geq 85$  kg (See pharmacodynamic analysis below). Given the lower response rate in lighter patients and the clear exposure-response relationship observed in studies 1002 and 1003, it is reasonable to assume a higher exposure in these patients will improve the response rate and the higher exposure achieved in heavier patients can serve as the target exposure level with acceptable safety profile. The pharmacometrics reviewer explored several methods in which to optimize exposure in the patients with low plerixafor exposure. One strategy to match the exposure in lighter patients to that in heavier patients, involves administration of an absolute fixed dose of 20 mg to patients  $< 85$  kg. The 20 mg fixed dose is equal to the 240 mcg/kg dose of an 85 kg patient and is predicted to increase exposure to that observed in patients within the weight range of 85 kg to 160 kg (median body weight in study 3101 and 3102 was 85 kg) (Figure 17 (Right)). This optimized exposure level in patients  $< 85$  kg was evaluated in the applicant's phase 3 trials and is well characterized in terms of efficacy and safety parameters.

The individual predicted  $AUC_{0-24h}$ s for the subjects in studies AMD3100- C201, 2106, 1101,

1002 (population PK data) following 1) 240 mcg/kg, 2) 240 mcg/kg in patients > 85 kg, with a fixed dose of 20 mg for patients < 85 kg and 3) 240 mcg/kg in patients > 85 kg, with a fixed dose of 20 mg for patients < 85 kg and one-third dose reduction in patients with  $CL_{CR} \leq 50$  mL/min are shown sequentially in Figure 17 below.

**Figure 17** Individual predicted AUC vs. body weight following (Left) 240 mcg/kg, (Middle) 240 mcg/kg with a fixed dose of 20 mg for patients < 85 kg, and (Right) a 1/3 dose reduction for all patients with  $CL_{CR} \leq 50$  mL/min (moderate and severe renal impairment) in addition to a fixed dose of 20 mg for patients < 85 kg.



### Pharmacometrics Reviewer's Pharmacodynamic Analysis:

The Pharmacometrics reviewer assessed the impact of differences in exposure on efficacy. Peripheral blood CD34+ cell count has previously been demonstrated to correlate positively with apheresis yield with peak mobilization after G-CSF alone usually occurring four to five days after initiation of G-CSF. A dose-proportional increase in CD34+ cells was observed when plerixafor alone was given at doses from 40 mcg/kg to 240 mcg/kg in healthy subjects (study 1002).

Taken together, the results from Phase 1 and early Phase 2 studies established the dose and administration schedule of plerixafor as a 4-day regimen of G-CSF, followed by plerixafor at 240 mcg/kg starting 6 to 11 hours prior to the first apheresis on the 5<sup>th</sup> day. Patients continue to receive daily doses of G-CSF and plerixafor prior to each subsequent apheresis session.

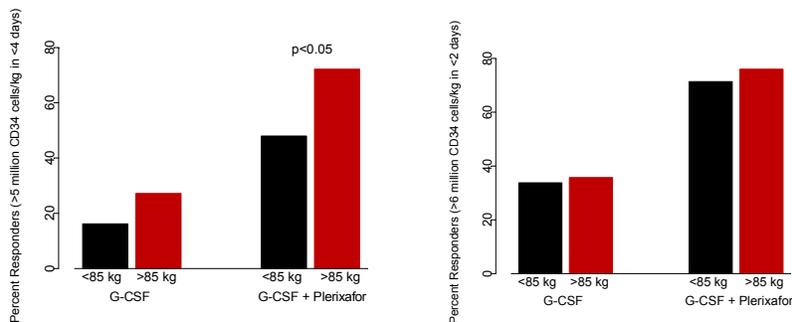
The primary endpoint in the phase 3 studies was defined as the number of patients reaching a target of  $\geq 5/6 \times 10^6$  CD34+ cells/kg in 4/2 or less days of apheresis for NHL and MM patients, respectively.

The mean cumulative CD34+ cells/kg collected in the phase 3 studies in NHL (study 3101) and MM (study 3102) patients following a plerixafor dose of 240 mcg/kg and 10 mcg/kg G-CSF are shown in Figure 18. It is observed that the mean CD34+ cells/kg is lower for lighter NHL patients weighing less than the median body weight of 85 kg compared to heavier patients. This is not seen for MM patients since the endpoint of  $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or less apheresis days appears to be easier to reach compared to NHL patients.

When considering the time frame in which patients were administered G-CSF and plerixafor in

study 3101 and 3102, the response rates for G-CSF + Plerixafor treated patients were found to be significantly lower in patients weighing less than 85 kg (48% (95% CI 36-60%)) compared to patients  $\geq$  85 kg (72% (95% CI 61-82%)) in NHL patients (study 3101) (Figure 18, Left panel). The same numerical trend was seen for G-CSF treated patients however not statistical significant. No differences in response rate between low and high body weight groups were observed for MM patients (study 3102) (Figure 18, Right panel).

**Figure 18** Percent responders for patients above or below the median body weight of 85 kg in (Left panel) NHL patients (study 3101) and (Right panel) MM patients (study 3102) receiving G-CSF (black bars) and G-CSF + Plerixafor (red bars).



The conclusions from the Pharmacometrics Review suggest (assuming baseline CD34+ cells is balanced between treatment arms on apheresis day 0) that it is not the response rate definition ( $>5 \times 10^6$  cells/kg on apheresis day 4) that causes the observed differences in response rates between lighter and heavier patients but that it is the inadequacy of the 240 mg/kg plerixafor dose to achieve similar exposure across body weight that translates into significantly lower response rates for lighter patients.

**Statistical analysis to confirm the results from the Pharmacometrics Review: Both low CD34+ count at baseline and decreased plerixafor exposure results in poor response to plerixafor**

A logistic regression analysis conducted by OCP also showed that both low body weight (i.e. low exposure) and low CD34+ baseline cell counts, were predictors of poor response to CD34+ mobilization therapy with plerixafor + G-CSF (See attached Pharmacometrics Review). Based on these data the dose of plerixafor needs to be optimized in patients with low exposure and low CD34+ baseline values, as these are predictors of poor response. The OCP p phase 4 commitments include a study to address optimization of the plerixafor dose in patients with low body weight and those who are predicted to be poor responders to plerixafor based CD34+ baseline cell count. This study will consider predictors of poor response such as low exposure and baseline CD34+ count, and will 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. OCP further recommends a maximum dose of 27 mg in patients with renal impairment ( $CL_{CR} \leq 50$  mL/min), (equivalent to 160 mcg/kg dose of a 160 kg patient).

In an additional statistical exploratory analysis (conducted by the OCP biostatistician (Weishi (Vivian) Yuan) assigned to this NDA), the effect of weight ( $< 85$  kg vs.  $\geq 85$  kg) on the primary

endpoint in patients with NHL (protocol 3101) and patients with MM (protocol 3102) was assessed. The analysis confirmed that in the patients with MM, the estimated treatment effect was similar in patients weighing < 85 kg vs. those weighing ≥ 85 kg (Table 21). The analysis also confirmed the Pharmacometrics review findings, indicating that the estimated treatment effect was decreased in NHL patients < 85 kg vs. those weighing ≥ 85 kg (Table 22).

**Table 21** Primary Endpoint Mobilization of ≥ 6 x 10<sup>6</sup> CD34+ cells/kg within 2 days by weight in MM patients\* (Protocol 3102)

| CD34+ cells mobilized               | Weight <85           |           | Weight >85           |           |
|-------------------------------------|----------------------|-----------|----------------------|-----------|
|                                     | G/plerixafor         | G/placebo | G/plerixafor         | G/placebo |
|                                     | (n = 69)             | (n = 80)  | (n = 75)             | (n = 70)  |
| ≥ 5 x 10 <sup>6</sup> /kg           | 49 (71%)             | 28 (35%)  | 57 (76%)             | 25 (36%)  |
| < 5 x 10 <sup>6</sup> /kg           | 20 (29%)             | 52 (65%)  | 18 (24%)             | 45 (64%)  |
| Estimated treatment effect (95% CI) | 36.0% (20.8%, 51.3%) |           | 40.3% (25.3%, 55.3%) |           |

\* Eight patients' data are missing. 85kg is about the mean and median

**Table 22** Primary Endpoint Mobilization of ≥ 5 x 10<sup>6</sup> CD34+ cells/kg within 4 days by weight in NHL patients\* (Protocol 3101)

| CD34+ cells mobilized               | Weight <85           |           | Weight >85           |           |
|-------------------------------------|----------------------|-----------|----------------------|-----------|
|                                     | G/plerixafor         | G/placebo | G/plerixafor         | G/placebo |
|                                     | (n = 71)             | (n = 67)  | (n = 76)             | (n = 75)  |
| ≥ 5 x 10 <sup>6</sup> /kg           | 33 (46%)             | 12 (18%)  | 56 (74%)             | 17 (23%)  |
| < 5 x 10 <sup>6</sup> /kg           | 38 (54%)             | 55 (82%)  | 20 (26%)             | 58 (77%)  |
| Estimated treatment effect (95% CI) | 28.6% (13.4%, 43.7%) |           | 51.0% (37.1%, 67.9%) |           |
| P-value                             | < 0.001              |           | < 0.001              |           |

\* Nine patients' data are missing. 85kg is about the mean and median.

**Statistical analysis by the OCP biostatistician (Weishi (Vivian) Yuan) to determine if PB CD34+ cell count (obtained just prior to apheresis, and following 4 days of G-CSF treatment and a single dose of plerixafor) could predict response to plerixafor in patients with NHL**

A significantly larger number of patients with NHL (protocol 3101), compared to patients with MM (protocol 3102), did not respond to treatment with plerixafor in conjunction with G-CSF. Therefore, a further exploratory analysis was done in patients with NHL, to investigate whether the PB CD34+ cell count obtained just prior to apheresis, and following administration of the first dose of plerixafor, predicted response to plerixafor. The reviewer chose the 0.93 x 10<sup>6</sup> cells/kg CD34+ cell count (obtained after the first dose of plerixafor) as the cut point to divide the NHL patients into two sub groups (patients with a CD34+ count ≤ 0.93 x 10<sup>6</sup> and patients with a CD34+ count > 0.93 x 10<sup>6</sup>). This value was chosen as all NHL patients within the subgroup of who did not reach the target CD34+ count (for either the primary endpoint (cell count > 5 x 10<sup>6</sup> cells/kg) or secondary endpoint (cell count > 2 x 10<sup>6</sup> cells/kg)) had a CD34+ count that was ≤ 0.93 x 10<sup>6</sup> cells/kg. The analysis indicated that a CD34+ count ≤ 0.93 x 10<sup>6</sup>

cells/kg could predicted a lack of response in NHL patients treated within both the Plerixafor + G-CSF Arm and the Placebo + G-CSF Arm. Specifically, in the group with a CD34+ cell count  $\leq 0.93 \times 10^6$  cells/kg, 90.3 % of patients in the Plerixafor + G-CSF Arm and 98.8% of patients in the Placebo + G-CSF Arm did not reach the primary endpoint. In the group with a CD34+ count  $> 0.93 \times 10^6$  cells/kg, 25.9 % of patients in the Plerixafor + G-CSF Arm and 53.3 % of patients in the Placebo + G-CSF Arm did not reach the primary endpoint (Table 23). Overall, a CD34+ count  $\leq 0.93 \times 10^6$  could identify 28/58 NHL patients who did not reach the primary endpoint of response to plerixafor.

**Table 23** Primary Endpoint Mobilization of  $\geq 5 \times 10^6$  CD34+ cells/kg within 4 days by CD34 count on Day 5\*

| CD34+ cells mobilized               | CD34 $< 0.93 \times 10^6$ cells/kg |            | CD34 $> 0.93 \times 10^6$ cells/kg |            |
|-------------------------------------|------------------------------------|------------|------------------------------------|------------|
|                                     | G/plerixafor                       | G/placebo  | G/plerixafor                       | G/placebo  |
|                                     | (n = 31)                           | (n = 82)   | (n = 116)                          | (n = 60)   |
| $\geq 5 \times 10^6$ /kg            | 3 (9.7%)                           | 1 (1.2%)   | 86 (74.1%)                         | 28 (46.7%) |
| $< 5 \times 10^6$ /kg               | 28 (90.3%)                         | 81 (98.8%) | 30 (25.9%)                         | 32 (53.3%) |
| Estimated treatment effect (95% CI) | 8.5% (0.8%, 16.1%)                 |            | 27.5% (13.0%, 42.0%)               |            |
| P-value                             | 0.03                               |            | 0.0003                             |            |

\* Nine patients' data are missing.

### Pharmacometrics Reviewer's Time to Event analysis (Mobilization/Apheresis)

Using Cox Proportional Hazards model, NHL patients treated with G-CSF + Plerixafor were 3.7 times more likely to reach the target number of CD34+ cells compared to those receiving G-CSF alone (Hazard ratio of 3.69 (95% CI 2.48-5.50)) for checking the proportional hazard assumption in Cox regression). Similarly for MM patients, the hazard ratio between G-CSF and G-CSF + Plerixafor was 3.24 (95% CI 2.39-4.40).

The probability of NHL patients treated with G-CSF + Plerixafor reaching the target number of CD34+ cells was found to be lower in lower body weight group. Univariate Cox regression showed that patients with body weight above 85 kg were twice as likely to respond (HR: 1.88 (95% CI 1.23-2.88),  $p=0.004$ ) compared to patients with low body weight.

The median estimated time to reach the target number of CD34+ cells in the high body weight group was 1 day of apheresis while patients weighing less than 85 kg took 3 days to reach target.

No significant difference between low and high body weight patients were found for G-CSF treated patients (HR:1.70 (95% CI: 0.82-3.50),  $p=0.15$ ). This finding together with the responder analysis suggests that it is plerixafor that is suboptimal for lighter patients since body weight category was not found to be a significant predictor for G-CSF treated patients.

Weight was not found to be a significant covariate for response in MM patients in study 3102. This might be because the 240 mg/kg dose is more than enough for MM patients to reach the target and it is therefore not possible to separate out the weight effect.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

Results from the Pharmacometrics Reviewer's analysis shows that exposure in patients with  $CL_{CR} > 80$  mL/min (normal renal function) weighing less than 85 kg receiving a fixed dose of 20 mg matches that of patients  $> 85$  kg getting 240 mcg/kg. No dose adjustments based on renal function are necessary for patients  $< 85$  kg and  $50 < CL_{CR} < 80$  mL/min (mild renal impairment) since the exposures match that of patients  $> 85$  kg. Patients with moderate or severe renal impairment ( $CL_{CR} \leq 50$  mL/min) across all weights should receive 2/3 the dose (160 mcg/kg) to match the exposure in patients with normal renal function.

**Possible Strategies to match exposure in patients with low body weight to that in heavier patients, and to decrease exposure in patients with impaired renal function:**

In order to match the exposure in lighter patients to that in heavier patients, the absolute dose should be capped (at the lower end) to that of an 85 kg patient (median body weight in study 3101 and 3102 was 85 kg), i.e.

|                                |  |
|--------------------------------|--|
| WT $< 85$ kg                   | 20 mg (fixed dose) ( $\sim 240$ mcg/kg * 85 kg)  |
| WT $\geq 85$ kg and $< 160$ kg | 240 mcg/kg                                       |
| WT $\geq 160$ kg               | 40 mg (fixed dose) ( $\sim 240$ mcg/kg * 160 kg) |

For patients with moderate or severe renal impairment ( $CL_{CR} \leq 50$  mL/min), the dose should be reduced by 1/3 across all body weights, i.e.

|   |  |
|---|--|
| WT $< 85$ kg and $CL_{CR} \leq 50$ mL/min     | 13.5 mg ( $\sim 2/3$ * 240 mcg/kg * 85 kg) |
| WT $\geq 85$ kg and $CL_{CR} \leq 50$ mL/min  | 160 mcg/kg                                 |
| WT $\geq 160$ kg and $CL_{CR} \leq 50$ mL/min | 27 mg ( $\sim 2/3$ * 240 mcg/kg * 160 kg)  |

**Administration of a single absolute dose to all patients in order to optimize response in patients with decreased exposure, or who are predicted to have a poor response to plerixafor based on baseline CD34+ counts:**

The pharmacometrics reviewer explored administration of a single absolute dose across all weight groups. This dose could be optimized further based on  $CL_{CR}$ . This alternative proposed dosing strategy aims to improve response to patients with decreased exposure, or low baseline CD34+ cell counts. It will be explored in the applicant's phase 4 commitments (see attached pharmacometrics review for the detailed analysis).

**2.3.2.1 Pediatric patients**

There were no pediatric studies in the current submission. Pursuant to 21 CFR 314.55(d) "Exemption for orphan drugs", plerixafor injection is exempt from pediatric study requirements. (b) (4)

The same PIP was submitted to the FDA on 23 January 2008. OCP's dose adjustments based on body weight, need to be considered in the

further development of the applicant's pediatric study designs.

### 2.3.2.2 Renal impairment

The applicant conducted a phase 1, open-label, multi-centre study to evaluate the safety, PK parameters, and hematological activity of plerixafor in subjects with renal impairment. The study evaluated the effects of a single SC dose of 240 µg/kg of plerixafor on pharmacodynamic, pharmacokinetic, and safety parameters. Subjects were stratified into four cohorts with various degrees of renal impairment (Control, Mild Impairment, Moderate Impairment, and Severe Impairment) based on their measured  $CL_{CR}$  values determined by a screening 24-hour urine collection using the Cockcroft-Gault formula (Table 24). The pharmacodynamic activity of plerixafor was assessed by measuring the number of CD34+ cells circulating in blood using FACS analysis.

**Table 24** Stratification of subjects according to renal clearance (based on a screening 24 hour urine collection) in study 1101

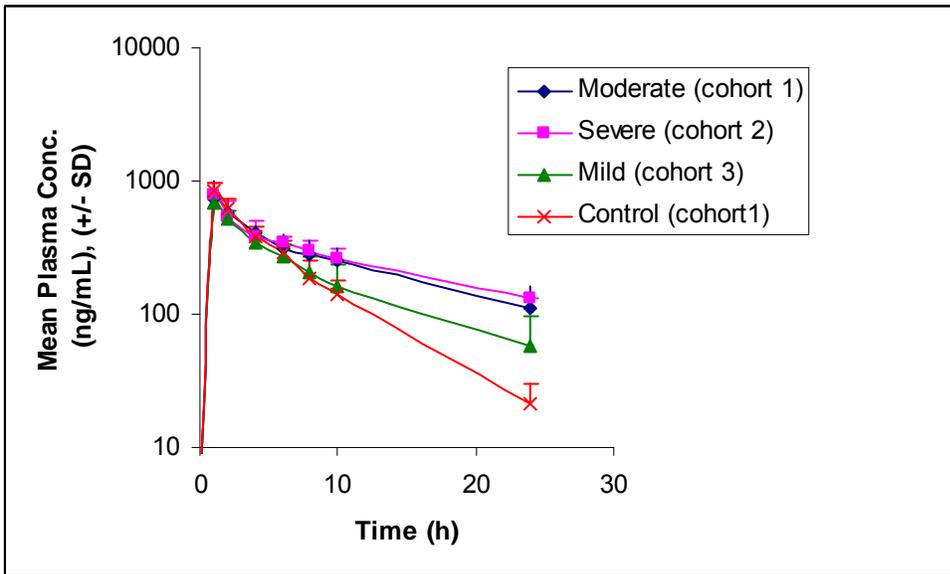
| Cohort              | Number of Subjects | Renal Function | Average Renal Clearance (mL/min) <sup>a</sup> |
|---------------------|--------------------|----------------|---|
| Severe Impairment   | 6                  | Severe         | <31, not requiring dialysis                   |
| Moderate Impairment | 6                  | Moderate       | 31-50   |
| Mild Impairment     | 5                  | Mild           | 51-80   |
| Control             | 6                  | Normal         | >90   |

Because of the large percent of area extrapolated in the calculation of  $AUC_{0-\infty}$ , which exceeded 20% in subjects with moderate or worse renal impairment, the primary endpoint was  $AUC_{0-24}$  in addition to  $C_{max}$ .  $AUC_{0-24h}$  increased with decreasing renal function. Analysis of variance was used to test for differences among treatment groups using  $AUC_{0-24h}$  and  $C_{max}$  as the primary analysis variables. Data were ln-transformed prior to analysis. Renal impairment was considered to have no effect on plerixafor pharmacokinetics if the 90% geometric confidence intervals (CIs) of the ratios of least-square means for Mild/Control, Moderate/Control and Severe/Control were no less than 80% and no more than 125% for  $AUC_{0-24h}$ ; the limits were 70% and 143% for  $C_{max}$ . The ratios of least-squares means and associated 90% geometric CIs indicate that plerixafor PK were affected by renal function, such that patients with moderate and severe renal impairment had increased exposure ( $AUC_{0-24h}$ ) compared to subjects with normal renal function (Table 25 and Figure 19).

**Table 25** Treatment comparison for dose-normalized parameters after ln-transformation in study 1101.

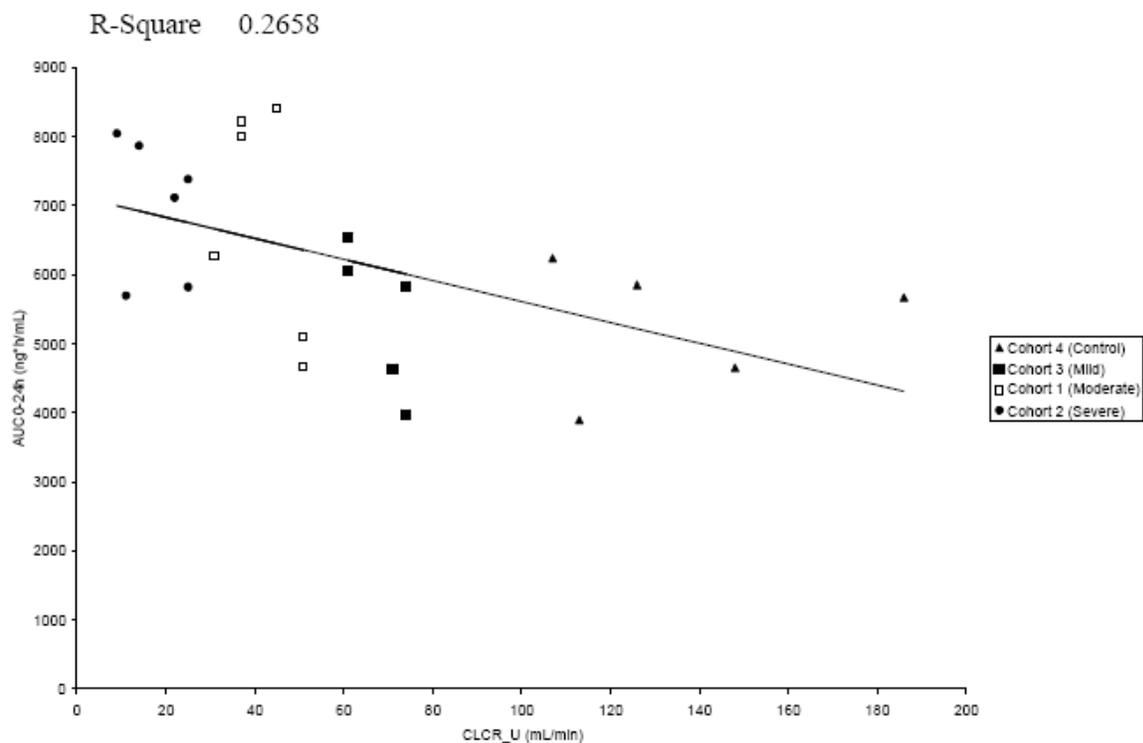
| Comparison                                | Least-Square Means   |                                 | Ratio (%)        |        | 90% Geometric Confidence Interval |        |
|---|----------------------|---------------------------------|------------------|--------|-----------------------------------|--------|
|   | Control <sup>a</sup> | Impaired RF Cohort <sup>a</sup> |                  |        | Lower                             | Upper  |
| Dose-Normalised Ln (C <sub>max</sub> )    | 0.043508             | Mild: 0.037891                  | Mild/Control     | 87.09  | 63.59                             | 119.26 |
|   |                      | Moderate: 0.046381              | Moderate/Control | 106.60 | 78.99                             | 143.87 |
|   |                      | Severe: 0.046451                | Severe/Control   | 106.76 | 79.11                             | 144.08 |
| Dose-Normalised Ln (AUC <sub>0-24</sub> ) | 0.22517              | Mild: 0.27412                   | Mild/Control     | 121.74 | 91.86                             | 161.43 |
|   |                      | Moderate: 0.34101               | Moderate/Control | 151.44 | 115.78                            | 198.09 |
|   |                      | Severe: 0.38169                 | Severe/Control   | 169.51 | 129.59                            | 221.72 |

**Figure 19** Plerixafor plasma concentration-time profiles following a single 240 mcg/kg dose of plerixafor in healthy subjects with normal renal function and mild, moderate and severe renal impairment (protocol 1101)

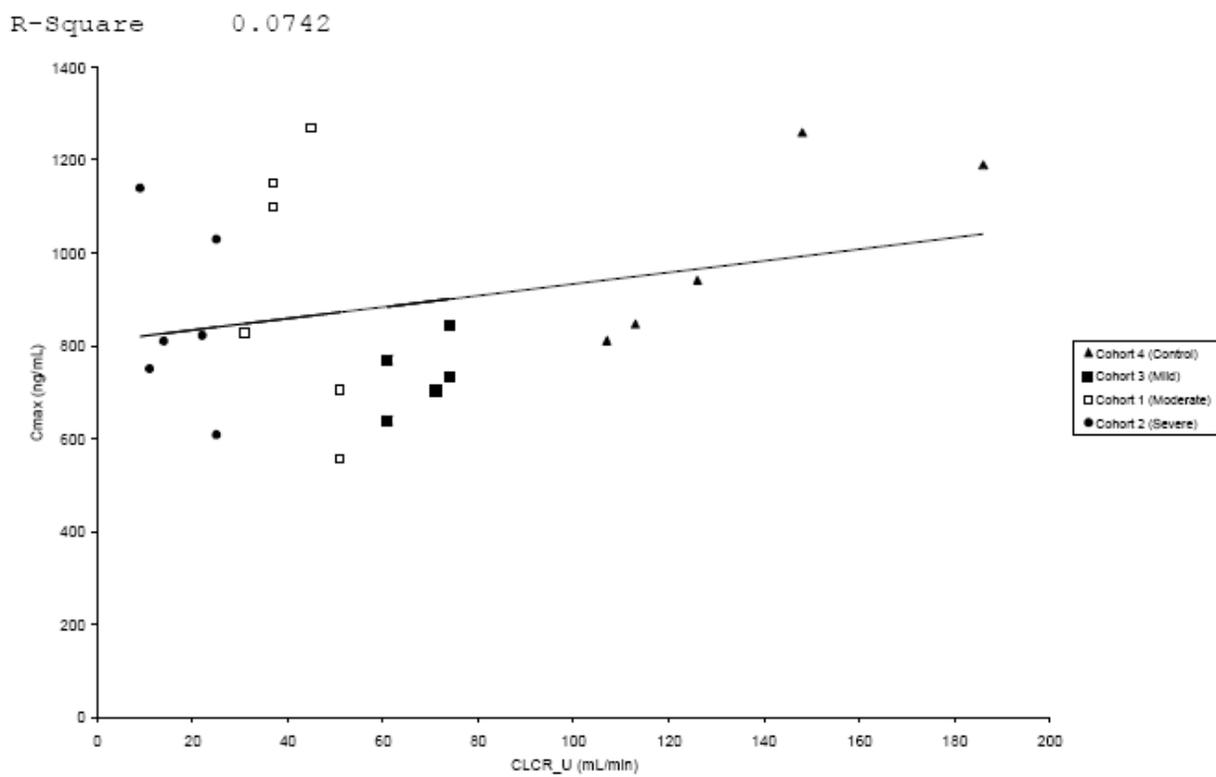


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**Figure 20** Plot of linear regression: AUC<sub>0-24h</sub> and CL<sub>CrU</sub>



**Figure 21** Plot of linear regression:  $C_{max}$  and  $CL_{CrU}$



Statistically significant differences among cohorts were closely related to parameters associated

with elimination processes ( $AUC_{0-24h}$ ,  $AUC_{0-\infty}$ ,  $Cl/F$ ,  $Kel$  and  $T_{1/2}$  el). Parameters generally associated with rate of absorption ( $T_{max}$  and  $C_{max}$ ) did not demonstrate statistically significant differences among cohorts (Figure 20 and Figure 21, and Table 26).

**Table 26** PK parameters in healthy subjects with normal and impaired renal function (study 1101).

|  |               | Control             | Mild                | Moderate            | Severe              |
|--|---------------|---------------------|---------------------|---------------------|---------------------|
| $T_{max}$ (h)  | Median        | 0.559               | 0.500               | 0.500               | 0.750               |
|  | Min, Max      | 0.50, 1.02          | 0.50, 1.00          | 0.25, 1.00          | 0.50, 1.00          |
| $C_{max}$ (ng/mL)                                      | Mean $\pm$ SD | 980 $\pm$ 196       | 739 $\pm$ 76.1      | 936 $\pm$ 280       | 861 $\pm$ 193       |
|  | Min, Max      | 812, 1260           | 640, 845            | 559, 1270           | 609, 1140           |
| $C_{max}$ (ng/mL/ $\mu$ g) <sup>a</sup>                | Mean $\pm$ SD | 0.0452 $\pm$ 0.0145 | 0.0388 $\pm$ 0.0095 | 0.0490 $\pm$ 0.0150 | 0.0475 $\pm$ 0.0110 |
|  | Min, Max      | 0.0312, 0.0700      | 0.0282, 0.0535      | 0.0215, 0.0639      | 0.0374, 0.0644      |
| $AUC_{0-24h}$ (ng $\times$ h/mL)                       | Mean $\pm$ SD | 5070 $\pm$ 979      | 5410 $\pm$ 1070     | 6780 $\pm$ 1660     | 6990 $\pm$ 1010     |
|  | Min, Max      | 3900, 6240          | 3970, 6540          | 4680, 8410          | 5700, 8050          |
| $AUC_{0-24h}$ (h $\times$ ng/mL/ $\mu$ g) <sup>a</sup> | Mean $\pm$ SD | 0.2277 $\pm$ 0.0360 | 0.2866 $\pm$ 0.0854 | 0.3550 $\pm$ 0.0965 | 0.3872 $\pm$ 0.0688 |
|  | Min, Max      | 0.1717, 0.2584      | 0.1528, 0.3694      | 0.1801, 0.4570      | 0.2848, 0.4615      |
| $AUC_{0-10h}$ (ng $\times$ h/mL)                       | Mean $\pm$ SD | 3940 $\pm$ 637      | 3700 $\pm$ 493      | 4220 $\pm$ 1060     | 4160 $\pm$ 704      |
|  | Min, Max      | 3160, 4750          | 3140, 4140          | 3090, 5270          | 3230, 5000          |
| $AUC_{0-t}$ (ng $\times$ h/mL)                         | Mean $\pm$ SD | 5070 $\pm$ 982      | 5410 $\pm$ 1060     | 6810 $\pm$ 1660     | 7020 $\pm$ 1010     |
|  | Min, Max      | 3880, 6240          | 3980, 6540          | 4710, 8410          | 5750, 8110          |
| $AUC_{0-inf}$ (ng $\times$ h/mL)                       | Mean $\pm$ SD | 5220 $\pm$ 1050     | 6150 $\pm$ 1580     | 8750 $\pm$ 2000     | 10200 $\pm$ 1440    |
|  | Min, Max      | 3960, 6420          | 4060, 7910          | 5570, 10500         | 8310, 11900         |
| R. Area (%)  | Mean $\pm$ SD | 2.78 $\pm$ 1.06     | 10.76 $\pm$ 6.34    | 22.13 $\pm$ 5.34    | 30.57 $\pm$ 10.55   |
|  | Min, Max      | 1.59, 4.36          | 1.93, 17.23         | 15.54, 29.16        | 17.10, 48.53        |
| $K_{el}$ (1/h)   | Mean $\pm$ SD | 0.1440 $\pm$ 0.0157 | 0.0957 $\pm$ 0.0319 | 0.0584 $\pm$ 0.0095 | 0.0479 $\pm$ 0.0147 |
|  | Min, Max      | 0.1208, 0.1592      | 0.0684, 0.1484      | 0.0463, 0.0715      | 0.0259, 0.0709      |
| $T_{1/2}$ (h)  | Mean $\pm$ SD | 4.87 $\pm$ 0.562    | 7.80 $\pm$ 2.15     | 12.1 $\pm$ 2.06     | 15.8 $\pm$ 5.79     |
|  | Min, Max      | 4.35, 5.74          | 4.67, 10.1          | 9.69, 15.00         | 9.78, 26.8          |
| $Vz/F$ (mL/kg) <sup>b</sup>                            | Mean $\pm$ SD | 332 $\pm$ 43.8      | 433 $\pm$ 37.0      | 512 $\pm$ 143       | 531 $\pm$ 145       |
|  | Min, Max      | 261, 376            | 380, 478            | 383, 731            | 390, 793            |
| $Cl/F$ (mL/h) <sup>b</sup>                             | Mean $\pm$ SD | 4380 $\pm$ 821      | 3500 $\pm$ 1690     | 2420 $\pm$ 1110     | 1820 $\pm$ 380      |
|  | Min, Max      | 3700, 5730          | 2430, 6410          | 1750, 4670          | 1520, 2550          |
| $Cl_{r0-24h}$ (mL/h)                                   | Mean $\pm$ SD | 3150 $\pm$ 1700     | 1640 $\pm$ 1060     | 827 $\pm$ 404       | 346 $\pm$ 134       |
|  | Min, Max      | 854, 5830           | 860, 3490           | 533, 1610           | 123, 470            |
| $Fe_{0-24h}$ (%)                                       | Mean $\pm$ SD | 71.09 $\pm$ 42.78   | 40.46 $\pm$ 9.62    | 26.52 $\pm$ 5.29    | 13.57 $\pm$ 6.58    |
|  | Min, Max      | 20.48, 150.22       | 26.82, 53.37        | 19.50, 33.57        | 4.94, 21.68         |

<sup>a</sup> Dose normalized

<sup>b</sup> Normalized by subject's body weight in kg.

$Cl/F$ : apparent total body clearance,  $Fe$ : Fraction (in percent) excreted in urine,  $Ln$ : Natural logarithm,  $CV$ : coefficient of variation,  $Vz/F$ : apparent volume of distribution based on the terminal elimination phase.

The applicant's primary statistical analysis describe above was done using the dose-normalized  $C_{max}$  and  $AUC_{0-24h}$ . This analysis seems inappropriate when considering the fact that the dose

administered to patients is weight normalized (mcg/kg). This analysis was thus repeated, by first Ln transforming the AUC<sub>0-24h</sub> without dose-normalization, and subsequently determining the AUC<sub>0-24h</sub> ratios of geometric means for Mild/Control, Moderate/Control and Severe/Control. This ratios of least-squares geometric means indicated that compared to subjects with normal renal function, subjects with mild, moderate, or severe renal impairment had average respective increases in systemic exposure (AUC<sub>0-24h</sub>) of 7%, 32%, and 39% (Table 27).

**Table 27** Treatment comparison for non-dose-normalized parameters after ln-transformation in study 1101.

| <b>Summary of Statistical Analysis for the Primary Endpoints</b> |                 |           |           |           |          |                |
|--|-----------------|-----------|-----------|-----------|----------|----------------|
| <b>Parameter</b>   | <b>Source</b>   | <b>DF</b> | <b>SS</b> | <b>MS</b> | <b>F</b> | <b>Pr&gt;F</b> |
| Ln(C <sub>max</sub> )  | Model           | 3         | 0.215     | 0.072     | 1.37     | 0.2821         |
|  | Error           | 19        | 0.992     | 0.052     |          |                |
|  | Corrected total | 22        | 1.207     |           |          |                |
| Ln(AUC <sub>0-24h</sub> )  | Model           | 3         | 0.451     | 0.150     | 3.53     | 0.0349         |
|  | Error           | 19        | 0.810     | 0.043     |          |                |
|  | Corrected total | 22        | 1.261     |           |          |                |

| <b>Parameter</b>       | <b>Least-Square Means</b> |                        | <b>Treatment Comparison</b> | <b>Ratio of Least-square Means(%)</b> | <b>90% Geometric C.I.</b> |              |
|------------------------|---------------------------|------------------------|-----------------------------|---------------------------------------|---------------------------|--------------|
|                        | <b>Control</b>            | <b>Impaired Cohort</b> |                             |                                       | <b>Lower</b>              | <b>Upper</b> |
| Ln C <sub>max</sub>    | 964                       | Mild: 735              | Mild/Control                | 76.27                                 | 60.03                     | 96.90        |
|                        |                           | Moderate: 898          | Moderate/Control            | 93.14                                 | 74.13                     | 117.02       |
|                        |                           | Severe: 843            | Severe/Control              | 87.40                                 | 69.56                     | 109.81       |
| Ln AUC <sub>0-24</sub> | 4990                      | Mild: 5320             | Mild/Control                | 106.61                                | 85.87                     | 132.36       |
|                        |                           | Moderate: 6600         | Moderate/Control            | 132.31                                | 107.65                    | 162.62       |
|                        |                           | Severe: 3930           | Severe/Control              | 138.76                                | 112.90                    | 170.55       |

Consistent with the observed increase in systemic exposure with increasing renal dysfunction, mean CL/F and Cl<sub>r0-24</sub> were reduced in subjects with renal impairment (Table 28). PBCD34+ levels appeared to increase more slowly in the renal impairment cohorts, but due to the small sample size and absence of data between the 10-24 h time-points, definitive conclusions regarding the effect of renal impairment on response can not be assessed. Injection site reactions and GI effects were all mild to moderate in severity in all subjects. The frequency and severity of GI effects and injection site reactions did not increase with severity of renal impairment. Overall, the AE profile in subjects with renal impairment was similar to that observed in control subjects.

**Table 28** Clearance and excretion of plerixafor in healthy subjects with normal renal function and renal impairment, after a single 240- $\mu$ g/kg dose of plerixafor in Study 1101 (Mean  $\pm$  SD)

| PK Parameter               | Control<br>N = 6  | Mild<br>N = 6    | Moderate<br>N = 5 | Severe<br>N = 6  |
|----------------------------|-------------------|------------------|-------------------|------------------|
| Cl <sub>0-24</sub> (mL/hr) | 3150 $\pm$ 1700   | 1640 $\pm$ 1060  | 827 $\pm$ 404     | 346 $\pm$ 134    |
| Fe <sub>0-24</sub> (%)     | 71.09 $\pm$ 42.78 | 40.46 $\pm$ 9.62 | 26.52 $\pm$ 5.29  | 13.57 $\pm$ 6.58 |

### 2.3.2.3 Hepatic impairment

Hepatic clearance is not a major pathway of elimination and a hepatic impairment study was not required or conducted.

### 2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of plerixafor and its metabolites in the milk of humans or animals were provided. The potential for plerixafor-induced embryo-fetal toxicity was evaluated in a GLP reproductive toxicity study in rats. There was evidence of embryoletality (increased incidence of resorption), fototoxicity (decreased Fetal weights and indications of retardation in skeletal development), and fetal abnormalities at the 15 mg/kg/day dose level. Based on these results, plerixafor administration is considered to present a risk to the fetus. The risk of plerixafor administration on male and female fertility is unknown.

## 2.4 EXTRINSIC FACTORS

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

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of plerixafor.

### 2.4.2 Drug-drug interactions

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Since plerixafor does not undergo metabolism, the potential for *in vivo* drug-drug interactions with drugs that are substrates, inhibitors or inducers of cytochrome P450 isozymes appears to be remote. The applicant did not assess whether plerixafor is a substrate or inhibitor of P-glycoprotein (P-gp), and therefore, the potential for *in vivo* drug-drug interactions with P-gp substrates and inhibitors remains unknown.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Plerixafor was screened *in vitro* using human liver microsomes, and was found not to be a substrate for CYP450 enzymes.

Study report GT-249-PK-1 and report AMD 0038 evaluated the *in vitro* metabolic stability of plerixafor in human liver microsomes. Testosterone 6 $\beta$ -hydroxylation was used as a marker substrate reaction for human liver microsomes. Plerixafor was incubated at 0.1  $\mu$ M, 1.0  $\mu$ M and 10  $\mu$ M in human liver microsomes from a mixed gender pool of 50 donors. No loss of plerixafor was observed in the incubations (with and without co-factors), demonstrating that plerixafor is metabolically stable at the concentrations tested. The intrinsic clearance in human liver microsomes with and without co-factor was determined to be < 4.5  $\mu$ L/min/mg protein.

### 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

#### In-vitro induction

The results from the applicant's *in vitro* studies indicate that plerixafor is not an inducer of CYP2B6, CYP1A2 and CYP3A4 at the concentration range (0.1, 1.0, and 10  $\mu$ M) studied.

The applicant determined the effects of plerixafor on CYP450 isozyme activity and mRNA content in three separate primary human hepatocyte cultures (Hu689, Hu693 and Hu695) (study report DMPK-08-R001) (Table 29). Hepatocyte cultures were treated for three consecutive days with plerixafor (0.1, 1.0, and 10  $\mu$ M) and the specific activities and mRNA content for CYP1A2, CYP2B6 and CYP3A4 were determined. Results indicated no plerixafor mediated mRNA induction for all three CYP450 isozymes at the concentrations examined. In addition there was no significant induction responses (> 40% of the adjusted positive control) for CYP2B6, CYP1A2 and CYP3A4 at the concentrations investigated. Based on the FDA Drug-drug interaction guidance, a drug that produces a change that is equal to or greater than 40% of the positive control can be considered as an enzyme inducer.

**Table 29** Induction potential of plerixafor in human hepatocytes: Summary of enzyme activity (% adjusted positive control) after treatment with plerixafor.

| Treatment                    | CYP1A2 |       |       | CYP2B6 |       |       | CYP3A4 |       |       |
|------------------------------|--------|-------|-------|--------|-------|-------|--------|-------|-------|
|                              | Hu689  | Hu693 | Hu695 | Hu689  | Hu693 | Hu695 | Hu689  | Hu693 | Hu695 |
| 3-MC (2 $\mu$ M)             | 100    | 100   | 100   | 0.03   | 7.8   | 2.0   | -7.8   | -2.6  | -0.54 |
| Phenobarbital (1000 $\mu$ M) | 1.1    | 0.84  | 2.0   | 100    | 100   | 100   | 43.4   | 27.5  | 34.7  |
| Rifampicin (10 $\mu$ M)      | 0.40   | 1.0   | 1.9   | 15.2   | 46.6  | 73.7  | 100    | 100   | 100   |
| Plerixafor (0.1 $\mu$ M)     | 0.64   | 0.25  | 0.1   | 0.71   | -0.24 | 2.1   | -0.30  | 0.67  | 3.6   |
| Plerixafor (1 $\mu$ M)       | 0.03   | 0.34  | 0.25  | -0.14  | -0.05 | -1.14 | -1.7   | -3.2  | 0.32  |
| Plerixafor (10 $\mu$ M)      | -0.07  | 0.38  | 0.50  | -0.02  | -1.47 | -0.17 | -2.2   | -3.4  | 0.20  |

#### In-vitro inhibition

The results from the applicant's *in vitro* studies indicate that plerixafor is not an inhibitor of CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

The applicant evaluated the ability of plerixafor to inhibit the major CYP enzymes in human liver microsomes, with the aim of ascertaining the potential for plerixafor to inhibit the metabolism of other drugs (Study report XT055036). The inhibitory potencies of AMD3100 were determined *in vitro* by measuring the activity of each CYP enzyme in human liver microsomes in the presence or absence of plerixafor. Under the experimental conditions examined, there was no evidence to indicate that AMD3100 is a direct inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (as measured by testosterone 6 $\beta$ -hydroxylation

and midazolam 1'-hydroxylation), as no inhibition was observed at the highest concentration examined (100 µM). The IC<sub>50</sub> values for these enzymes were reported as >100 µM. Under the experimental conditions examined, there was no evidence that AMD3100 caused metabolism-dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (as measured by testosterone 6β-hydroxylation and midazolam 1'-hydroxylation), as an increase in inhibition was not observed upon pre-incubation. In study report AOM0067, the IC<sub>50</sub>s of AMD3100 mediated inhibition of the cytochrome P450 isoforms CYP1A2, 2C9, 2C19, 2D6, and 3A4) were determined using fluorescent substrates in conjunction with the supersome system. AMD3100 did not inhibit any of the tested isoforms more than 15 % at the highest concentration tested, 100 µM, indicating that its IC<sub>50</sub> is well above 100 µM for all isoforms. The 100 µM concentration of plerixafor tested is well above the C<sub>max</sub> (1.7 µM) for plerixafor obtained from clinical studies at the 240 mcg/kg dose. The results from the applicant's studies are consistent with the FDA guidance. The I/IC<sub>50</sub> ratios, estimated from the C<sub>max</sub>/IC<sub>50</sub> values (1.7 µM/100 µM) are < 0.1, which indicates that the potential for an *in vivo* drug-drug interaction is remote.

**Table 30** Summary of results: In vitro evaluation of plerixafor as an inhibitor of CYP450 enzymes.

| Enzyme   | CYP Reaction                             | Direct inhibition          |   | Metabolism-dependent inhibition |   | Potential for metabolism-dependent inhibition |
|----------|--|----------------------------|---|---------------------------------|---|---|
|          |  | Zero-minute pre-incubation |   | 30-minute pre-incubation        |   |   |
|          |  | IC <sub>50</sub> (µM)      | Maximum inhibition at 100 µM (%) <sup>a</sup> | IC <sub>50</sub> (µM)           | Maximum inhibition at 100 µM (%) <sup>a</sup> |   |
| CYP1A2   | Phenacetin <i>O</i> -deethylation        | >100                       | NA  | >100                            | NA  | No  |
| CYP2C9   | Diclofenac 4'-hydroxylation-plate 1      | >100                       | NA  | >100                            | NA  | No  |
| CYP2C9   | Diclofenac 4'-hydroxylation-plate 2      | >100                       | NA  | >100                            | NA  | No  |
| CYP2C19  | <i>S</i> -Mephenytoin 4'-hydroxylation   | >100                       | NA  | >100                            | NA  | No  |
| CYP2D6   | Dextromethorphan <i>O</i> -demethylation | >100                       | NA  | >100                            | NA  | No  |
| CYP3A4/5 | Testosterone 6β-hydroxylation            | >100                       | 2.6   | >100                            | 5.9   | No  |
| CYP3A4/5 | Midazolam 1'-hydroxylation               | >100                       | NA  | >100                            | NA  | No  |

Notes Values were calculated using the average data obtained from duplicates for each incubation condition. The IC<sub>50</sub> values were calculated using XLfit.

a Maximum inhibition (%) is calculated using the following formula and data for the highest concentration of test article for which usable data were collected (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent of solvent control activity

NA Inhibition was not observed at the highest concentration of AMD3100 studied (100 µM) as indicated by a "percent of solvent control activity" greater than 100%.

### In-vivo evaluation of inhibition

The *in-vivo* inhibition of CYP450 isozymes by plerixafor was not investigated.

#### 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The ability of plerixafor to act as a substrate, inhibitor and inducer of P-glycoprotein was not evaluated. This will be addressed in the OCP phase 4 commitments.

#### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

None have been identified.

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

All clinical trials supporting the efficacy and safety of plerixafor in cancer patients were conducted with a dosing regimen consisting of plerixafor in conjunction with G-CSF in (protocols: 3101, 3102, 2106 and 2101). The dosing regimen was chosen based on results from clinical studies which indicated that plerixafor in conjunction with G-CSF elicited the highest absolute CD34+ cell level in peripheral blood, compared to either plerixafor or G-CSF administration alone (Protocol 1003 and 1004). The proposed daily dosing regimen involves administration of G-CSF at 10 to 11 hours after the administration of a single dose of plerixafor. There is no preclinical or clinical evidence suggesting a PK drug-drug interaction with plerixafor and G-CSF, and the interaction potential between these agents has not been formally studied.

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

Nonclinical data presented indicate that plerixafor has a low potential for involvement in CYP450-dependent drug-drug interactions. Formal clinical drug-drug interactions studies were not included in the current NDA submission.

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

Not applicable.

**2.5.2 What is the composition of the to-be-marketed formulation?**

Plerixafor injection, 20 mg/ml, (proposed trade name: Mozobil™) is a sterile, preservative-free, clear, colorless to pale yellow, isotonic, 20 mg/ml solution of plerixafor 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.

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**Table 31** The composition of plerixafor injection, 20 mg/mL (to-be-marketed formulation).

| Component                       | Quality Standard | Function       | Quantity per Millilitre            | Quantity per Vial <sup>b</sup>     | Quantity per Batch                 |
|---------------------------------|------------------|----------------|------------------------------------|------------------------------------|------------------------------------|
| Plerixafor <sup>a</sup>         | In-house         | Drug substance | 20.0 mg                            | 24.0 mg                            | (b) (4)                            |
| Sodium chloride                 | PhEur and USP-NF | (b) (4)        | (b) (4)                            | 5.9 mg                             | (b) (4)                            |
| Hydrochloric acid, concentrated | PhEur and USP-NF | pH adjustment  | Sufficient to adjust to pH 6.0-7.5 | Sufficient to adjust to pH 6.0-7.5 | Sufficient to adjust to pH 6.0-7.5 |
| Sodium hydroxide                | PhEur and USP-NF | pH adjustment  | Sufficient to adjust to pH 6.0-7.5 | Sufficient to adjust to pH 6.0-7.5 | Sufficient to adjust to pH 6.0-7.5 |
| Water for injection             | PhEur and USP-NF | Diluent        | Sufficient to reach (b) (4)        | Sufficient to reach 1.20 ml        | Sufficient to reach (b) (4)        |
| (b) (4)                         | PhEur and USP-NF | (b) (4)        | Sufficient                         | Sufficient                         | Sufficient                         |

USP-NF: United States Pharmacopoeia - National Formulary; PhEur – European Pharmacopoeia

<sup>a</sup> The weight of plerixafor used is corrected for water content and purity.

<sup>b</sup> These values are calculated for the label claim of 1.2 ml (b) (4)

(b) (4)

### 2.5.3 What moieties should be assessed in bioequivalence studies?

Plerixafor should be assessed in human plasma.

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

Plerixafor is administered via SC injection and therefore a food-effect BA study is not required.

### 2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Not applicable.

## 2.6 ANALYTICAL SECTION

### 2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

PK results from Studies AMD3100-1002, AMD3100-C201, AMD3100-2106, and AMD3100-1101 were used to support pharmacokinetic claims. All of the studies listed above except AMD3100-1002 (which used the HPLC ECD method) utilized two liquid-chromatography/Mass-Spectrometric/Mass-Spectrometric (LC-MS/MS) methods to assess the plasma and urine concentrations of plerixafor parent drug from human samples. Analysis for only the parent drug in plasma and urine was appropriate as plerixafor is not metabolized in humans.

## 2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Both LC/MS/MS assays (b) (4) and the HPLC-ECD (b) (4) were validated. These bioanalytical methods were acceptable, except for the deficiencies in the HPLC-ECD method described below.

### **Bioanalytical Methods Used:**

Two validated bioanalytical methods were used for the determination of plasma plerixafor concentrations: high performance liquid chromatography with electrochemical detection (HPLC-ECD) (b) (4) and liquid chromatography with tandem mass spectrometry (LC/MS/MS) (b) (4). Due to concerns raised in audits of the testing laboratory (b) (4) some of the data obtained with the HPLC-ECD method (studies 98-01, 2001, and 1005) are not used by the applicant to support statements concerning the bioavailability or PK of plerixafor, and were provided by the applicant for informational use only. Audit deficiencies were not identified in the bioanalytical data for study 1002 which also utilized the HPLC-ECD bioanalytical method (b) (4). Due to the audit deficiencies identified with the HPLC-ECD method, the LC-MS/MS method (b) (4) was subsequently used for analysis of plasma samples from two phase 2 studies in cancer patients (C201 and 2106), and a phase 1 study in subjects with renal impairment (1101), and samples from patients with renal impairment from the compassionate use program (CUP001). The LC-MS/MS method (b) (4) for the analysis of urine samples was also validated by (b) (4) and used in the analysis of urine samples from studies 1101 and C201. Data from urine were not used to support the NDA submission.

### **LC/MS/MS (b) (4) – Plasma Plerixafor**

In some studies human urine samples were assayed for plerixafor concentrations; however the sponsor only used the plasma data to support the PK of plerixafor. The validated LC/MS/MS method (Study reference 06-2450 in the table below) used to quantify the plasma plerixafor concentrations utilized a stable-label internal standard, (b) (4), to control for variability in sample preparation, injection volume and detector response. Analysis of plerixafor in plasma was appropriate, based on the characteristic RBC/plasma ratio for plerixafor. The validated quantitative range of plerixafor concentrations was from 5.00 ng/mL to 1000 ng/mL, which covers the range of plasma concentrations obtained in the clinical protocols.

The LC/MS/MS method (study reference 06-2450) validation included the evaluation of specificity, sensitivity, reproducibility, carryover, accuracy, precision, recovery, and stability. The freeze/thaw stability of plerixafor in plasma was 3 cycles prior to sample extraction and analysis, and the accuracies for plerixafor were -1% and +3 % for the low (12.5 ng/mL) and high (750 ng/mL) quality control (QC) samples with corresponding precisions at 2% for both QC levels. The post preparative stability of the samples was for up to 7 days stored at 2 °C to 8 °C. The long term stability of plerixafor in plasma was 349 days. The accuracy and precision of the analytical methods were < 15%, with all validation results meeting the validation criteria of ± 15% relative error (RE) and ≤ 15% relative standard deviation (RSD).

## HPLC-ECD (b) (4) – Plasma Plerixafor:

The HPLC-ECD methodology (study reference 980984/JGL in the table below) was used to assay plasma samples from protocol AMD3100-1002 for plerixafor concentrations. This method used (b) (4) as the internal Standard, and validation included the assessment of specificity, sensitivity, reproducibility, carryover, accuracy, precision, recovery, and stability. Long term stability of AMD3100 in human plasma, using replicate low and high QC stability samples, maintained at a nominal temperature of -22°C for a designated period showed that plerixafor is stable at -22 °C for 105 days. Plerixafor was stable in human plasma for 4.0 hours at 22°C, and stable in human plasma unextracted following 3 freeze/thaw cycles. This method was validated to determine plerixafor concentrations in human plasma has met the requirements of specificity, sensitivity, linearity, recovery, precision and accuracy and dilution integrity, spanning a concentration range of 5.11 ng/mL to 249.39 ng/mL.

**Table 32** Validation parameters of bioanalytical methods

| Study Reference | Matrix | Assay  | Assay Volume (µL) | LLOQ <sup>a</sup> (ng/mL) | ULOQ <sup>b</sup> (ng/mL) | QC <sup>c</sup> Levels (ng/mL)      | Intra-Run                 |                           | Inter-Run                 |                           | LTS <sup>d</sup> (days) |
|-----------------|--------|--------|-------------------|---------------------------|---------------------------|-------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------------------|
|                 |        |        |                   |                           |                           |                                     | RE <sup>e</sup> range (%) | CV <sup>f</sup> range (%) | RE <sup>e</sup> range (%) | CV <sup>f</sup> range (%) |                         |
| 980984/JGL      | plasma | LC-ECD | 1000              | 5.11                      | 249.39                    | 5.11, 14.92, 114.48, 200.33, 746.13 | -3.5 to -1.6              | 1.1 to 5.7                | -2.7 to -1.4              | 0.6 to 3.5                | -                       |
| 06-2450         | plasma | LC-MS  | 200               | 5.00                      | 1000                      | 12.5, 75.0, 750, 2000               | -3 to 11                  | 1 to 5                    | -2 to 3                   | 1 to 4                    | 349                     |
| 06-2490         | urine  | LC-MS  | 20                | 100                       | 10000                     | 250, 2500, 7500, 20000              | -8 to 1                   | 1 to 5                    | -4 to -1                  | 2 to 4                    | 365                     |

<sup>a</sup>LLOQ = lower limit of quantitation

<sup>b</sup>ULOQ = upper limit of quantitation

<sup>c</sup>QC = quality control

<sup>d</sup>LTS = long term stability

<sup>e</sup>RE = relative error

<sup>f</sup>CV = coefficient of variation

### 3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included.

(b) (4)

**3 Page(s) of Draft Labeling are Withheld after this page as B4 (CCI/TS)**

## 4 APPENDICES

### 4.1 INDIVIDUAL STUDY REVIEWS

#### 4.1.1 Individual study report reviews not included.

### 4.2 QT REVIEW

Title: Escalating doses of plerixafor in healthy subjects. (Investigator Sponsored). (Ongoing Study H0156 – final study report to be submitted by sponsor following NDA action date.)

Clinical Phase: 1

Objectives: The primary objective of the study is to assess the safety and tolerability profile of plerixafor

when administered in escalating higher doses (240, 320, 400, and 480 µg/kg) in humans.

The secondary objectives are to:

1. Determine the peak CD34+ cell mobilization kinetics of plerixafor in successive cohorts of healthy subjects receiving 2 different doses of plerixafor
2. Determine if doses of plerixafor greater than 340 µg/kg increase the number of PB CD34+ cells mobilized into the circulation of healthy volunteers
3. Further study the phenotypic and immunological properties of plerixafor mobilized cells

Design: This Phase 1, healthy volunteer study is being conducted in order to examine the safety, efficacy, and most effective dose of plerixafor in mobilizing CD34+ progenitor cells into peripheral circulation for collection and subsequent allogeneic transplantation. In addition, this study is designed to examine the effects of plerixafor on cardiac repolarization (QT/QTc interval), arrhythmogenic potential using telemetry, and the pharmacokinetics (PK) of plerixafor at high doses ( $\geq 400$  µg/kg). This brief report includes cardiac and PK data that were available as of 01 November 2007.

After enrollment, subjects will receive their first dose of plerixafor. The amount of study drug administered is based on subject's weight, obtained within 30 days of dosing. Subjects are reweighed immediately prior to dosing and the dose is recalculated in the event that a subject's weight has changed more than 5% from the previous measurement. Plerixafor is administered subcutaneously (SC) in the abdominal area by nurse or physician in the in-patient unit of the hospital.

Vital signs are measured at baseline (within 3 months prior to plerixafor administration) and subjects are observed for 15 to 30 minutes post-dose. Complete blood count (CBC) and flow cytometry for CD34+ cells are performed prior to each dose of plerixafor and at 2, 4, 6, 8, 10, 12, 14, 18 and 24 hours post-dose (Figure 4-1).

A baseline and pre-dose EKG is performed on all subjects in Dose levels 2 and 3. In addition, the protocol was amended after Dose level 2 was completed such that all subjects receiving 400 and 480 µg/kg doses of plerixafor had EKGs at 8, 12, and 24 hours post-dose. As a result, the EKG data for subjects in Dose level 2 is not as comprehensive as for subjects in Dose level 3.

The protocol amendment also stipulated that subjects receiving doses of 400 and 480 µg/kg of plerixafor are monitored by continuous telemetry from 2 to 4 hours pre-dose through 24 hours post-dose, since 3 patients in a previous Phase 1 HIV study (Hendrix, 2004, *J Acquir Immune Defic Syndr*) experienced ventricular ectopy when receiving high, cumulative doses of plerixafor.

The number of subjects who achieved absolute values of QT or QTc following plerixafor administration was assessed using the following cut-off values:

1. QT or QTc > 450 ms
2. QT or QTc > 480 ms.
3. QT or QTc > 500 ms

Four (4) subjects fell into category 1, Subject 13, 15, 16, and 17 (Table 5-3). Subjects 13 and 15 had QT values of 468 ms and 456 ms at 12 and 24 hours post-dose, respectively, following an initial plerixafor dose of 400 µg/kg. Subject 16 had a QT value of 452 ms 12 hours after administration of the second plerixafor dose of 480 µg/kg. None of these subjects (13, 15, and 16) had prolonged QTc intervals above 450 ms. Of note, Subjects 15 and 16 did not show a QT interval above 450 ms when given the higher plerixafor dose of 480 µg/kg.

At baseline and pre-dose, Subject 17 had QTc values above 450 ms (457 and 452 ms, respectively). Following a 400 µg/kg dose of plerixafor, QTc values for Subject 17 were also above 450 ms: 455, 466, and 457 at 8, 12, and 24 hours post-dose, respectively.

No subjects fell into categories 2 or 3 with readings above 480 or 500 ms.

Formulation and Batch #: Not presented in study report.

Pharmacokinetics: Blood samples for PK analysis are being collected for the first 6 subjects who receive a dose of 400 µg/kg and the first 6 subjects who receive a dose of 480 µg/kg since the PK of plerixafor at lower doses has previously been evaluated. Samples for PK analysis are being collected prior to dosing and at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 24 hours post-dose.

Pharmacokinetic Analysis: PK parameters were determined from non-compartmental methods using nominal times of blood collection with WinNonlin Professional, version 5.2<sup>(b) (4)</sup>. Pre-dose concentrations below the lower limit of quantitation were set equal to 0 for the purposes of the analysis.

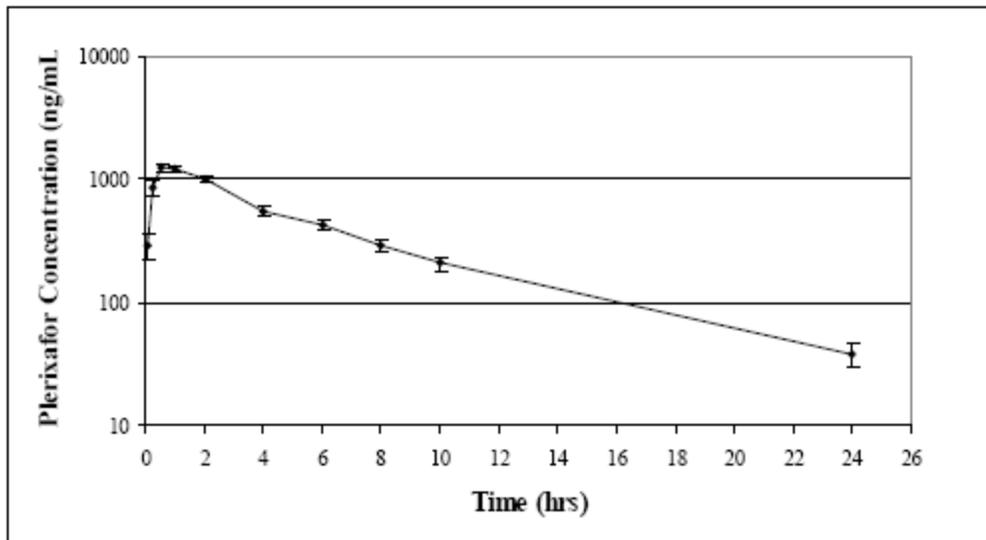
Assay Method: Not presented in study report.

#### Pharmacokinetic Results:

Blood samples were collected for the determination of plerixafor concentrations for subjects in Dose level 2 following their second plerixafor dose of 400 µg/kg. Calculated PK parameters included maximal plasma concentration (C<sub>max</sub>), terminal elimination half-life (T<sub>1/2</sub>), area under the concentration-time curve from time 0 to 10 hours post-dose (AUC<sub>0-10</sub>), and from time 0 to 24 hours post-dose (AUC<sub>0-24</sub>; Table 5-1). Systemic plerixafor exposure following a 400 µg/kg dose appeared to be linearly related to lower doses previously evaluated in clinical studies (Figure 5-1)(Hendrix, 2004, *J Acquir Immune Defic Syndr*; Hubel, 2004, Supportive Cancer Therapy; MacFarland, 2007, Blood (ASH Annual Meeting Abstracts)). Plerixafor was rapidly absorbed, reaching peak concentrations approximately 30 minutes to 1 hour post-dose, and had an elimination half-life of 5.3 ± 1.1 hours. Values of C<sub>max</sub>, AUC<sub>0-10</sub>, and AUC<sub>0-24</sub> were 1368 ± 169 ng/mL, 5930 ± 726 hr\*ng/mL, and 7670 ± 1280 hr\*ng/mL, respectively

**Table 5-1 Pharmacokinetic Data from Subjects Receiving a 400 µg/kg Dose of Plerixafor**

| ID #          | C <sub>max</sub><br>(ng/mL) | T <sub>max</sub> (hr) | T <sub>1/2</sub> (hr) | CL/F<br>(mL/hr) | V <sub>z</sub> (mL) | AUC <sub>0-10</sub><br>(hr*ng/<br>mL) | AUC <sub>0-24</sub><br>(hr*ng/<br>mL) |
|---------------|-----------------------------|-----------------------|-----------------------|-----------------|---------------------|---------------------------------------|---------------------------------------|
| 7             | 1440                        | 1.0                   | 5.8                   | 3663            | 30623               | 7149                                  | 9756                                  |
| 8             | 1320                        | 1.0                   | 7.3                   | 3731            | 39214               | 6238                                  | 8660                                  |
| 9             | 1230                        | 1.0                   | 5.0                   | 3633            | 26237               | 5754                                  | 7225                                  |
| 10            | 1190                        | 0.5                   | 4.1                   | 4402            | 25727               | 4983                                  | 6316                                  |
| 11            | 1370                        | 0.5                   | 4.8                   | 4123            | 28318               | 5577                                  | 6943                                  |
| 12            | 1660                        | 0.5                   | 4.7                   | 3088            | 20789               | 5879                                  | 7122                                  |
| <hr/>         |                             |                       |                       |                 |                     |                                       |                                       |
| <b>N</b>      | 6                           | 6                     | 6                     | 6               | 6                   | 6                                     | 6                                     |
| <b>Mean</b>   | 1368                        | 0.8                   | 5.3                   | 3773            | 28485               | 5930                                  | 7670                                  |
| <b>SD</b>     | 169                         | 0.3                   | 1.1                   | 452             | 6190                | 726                                   | 1280                                  |
| <b>Min</b>    | 1190                        | 0.5                   | 4.1                   | 3088            | 20789               | 4983                                  | 6316                                  |
| <b>Median</b> | 1345                        | 0.8                   | 4.9                   | 3697            | 27277               | 5816                                  | 7174                                  |
| <b>Max</b>    | 1660                        | 1.0                   | 7.3                   | 4402            | 39214               | 7149                                  | 9756                                  |
| <b>CV%</b>    | 12.4                        | 36.5                  | 21.7                  | 12.0            | 21.7                | 12.2                                  | 16.7                                  |



Plerixafor was rapidly absorbed, reaching peak concentrations approximately 30 minutes to 1 hour post-dose. Values of C<sub>max</sub> and AUC determined for the 400 µg/kg dose were proportionately higher than those observed at a plerixafor dose of 240 µg/kg in previous studies.

QT/QTc Results:

**Table 5-3 QT or QTc Values > 450 ms Post-Dose**

| ID #                   | Dose | Dose # | Baseline <sup>a</sup> | Pre-Dose | Post-Dose  |            |            |
|------------------------|------|--------|-----------------------|----------|------------|------------|------------|
|                        |      |        |                       |          | 8 Hours    | 12 Hours   | 24 Hours   |
| <b>QT &gt; 450 ms</b>  |      |        |                       |          |            |            |            |
| 13                     | 1    | 400    | 432                   | 428      | 448        | <b>468</b> | 408        |
| 15                     | 1    | 400    | 432                   | 432      | 424        | 424        | <b>456</b> |
| 16                     | 2    | 480    | 412                   | 412      | 416        | <b>452</b> | 428        |
| <b>QTc &gt; 450 ms</b> |      |        |                       |          |            |            |            |
| 17                     | 1    | 400    | 457                   | 452      | <b>455</b> | <b>466</b> | <b>457</b> |

<sup>a</sup> Within 3 months of plerixafor administration  
 Values > 450 ms indicated in bold.

The number of subjects who had noteworthy QT or QTc increases following plerixafor administration was assessed using the following cut-off values:

1. QT or QTc increase of > 30 ms
2. QT or QTc increase of > 60 ms

QT/QTc increases were calculated based on either the baseline or pre-dose value, whichever was lower. This is the most conservative approach, although the change from pre-dose might be considered the more appropriate comparison to accurately reflect potential drug-related QT/QTc changes. Five (5) subjects fell into category 1 and had QT or QTc increases greater than 30 ms. These were Subjects 10, 12, 13, 14, 16 (Table 5-4). Subjects 13, 14, and 16 had QT changes greater than 30 ms 12 hours following administration of plerixafor at a dose of 400 µg/kg (Subjects 13 and 14) or 480 µg/kg (Subjects 14 and 16). In addition, Subject 14 also had a QTc change of greater than 30 ms 8 hours post plerixafor administration (480 µg/kg) compared to baseline (392 ms) but not compared to pre-dose (404 ms). It is of note that the 12 hour post-dose QT values for Subject 14 following both the 400 and 480 µg/kg dose of plerixafor were actually lower (413 and 436, respectively) than the QT value recorded pre-dose (416 and 452, respectively).

Subjects 10, 12, and 14 all showed an increase in QTc greater than 30 ms 12 hours following a 400 µg/kg dose of plerixafor (445, 445, and 436 ms, respectively). Subject 12 also had a QTc value 30 ms greater than baseline at 24 hours post-dose (435 ms compared to 404 ms). However, the QTc values observed at 12 and 24 hours post-dose for Subject 12 (445 and 435 ms, respectively) were lower than the QTc value observed pre-dose (447 ms).

No subjects had an increase in QT or QTc greater than 60 ms.

**Table 5-4 QT or QTc Changes > 30 ms Post-Dose Compared to Baseline or Pre-Dose Value**

|             |      |        |                       |          | Post-Dose  |            |            |
|-------------|------|--------|-----------------------|----------|------------|------------|------------|
| ID #        | Dose | Dose # | Baseline <sup>a</sup> | Pre-Dose | 8 Hours    | 12 Hours   | 24 Hours   |
| QT > 30 ms  |      |        |                       |          |            |            |            |
| 13          | 400  | 1      | 432                   | 428      | 448        | <b>468</b> | 408        |
| 14          | 400  | 1      | 398                   | 416      | 387        | <b>413</b> | 412        |
|             | 480  | 2      | 398                   | 452      | 420        | <b>436</b> | 404        |
| 16          | 480  | 2      | 412                   | 412      | 416        | <b>452</b> | 428        |
| QTc > 30 ms |      |        |                       |          |            |            |            |
| 10          | 400  | 2      | 430                   | 407      | 396        | <b>445</b> | ND         |
| 12          | 400  | 2      | 404                   | 447      | 420        | <b>445</b> | <b>435</b> |
| 14          | 400  | 1      | 392                   | 416      | 416        | <b>436</b> | 416        |
| 14          | 480  | 2      | 392                   | 404      | <b>423</b> | 409        | 393        |

<sup>a</sup> Within 3 months of plerixafor administration.

Changes > 30 ms are indicated in bold.

Calculations performed using either the baseline or pre-dose QT/QTc value, whichever was lower.

ND= Not done

The subjects evaluated in this report were administered plerixafor doses of 400 and 480 µg/kg which are 66% and 100% greater than the recommended dose of 240 µg/kg, respectively. At these high doses, only occasional premature atrial and premature ventricular beats were noted on telemetry and none were considered to be serious by the investigator. Additionally,

asymptomatic sinus tachycardia was observed in most subjects treated with 400 and 480 µg/kg doses of plerixafor, which were usually associated with activity and resolved quickly following rest. Since these events occurred soon after plerixafor administration, they may be related to the 400 and 480 µg/kg doses of plerixafor, which are higher than the 240 µg/kg dose used in other trials.

Plerixafor was rapidly absorbed, reaching peak concentrations approximately 30 minutes to 1 hour post-dose. Values of C<sub>max</sub> and AUC determined for the 400 µg/kg dose were proportionately higher than those observed at a plerixafor dose of 240 µg/kg in previous studies (Hendrix, 2004, J Acquir Immune Defic Syndr; Hubel, 2004, Supportive Cancer Therapy; MacFarland, 2007, Blood (ASH Annual Meeting Abstracts)).

No evidence for a consistent, plerixafor associated QT/QTc prolongation was observed. A categorical analysis of the QT/QTc interval data revealed that 4 of 9 subjects had absolute QT/QTc values exceeding 450 ms post-dose. No subjects had QT/QTc values in excess of 480

ms. Similarly, 5 of 9 subjects showed increases in any QT/QTc interval greater than 30 ms from baseline or pre-dose. No subjects had QT/QTc interval increases greater than 60 ms. These effects were sporadic, occurred at different times post-dose, and occurred well after the observed Tmax of plerixafor.

#### **4.3 BIOPHARMACEUTICS STUDIES AND ANALYTICAL METHODS**

Four different formulations of Mozobil have been used in the clinic. Initial clinical trial material used in the Phase 1 as well as early Phase 2 trials was produced as a 10 mg/ml formulation supplied in 1 ml or 5 ml (in study AMD3100-2001 only) ampoules. For later Phase 2 and the Phase 3 trials, the formulations were as described above (20 mg/ml formulation filled either to 1.7 or 1.2 ml in a 2 ml vial) with slight variations in the amount of sodium chloride present in the solution. Four studies (AMD3100-2104, -2106, -2108, and -C201) and the Compassionate Use Program (AMD3100-CUP001) used both the 10 mg/ml (1 ml ampoule) and 20 mg/ml formulations. A bioequivalence study to compare the 10 mg/ml and 20 mg/ml formulations was not conducted since this formulation change occurred during the early Phase 2 clinical development. The chemical components of the 10 mg/ml and 20 mg/ml formulations are identical (aqueous solutions of plerixafor free base and NaCl, pH adjusted using HCl and with NaOH, if required). The change from the 10mg/ml to the 20mg/ml formulation was necessitated because with the 10 mg/kg formulation, the 240 µg/kg Mozobil clinical dose sometimes required injection volumes of greater than 2 ml per patient. In order to reduce potential patient discomfort associated with multiple injections or injections of large volumes subcutaneously, a higher concentration drug product was developed. Since plerixafor is administered on a per kg basis, the change in formulation strength resulted in the use of lower subcutaneous (SC) injection volumes. The results are presented in the bioavailability (BA) study, AMD3100-98-01. In this study, healthy volunteers were given oral (PO), SC, and intravenous (IV) doses of plerixafor of 10 to 160 µg/kg. Comparative bioavailability studies were not conducted with the different formulations. However, the Population Pharmacokinetic (PK) analysis of the data obtained from two Phase 2 studies in cancer patients (AMD3100-C201 and -2106) and two Phase 1 studies (AMD3100-1002 and -1101) suggest that though both the assay and formulation differed between these four studies, there are no apparent differences in concentration-time profiles.

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**Table 2.3.P.2-3: Plerixafor Injection Batch Usage for Clinical Trials**

|  |                |              |                             |                             |                             |
|--|----------------|--------------|-----------------------------|-----------------------------|-----------------------------|
| Plerixafor injection batch               | 31288          | 101340       | PD04084                     | PD05044                     | PD06031                     |
| Plerixafor API batch                     | B1047-941001   | B1047-941001 | 46771-03                    | 51768-05                    | 55814-11                    |
| Formulation                              | 10 mg/ml       | 10 mg/ml     | 20 mg/ml                    | 20 mg/ml                    | 20 mg/ml                    |
| Container                                | 1 ml ampoule   | 5 ml ampoule | 2 ml vial                   | 2 ml vial                   | 2 ml vial                   |
| Site of manufacture                      | (b) (4)        | (b) (4)      | Patheon UK Ltd, Swindon, UK | Patheon UK Ltd, Swindon, UK | Patheon UK Ltd, Swindon, UK |
| Date of manufacture                      | 9 Mar 1998     | 11 Oct 2000  | 7 Jul 2004                  | 11 Apr 2005                 | 23 Sept 2006                |
| <b>Protocol Number</b>                   | <b>Country</b> |              |                             |                             |                             |
| <b>Phase I</b>                           |                |              |                             |                             |                             |
| 98-01                                    | US             | √            |                             |                             |                             |
| AMD3100-1002                             | US             | √            |                             |                             |                             |
| AMD3100-1003                             | US             | √            |                             |                             |                             |
| AMD3100-1004                             | US             | √            |                             |                             |                             |
| AMD3100-1005                             | US             | √            |                             |                             |                             |
| AMD3100-1101                             | US             |              |                             | √                           |                             |
| MOZ00207                                 | US             |              |                             |                             | √                           |
| MOZ00707                                 | US             |              |                             |                             | √                           |
| <b>Phase II</b>                          |                |              |                             |                             |                             |
| AMD3100-2001                             | US             | √            | √                           |                             |                             |
| AMD3100-2101                             | US             | √            |                             |                             |                             |
| AMD3100-2102                             | US             | √            |                             |                             |                             |
| AMD3100-2103                             | US             | √            |                             |                             |                             |
| AMD3100-2104                             | US             | √            |                             | √                           |                             |
| AMD3100-2105                             | US             | √            |                             |                             |                             |
| AMD3100-2106                             | US             | √            |                             | √                           |                             |
| AMD3100-2108                             | US             | √            |                             | √                           |                             |
| AMD3100-2109                             | US             |              |                             | √                           |                             |
| AMD3100-2110                             | US             |              |                             | √                           |                             |
| AMD3100-2112                             | US             |              |                             | √                           | √                           |
| AMD3100-2113                             | US             |              |                             | √                           | √                           |
| AMD3100-EU21                             | DE             |              |                             | √                           |                             |
| AMD3100-C201                             | CA             | √            |                             | √                           |                             |
| <b>Phase III</b>                         |                |              |                             |                             |                             |
| AMD3100-3101                             | US, CA         |              |                             | √                           | √                           |
| AMD3100-3102                             | US, CA, DE     |              |                             | √                           | √                           |
| <b>Compassionate Use/Expanded Access</b> |                |              |                             |                             |                             |
| AMD3100-CUP001                           | US, CA, AU     | √            |                             | √                           | √                           |
| AMD3100-EU23                             | Europe         |              |                             |                             | √                           |
| MOZ00607                                 | US, CA         |              |                             |                             | √                           |

Analytical Methods:

Two validated bioanalytical methods were employed for determination of plasma plerixafor concentrations. An initial method utilized high performance liquid chromatography with electrochemical detection (HPLC-ECD). This assay was used in the analysis of samples from three Phase 1 studies in healthy volunteers (AMD3100-98-01, -1002, and -1005), and the study conducted in HIV patients (AMD3100-2001). The assay was validated and sample analyses performed at (b) (4). Audits of (b) (4) undertaken by Genzyme and a third party (b) (4) have identified deficiencies in the conduct and

reporting of results for several of these studies. The findings from these audits are consistent with those identified by the FDA in the (b) (4) warning letter to (b) (4). For this reason, PK results obtained in these studies are not used to support statements concerning the BA or PK of plerixafor, with the exception of study AMD3100-1002 where the audit findings did not identify any deficiencies in the bioanalytical data that would be of concern. PK results are included with the clinical study reports for each study, with acknowledgment of the noted audit findings.

A liquid chromatography with tandem mass spectrometry (LC-MS/MS) method was subsequently developed and validated by (b) (4), and this method has been used for analysis of plasma samples from two Phase 2 studies in cancer patients (AMD3100-C201 and -2106), a Phase 1 study in subjects with renal impairment (AMD3100-1101), and samples from pediatric patients and patients with renal impairment from the compassionate use program (AMD3100-CUP001). An assay based on this method for the analysis of urine samples was also validated by (b) (4) and used in the analysis of urine samples from studies AMD3100-1101 and -C201. No metabolites of plerixafor were identified, and all PK determinations have been based on concentrations of parent plerixafor only.

As stated above, two bioanalytical assays were developed and validated for the determination of plerixafor in human plasma. A bioanalytical assay (Study 980984/JGL) was validated using high performance liquid chromatography with electrochemical detection (LC-ECD). The method validation included the evaluation of specificity, reproducibility, accuracy, precision, sensitivity, recovery and stability. The method used liquid-liquid extraction followed by back extraction. Plasma samples were basified and the analyte and internal standard (IS), (b) (4), were extracted using (b) (4). The (b) (4)

The extracts were analyzed by HPLC with (b) (4). The response of plerixafor and its IS were monitored at +250 mV and +720 mV. The peak height ratios of plerixafor/IS were fit to a linear equation with 1/x weighting, using least squares regression. The method was validated over the concentration range of 5.11 to 249.39 ng/ml (b) (4) treated human plasma sample. The plasma samples could be analyzed with up to 10 fold dilution with blank plasma.

A second bioanalytical assay (Study 06-2450) was developed and validated using LCMS/MS. The method validation included the evaluation of specificity, sensitivity, reproducibility, carryover, accuracy, precision, recovery, and stability. The method used (b) (4) to precipitate plasma proteins and extract plerixafor and its IS (b) (4)

The resulting samples were analyzed by liquid chromatography using a (b) (4). The responses of plerixafor and IS were obtained by monitoring the MS/MS transitions of (b) (4), respectively. The peak area ratios of plerixafor/IS were fit to a quadratic equation with 1/x<sup>2</sup> weighting, using least squares regression. The method was validated over the concentration range 5.00 to 1000 ng/ml (b) (4)

human plasma. The plasma samples could be analyzed with up to 10 fold dilution with blank plasma.

A bioanalytical assay (Study 06-2490) was developed and validated for the determination of plerixafor in human urine using LC-MS/MS. The method validation included the evaluation of specificity, sensitivity, reproducibility, carryover, accuracy, precision, recovery, and stability. Human urine samples were diluted 10 fold with blank human plasma. (b) (4) was used to precipitate proteins of the diluted samples and extract plerixafor and its IS, (b) (4)

The resulting samples were analyzed by liquid chromatography using a (b) (4). The responses of plerixafor and IS were obtained by monitoring the MS/MS transitions of (b) (4), respectively. The peak area ratios of plerixafor/IS were fit to a quadratic equation with 1/x<sup>2</sup> weighting, using least squares regression. The method was validated over the concentration range 100 to 10000 ng/ml using 20 µl of human urine sample. The urine samples could be analyzed with up to 10 fold dilution with blank urine. A tabular summary of the performance characteristics for the plasma and urine analytical methods is presented in Table 2.7.1-1 below.

Table 2.7.1-1 Summary of Bioanalytical Method Performance

| Study Reference | Matrix | Assay  | Assay Volume (µL) | LLOQ <sup>a</sup> (ng/mL) | ULOQ <sup>b</sup> (ng/mL) | QC <sup>c</sup> Levels (ng/mL)      | Intra-Run                 |                           | Inter-Run                 |                           | LTS <sup>d</sup> (days) |
|-----------------|--------|--------|-------------------|---------------------------|---------------------------|-------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------------------|
|                 |        |        |                   |                           |                           |                                     | RE <sup>e</sup> range (%) | CV <sup>f</sup> range (%) | RE <sup>e</sup> range (%) | CV <sup>f</sup> range (%) |                         |
| 980984/JGL      | plasma | LC-ECD | 1000              | 5.11                      | 249.39                    | 5.11, 14.92, 114.48, 200.33, 746.13 | -3.5 to -1.6              | 1.1 to 5.7                | -2.7 to -1.4              | 0.6 to 3.5                | -                       |
| 06-2450         | plasma | LC-MS  | 200               | 5.00                      | 1000                      | 12.5, 75.0, 750, 2000               | -3 to 11                  | 1 to 5                    | -2 to 3                   | 1 to 4                    | 349                     |
| 06-2490         | urine  | LC-MS  | 20                | 100                       | 10000                     | 250, 2500, 7500, 20000              | -8 to 1                   | 1 to 5                    | -4 to -1                  | 2 to 4                    | 365                     |

<sup>a</sup>LLOQ = lower limit of quantitation  
<sup>b</sup>ULOQ = upper limit of quantitation  
<sup>c</sup>QC = quality control  
<sup>d</sup>LTS = long term stability  
<sup>e</sup>RE = relative error  
<sup>f</sup>CV = coefficient of variation

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#### 4.4 PHARMACOMETRICS REVIEW

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**OFFICE OF CLINICAL PHARMACOLOGY:  
PHARMACOMETRIC REVIEW**

|                                 |                              |
|---------------------------------|------------------------------|
| <b>Application Number</b>       | 22311                        |
| <b>Submission Number (Date)</b> | June 16, 2008                |
| <b>Clinical Division</b>        | DDOP                         |
| <b>Primary PM Reviewer</b>      | Christoffer W. Tornoe, Ph.D. |
| <b>Secondary PM Reviewer</b>    | Yaning Wang, Ph.D.           |

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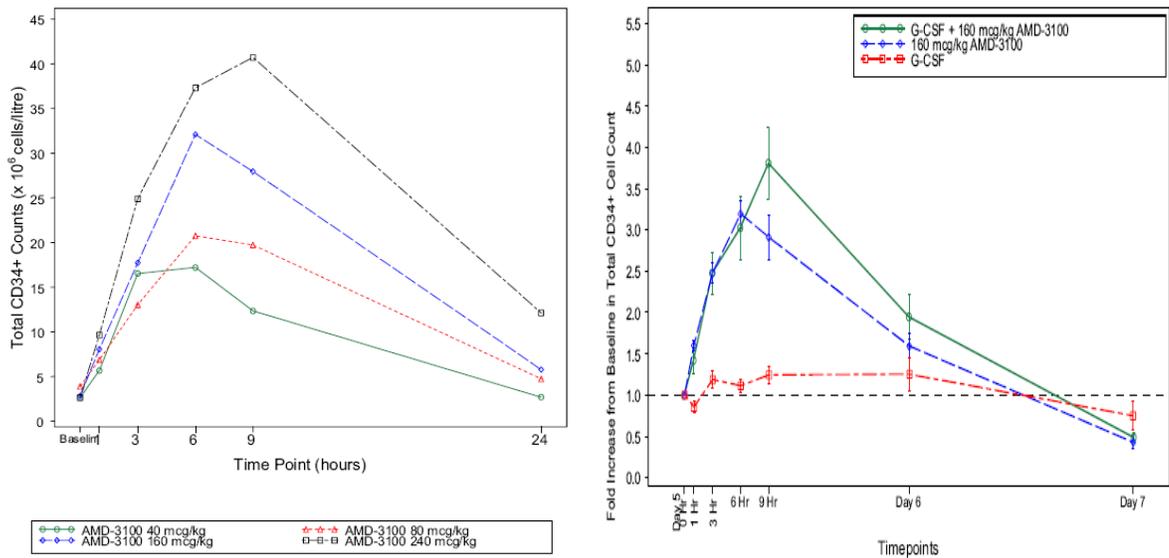
# 1 SUMMARY OF FINDINGS

## 1.4 Key Review Questions

The purpose of this review is to address the following key questions.

### 1.4.1 Is there evidence of exposure-response for effectiveness?

Yes, a dose-proportional increase in CD34+ cells was observed when plerixafor alone was given at doses from 40 mcg/kg to 240 mcg/kg in healthy subjects (study AMD3100-1002) (see left Figure below). When given to healthy subjects after a 4-day regimen of G-CSF, administration of plerixafor and G-CSF produced higher CD34+ cell counts than treatment with either plerixafor alone or G-CSF alone 9 hours after the first dose of plerixafor on the 5<sup>th</sup> day (study AMD3100-1003) (see right Figure below).



**Figure:** (Left) Mean CD34+ cell count following plerixafor doses of 40 (green), 80 (red), 160 (blue), and 240 (black) mcg/kg in study AMD3100-1002. (Right) Mean fold increase in CD34+ cell count following G-CSF (red), 160 mcg/kg plerixafor (blue), and G-CSF+160 mcg/kg plerixafor (green) in study AMD3100-1003.

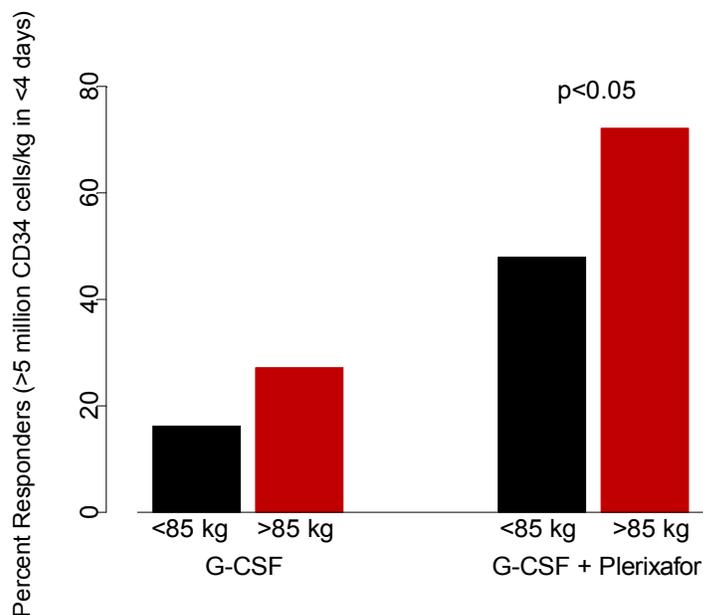
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#### 1.4.2 Is the proposed 240 mcg/kg plerixafor dose adequate for all patients?

No, the 240 mcg/kg dosing leads to increasing exposure (AUC) with increasing body weight. In order to match exposure across body weights, the plerixafor dose should either administer:

- 1) 240 mcg/kg for patients above 85 kg and 20 mg (fixed dose) for patients below 85 kg.
- 2) Fixed dose of <sup>(b)</sup><sub>(4)</sub> mg across all body weights

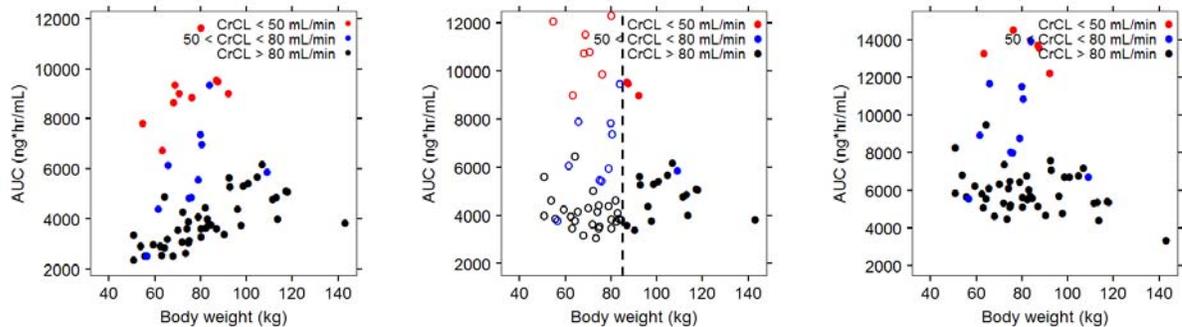
The response rates for G-CSF + Plerixafor treated patients were found to be significantly lower in patients weighing less than 85 kg (48% (95% CI 36-60%)) compared to patients  $\geq$  85 kg (72% (95% CI 61-82%)) in non-Hodgkin's lymphoma (NHL) patients (study 3101) (see Figure below). The same numerical trend was seen for G-CSF treated patients however not statistical significant.



**Figure1:** Percent responders for patients above or below the median body weight of 85 kg in non-Hodgkin's lymphoma patients (study 3101) receiving G-CSF (black bars) and G-CSF+Plerixafor (red bars).

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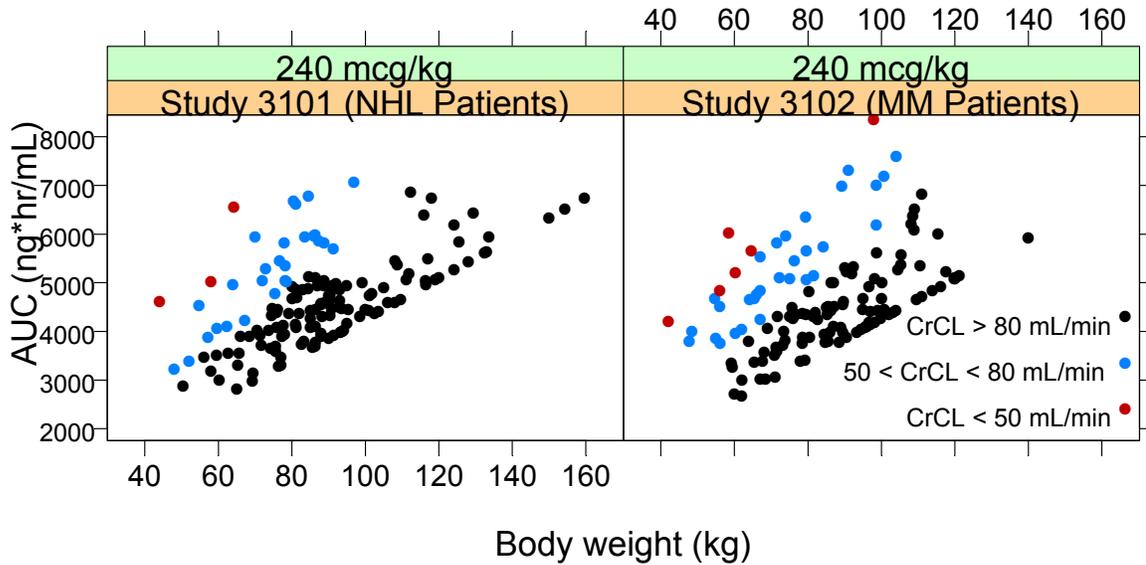
Given the lower response rate observed in lighter patients and the clear exposure-response relationship observed in studies AMD3100-1002 and -1003, it is reasonable to assume a higher exposure in these patients will improve the response rate and the higher exposure achieved in heavier patients can serve as the target exposure level with acceptable safety profile (see Left graph in Figure below). In order to match the exposure in lighter patients to that in heavier patients, the absolute dose should be capped (at the lower end) to that of an 85 kg patient ( $240 \text{ mcg/kg} \times 85 \text{ kg} \sim 20 \text{ mg}$ ) (median body weight in study 3101 and 3102 was 85 kg) (see Middle graph in Figure below). Alternatively, a 30 mg fixed plerixafor dose can be administered to all patients (see Right graph in Figure below). Adjustments for renal impairment will be addressed in Section 1.4.3.



**Figure:** Individual predicted AUC vs. body weight following (Left) 240 mcg/kg, (Middle) 240 mcg/kg with a fixed dose of 20 mg for patients < 85 kg, and (Right) 30 mg fixed dose to all patients.

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The sponsor states in the label that there is limited experience with plerixafor doses for patients weighing more than 175% of ideal body weight. The maximum dose should therefore be capped to that of a 160 kg patient (heaviest patient in study 3101, i.e. 40 mg, since plerixafor exposure increases with increasing body weight (see Figure below illustrating the predicted plerixafor exposure in the pivotal studies based on the patient's creatinine clearance).

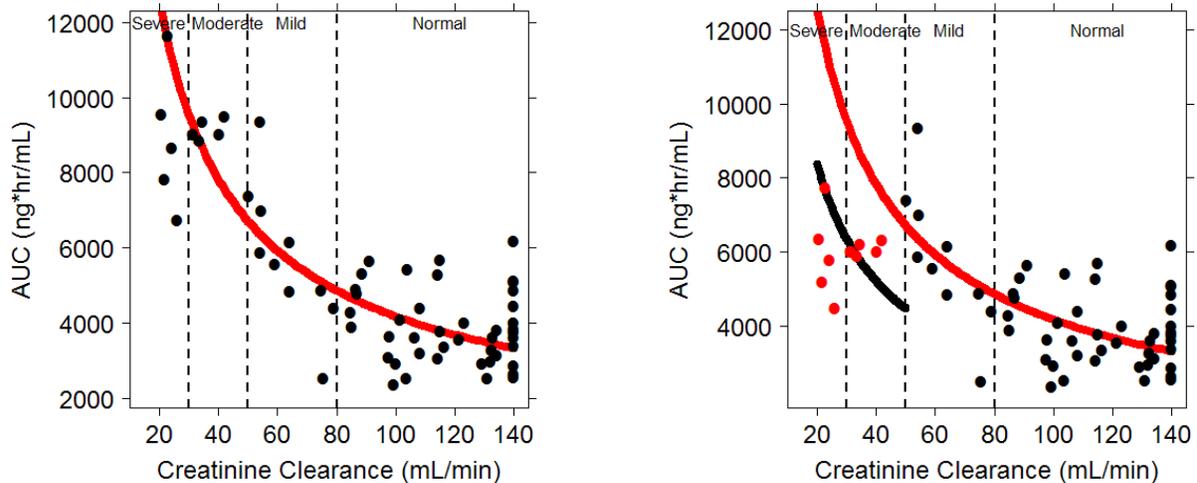


**Figure:** Predicted exposure ( $AUC = \text{Dose}/CL$  where  $CL = 4.59 * (CrCL/100)^{0.683}$ ) vs. body weight for NHL patients (study 3101) and MM patients (study 3102) following 240 mcg/kg and 1/3 dose reduction in patients with CrCL < 50 mL/min.

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### 1.4.3 Should the dose be reduced by 1/3 (from 240 to 160 mcg/kg) in patients with severe renal impairment (CrCL < 30 mL/min)?

Yes, but patients with moderate renal impairment (CrCL < 50 mL/min) should also have their dose reduced by 1/3 in order to bring down the exposure in these patients to a level that was studied and known not to cause unacceptable adverse events in the pivotal trials (see Figure below).



**Figure:** Individual predicted AUC (black dot) vs. CrCL following a dose of (Left) 240 mcg/kg and (Right) a dose reduction to 160 mcg/kg in patients with moderate and severe renal impairment (red dots). The population predicted AUC following 240 mcg/kg is shown as a red line and 160 mcg/kg is shown as a black line.

If a <sup>(b)</sup><sub>(4)</sub> mg fixed dose is used, the following dose adjustments based on renal function should be applied (see Figure 7):

|                                   |                       |                    |
|-----------------------------------|-----------------------|--------------------|
| Normal renal function:            | CrCL > 80 mL/min      | No dose adjustment |
| Mild renal impairment:            | 50 < CrCL < 80 mL/min | 20 mg (2/3 dose)   |
| Moderate-severe renal impairment: | CrCL < 50 mL/min      | 15 mg (1/2 dose)   |

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## 1.5 Recommendations

OCP finds the NDA is acceptable. The sponsor is recommended to conduct a post0-marketing study testing an alternative dosing regimen to optimize the response to plerixafor and match exposure across body weight and renal function.

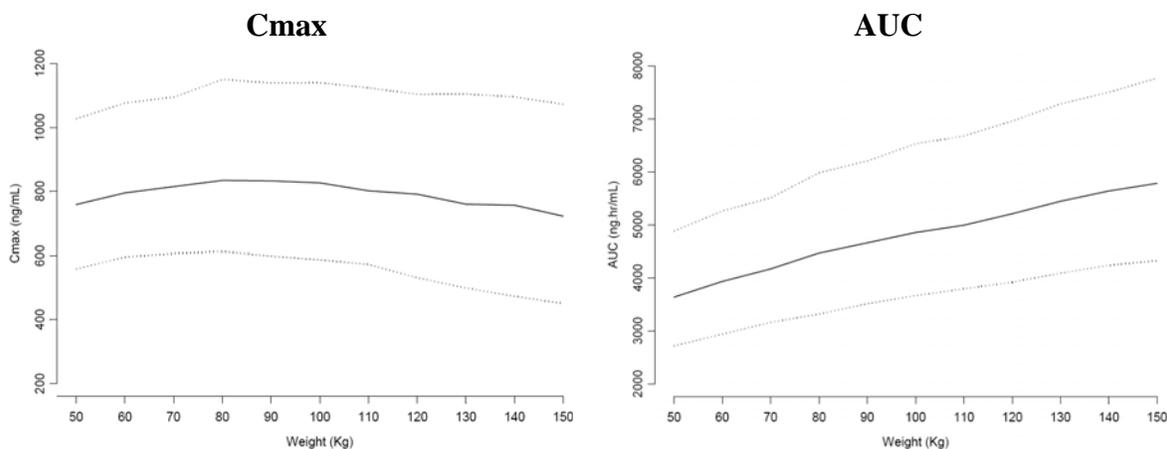
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## 2 RESULTS OF SPONSOR'S ANALYSIS

The key findings from sponsor's population PK analysis are summarized below:

- Total body weight and creatinine clearance were the most important covariates on volume of distribution and clearance, respectively.
- $C_{max}$  does not vary significantly as body weight increases, primarily as weight was the covariate included on  $V_c$ .
- AUC following a 240 mcg/kg dose increase with weight from 3600 ng\*hr/mL for a 50 kg patient to 5800 ng\*hr/mL for a 150 kg patient, which is a 61% increase in AUC over a 300% increase in weight.



**Figure 2. Effect of weight on  $C_{max}$  (left) and AUC (right) following a 240 mcg/kg dose.**

Source: Figure 19-20 on page 50 in sponsor's [population PK report](#).

*Reviewer's comments:*

*Sponsor's population PK analysis is generally adequate and the significant demographic covariates identified by the sponsor were reproduced.*

*However, the following limitations of sponsor's population PK analysis were identified:*

- 1) *The creatinine clearance (CrCL) was calculated using Cockcroft-Gault giving CrCL values between 20 and 400 mL/min. The CrCL should preferably have been capped at 140 mL/min which is considered to be the upper limit of CrCL.*
- 2) *Patient 02-112 (NONMEM ID 61) in study AMD3100-C201 had predose plerixafor levels of 143 ng/mL (likely due to assay error) which should have been removed from the analysis data.*
- 3) *Sponsor's population PK analysis did not provide rationale for the proposed dose reduction of 33% in patients with severe renal impairment.*

### 3 REVIEWER'S ANALYSIS

#### 3.4 Introduction

The body weight adjusted dosing (i.e. 240 mcg/kg) might not be appropriate since the absolute response rates were found to be significantly lower in lighter (<85 kg, 48% (95% CI 36-60%)) compared to heavier (>85 kg, 72% (95% CI 61-82%)) non-Hodgkin's lymphoma patients treated with G-CSF+plerixafor in study 3101.

This finding can either be due to the mg/kg dosing leading to lower AUCs in lighter patients as shown in Figure 2 or because it is inherently more difficult for lighter patients to respond due to the responder definition also being per kg body weight, i.e. response is defined as  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg in 4 days of apheresis or less.

These identified issues are addressed in reviewer's analysis below.

#### 3.5 Objectives

The reviewer's analysis objectives are:

1. To determine the adequacy of the proposed dosing regimen (240 mcg/kg) to provide acceptable risk/benefit for patients with different body weights.
2. To assess the need for dose adjustment in patients with renal impairment.
3. To explore the dose/exposure-response relationship for effectiveness for G-CSF and plerixafor.

#### 3.6 Methods

##### 3.6.1 Data Sets

Data sets used are summarized in Table 1.

**Table 1: Analysis Data Sets.**

| Study Number                   | Name  | Link to EDR  |
|--------------------------------|---|--|
| AMD3100-C201, 2106, 1101, 1002 | pkpop.xpt   | <a href="\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\population-pk\analysis">\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\population-pk\analysis</a>  |
| AMD3100-3101 (NHL)             | eaph1.xpt<br>labchem0.xp<br>blchar1.xpt<br>aphprod1.xpt | <a href="\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3101\analysis">\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3101\analysis</a><br><a href="\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3101\listings">\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3101\listings</a> |
| AMD3100-3102 (MM)              | eaph1.xpt<br>labchem0.xp<br>blchar1.xpt<br>aphprod1.xpt | <a href="\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3102\analysis">\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3102\analysis</a><br><a href="\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3102\listings">\\Cdsub1\evsprod\NDA022311\0000\m5\datasets\amd3100-3102\listings</a> |

##### 3.6.2 Software

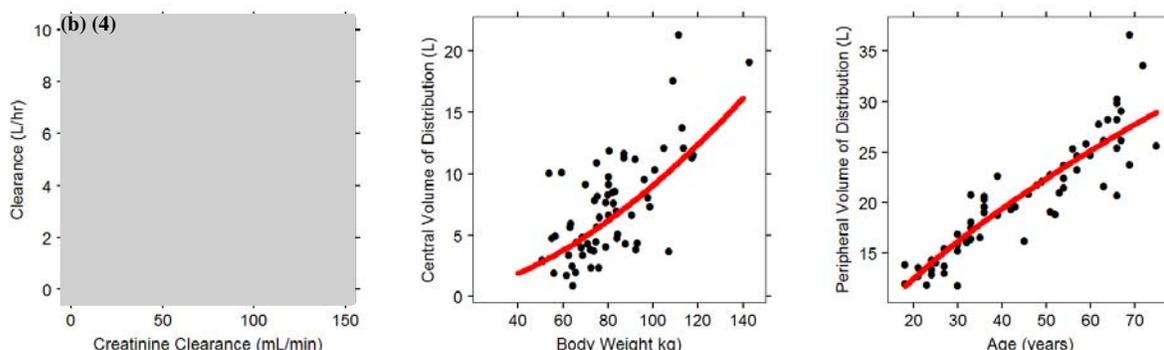
SAS, S-PLUS, NONMEM were used for the reviewer's analyses.

### 3.7 Results

#### 3.7.1 Population Pharmacokinetic Analysis

Similar to sponsor’s population PK findings, a two-compartment disposition model with first-order absorption and elimination was found adequate to describe the plerixafor concentration-time profile following a subcutaneous dose of 40-240 mcg/kg.

The parameter estimates, predicted concentration-time profiles, and goodness-of-fit graphs for the reviewer’s final PK model are shown in Appendix 4. Creatinine clearance (CrCL), body weight, and age were found to be significant PK covariates (see **Figure 3**) similar to sponsor’s findings.



**Figure 3:** Identified demographic covariate – PK parameter relationships for plerixafor. (Left) Clearance vs. CrCL, (Middle) Central volume of distribution vs. body weight, and (Right) Peripheral volume of distribution vs. age. Individual (black dots) and population (red line) predictions.

The estimated distribution half-life ( $t_{1/2,\alpha}$ ) is 0.3 hr and the terminal population half-life ( $t_{1/2,\beta}$ ) is 5.3 hr with a steady-state volume of distribution ( $V_{ss}$ ) estimate of 27.7 L.

The effects of impaired renal function on the pharmacokinetics of a single 240 mcg/kg dose of plerixafor were assessed in study AMD3100-1101. The results showed no effect of renal function on the PK parameters related to absorption (e.g.,  $t_{max}$ , maximum plasma concentration [ $C_{max}$ ]) but a decrease in drug clearance with renal impairment was observed.

The mean  $C_{max}$  and area under the curve ( $AUC_{0-24hr}$ ) in subjects with normal, mild, moderate, and severe renal impairment in study AMD3100-1101 are shown in Table 2.

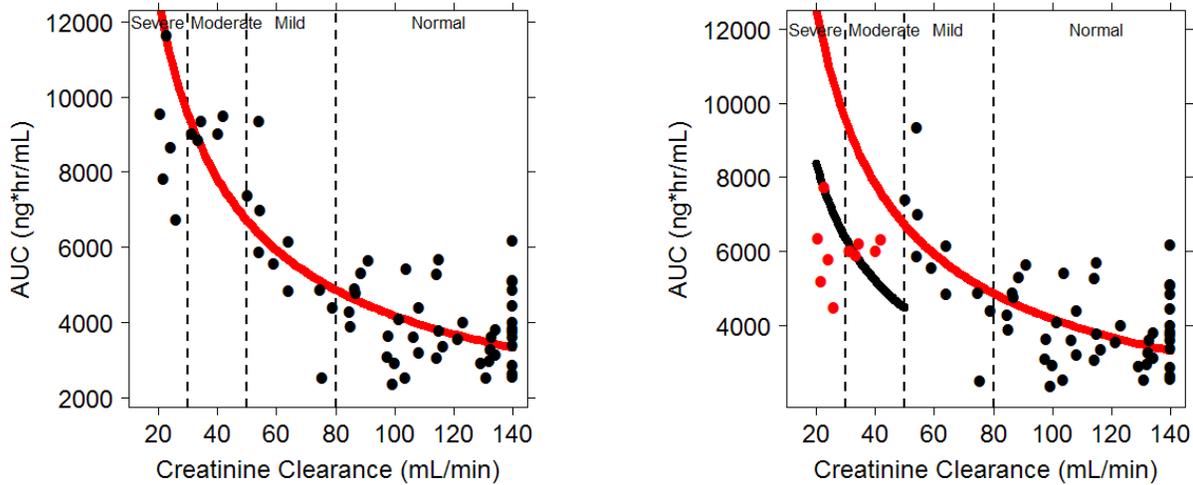
**Table 2:**  $C_{max}$   $AUC_{0-24}$  estimates across renal function in study AMD3100-1101.

|                         | Renal Impairment | Control (N=6)  | Mild (N=5)      | Moderate (N=6)  | Severe (N=6)    |
|-------------------------|------------------|----------------|-----------------|-----------------|-----------------|
| $C_{max}$ (ng/mL)       | Mean $\pm$ SD    | 980 $\pm$ 196  | 739 $\pm$ 76.1  | 936 $\pm$ 280   | 861 $\pm$ 193   |
|                         | Min, Max         | 812, 1260      | 640, 845        | 559, 1270       | 609, 1140       |
| $AUC_{0-24}$ (ng*hr/mL) | Mean $\pm$ SD    | 5070 $\pm$ 979 | 5410 $\pm$ 1070 | 6780 $\pm$ 1660 | 6990 $\pm$ 1010 |
|                         | Min, Max         | 3900, 6240     | 3970, 6540      | 4680, 8410      | 5700, 8050      |

Source: Table 11-5 in sponsor’s CSR for study AMD3100-1101 on page 55.

Based on these results, the sponsor recommends that patients with severe renal insufficiency (CrCL <30 mL/min) should have their dose of plerixafor reduced by 1/3 from 240 to 160 mcg/kg to minimize any potential risks caused by higher exposure to plerixafor and potential tissue accumulation.

Reviewer's population PK analysis and the mean AUC estimates in Table 2 from the renal impairment study (AMD3100-1101) suggest that the plerixafor dose should be reduced by 1/3 in patients with moderate-severe renal impairment (CrCL < 50 mL/min) in order to bring down the exposure in these patients to a level that was studied and known not to cause unacceptable adverse events in the pivotal trials (see Figure 4).



**Figure 4:** Individual predicted AUC (black dot) vs. CrCL following a dose of (Left) 240 mcg/kg and (Right) a dose reduction to 160 mcg/kg in patients with moderate and severe renal impairment (red dots). The population predicted AUC following 240 mcg/kg is shown as a red line and 160 mcg/kg is shown as a black line.

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Furthermore, there is a clear trend towards lower AUCs with lower body weight when plerixafor is being dosed on a body weight basis as seen in Figure 5 (Left) and shown by the sponsor in Figure 2.

Given the lower response rate observed in lighter patients and the clear exposure-response relationship observed in studies AMD3100-1002 and -1003, it is reasonable to assume a higher exposure in these patients will improve the response rate and the higher exposure achieved in heavier patients can serve as the target exposure level with acceptable safety profile. In order to match the exposure in lighter patients to that in heavier patients, the absolute dose should be capped (at the lower end) to that of an 85 kg patient (median body weight in study 3101 and 3102 was 85 kg) (see Figure 5 (Right)), i.e.

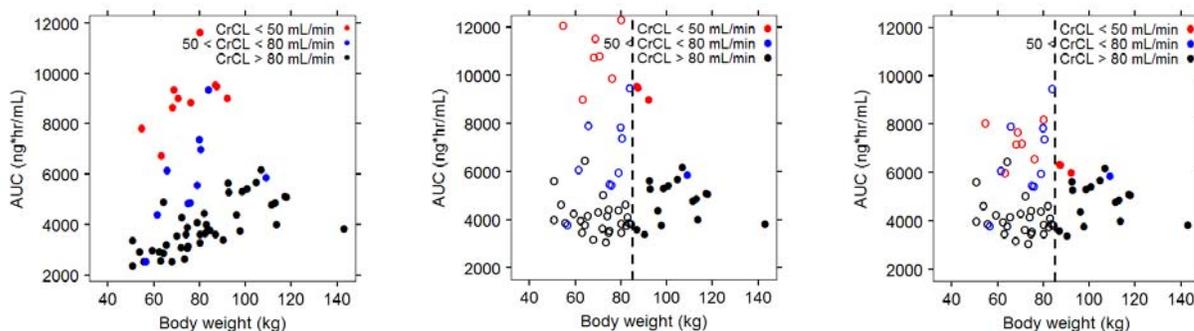
|            |   |
|------------|---|
| WT < 85 kg | 20 mg (fixed dose) (~ 240 mcg/kg * 85 kg) |
| WT ≥ 85 kg | 240 mcg/kg                                |

Since there is no clinical experience with patients above 160 kg, the total dose of plerixafor should not exceed 40 mg (~240 mcg/kg\*160 kg).

For patients with moderate-severe renal impairment (CrCL < 50 mL/min), the dose should be reduced by 1/3 across all body weights, i.e.

|                                 |                                     |
|---------------------------------|-------------------------------------|
| WT < 85 kg and CrCL < 50 mL/min | 13.5 mg (~ 2/3 *240 mcg/kg * 85 kg) |
| WT ≥ 85 kg and CrCL < 50 mL/min | 160 mcg/kg                          |

The individual predicted AUCs for the subjects in studies AMD3100- C201, 2106, 1101, 1002 (population PK data) following 240 mcg/kg, 240 mcg/kg with a fixed dose of 20 mg for patients < 85 kg, and 240 mcg/kg with a fixed dose of 20 mg for patients < 85 kg and 1/3 dose reduction in patients with CrCL<50 mL/min are shown in Figure 5.

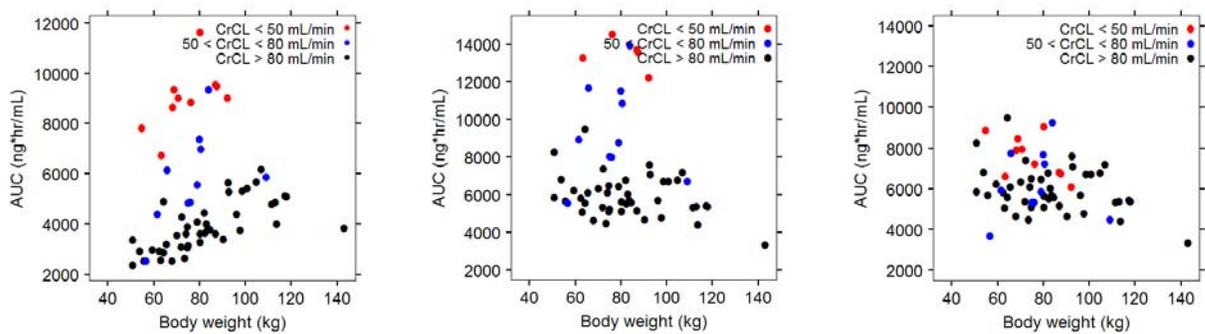


**Figure 5:** Individual predicted AUC vs. body weight following (Left) 240 mcg/kg, (Middle) 240 mcg/kg with a fixed dose of 20 mg for patients < 85 kg, and (Right) a 1/3 dose reduction for all patients with CrCL < 50 mL/min (moderate and severe renal impairment) in addition to a fixed dose of 20 mg for patients < 85 kg.

Alternatively, a 30 mg fixed plerixafor dose can be administered to all patients in order to match exposure across body weights.

If a <sup>(b)</sup><sub>(4)</sub> mg fixed dose is used, the following dose adjustments based on renal function should be applied:

|                                   |                       |                    |
|-----------------------------------|-----------------------|--------------------|
| Normal renal function:            | CrCL > 80 mL/min      | No dose adjustment |
| Mild renal impairment:            | 50 < CrCL < 80 mL/min | 20 mg (2/3 dose)   |
| Moderate-severe renal impairment: | CrCL < 50 mL/min      | 15 mg (1/2 dose)   |



**Figure 6:** Individual predicted AUC vs. body weight following (Left) 240 mcg/kg, (Middle) 30 mg (fixed dose), and (Right) 30 mg (fixed dose) with a 1/3 dose reduction (i.e. 20 mg) for patients with mild renal impairment (50 < CrCL < 80 mL/min), and 1/2 dose reduction (i.e. 15 mg) in patients with moderate and severe renal impairment (CrCL < 50 mL/min).

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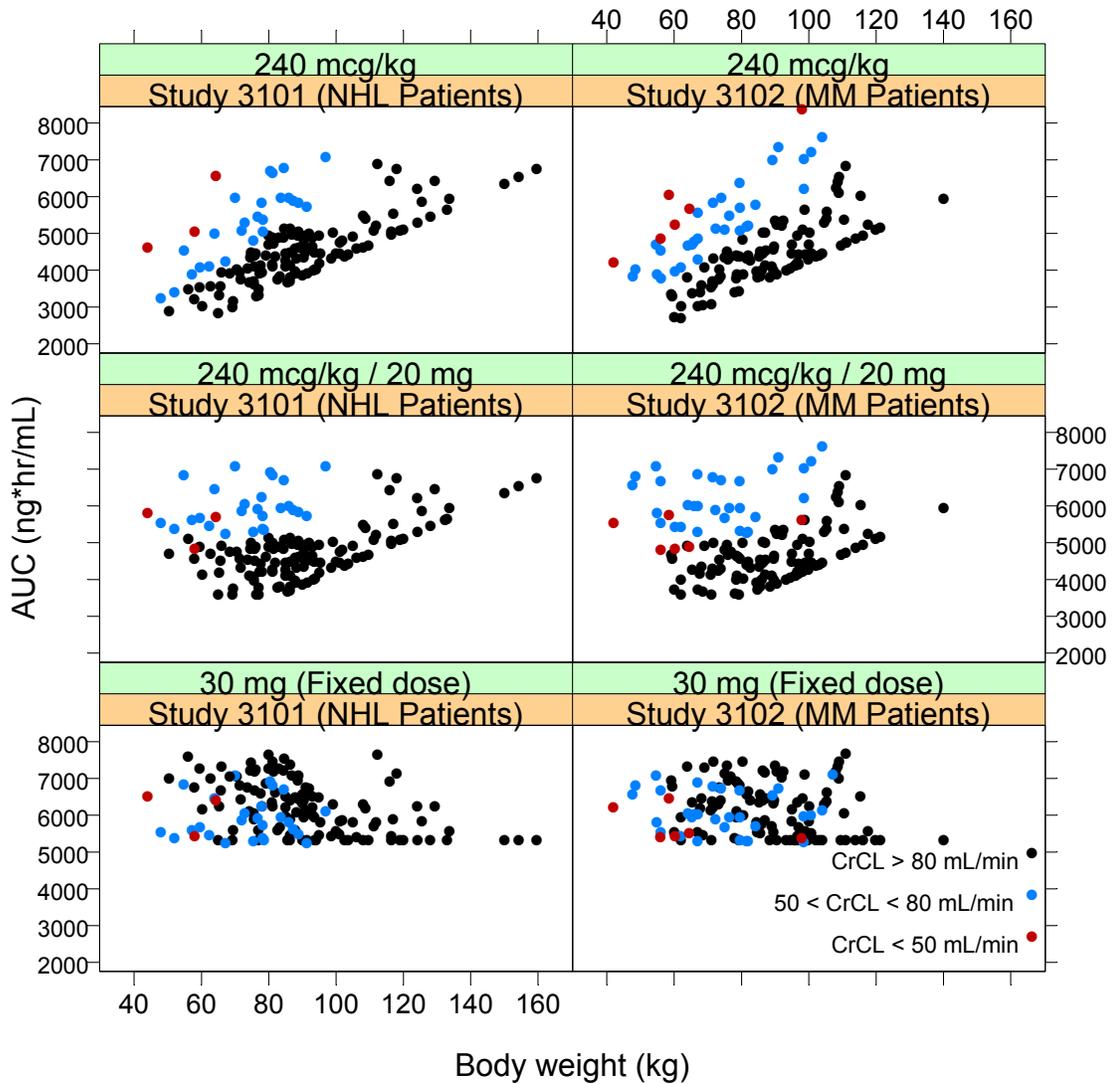
The predicted exposure ( $AUC = \text{Dose}/CL$  where  $CL = 4.59 * (\text{CrCL}/100)^{0.683}$ ) in NHL and MM patients from study AMD3100-3101 and -3102 following 240 mcg/kg, the 240 mcg/kg for patients above 85 kg and 20 mg (fixed dose) for patients weighing less than 85 kg, and 30 mg (fixed dose) is shown in Figure 7.

The exposure in patients with  $\text{CrCL} > 80$  mL/min (normal renal function) weighing less than 85 kg (black dots) receiving a fixed dose of 20 mg matches that of patients  $> 85$  kg getting 240 mcg/kg. No dose adjustments based on renal function are necessary for patients  $< 85$  kg and  $50 < \text{CrCL} < 80$  mL/min (mild renal impairment) when receiving a fixed dose of 20 mg since the exposure match that of patients  $> 85$  kg (blue dots). Patients with moderate-severe renal impairment ( $\text{CrCL} < 50$  mL/min, red dots) across all weights should receive 2/3 the dose to match the exposure in patients with normal renal function when receiving 20 mg (fixed dose).

The sponsor states in the label that there is limited experience with plerixafor doses for patients weighing more than 175% of ideal body weight. The maximum dose should therefore be capped to that of a 160 kg patient (heaviest patient in study 3101, i.e. 40 mg, since plerixafor exposure increases with increasing body weight (see Figure 4 illustrating the predicted plerixafor exposure in the pivotal studies based on the patients creatinine clearance).

The predicted exposure in the pivotal trials following 30 mg fixed plerixafor dose with 1/3 dose reduction (20 mg) in mild renally impaired and 1/2 dose reduction (15 mg) in moderate-severe renal impairment patients is shown in Figure 7 (bottom graphs) where the exposures are shown to match across body weights and renal function.

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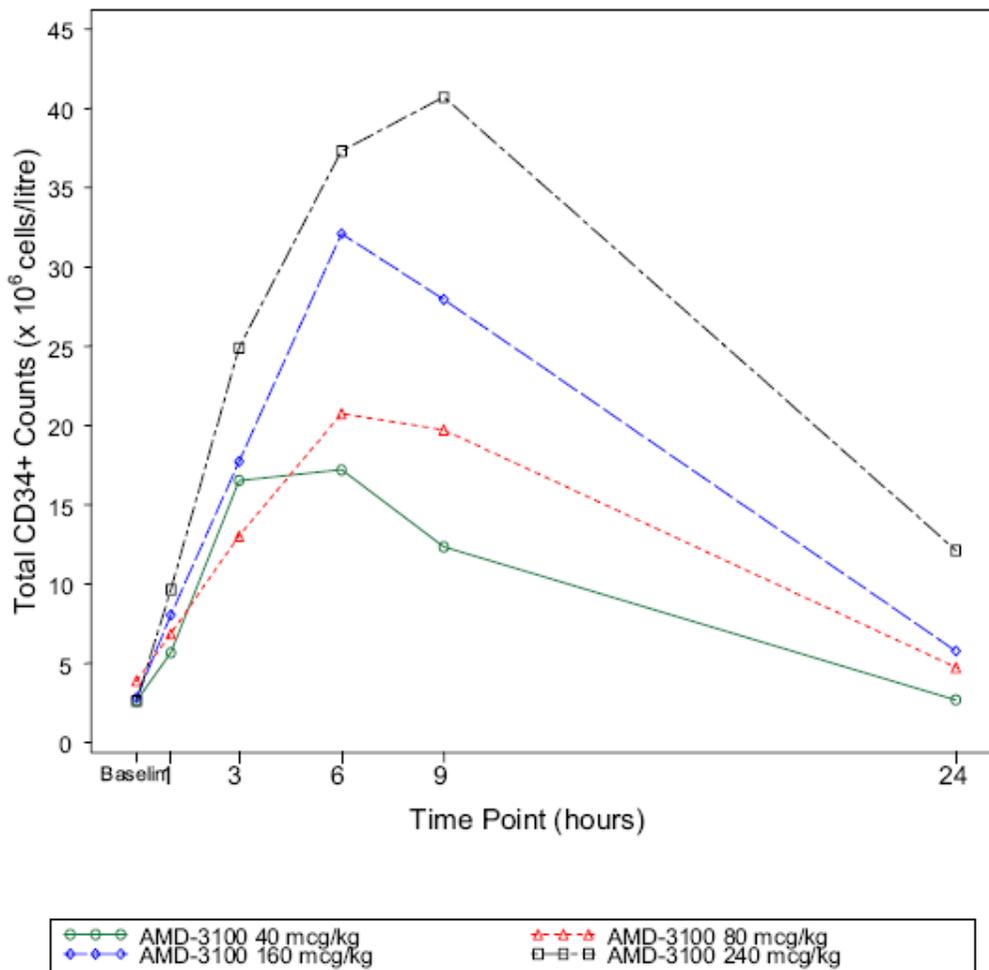
**Figure 7:** Predicted exposure ( $AUC = \text{Dose} / CL$  where  $CL = 4.59 * (\text{CrCL} / 100)^{0.683}$ ) vs. body weight for NHL patients (study 3101) and MM patients (study 3102) following (top) 240 mcg/kg, (middle) 240 mcg/kg for patients above 85 kg and a fixed dose of 20 mg for patients weighing less than 85 kg and 1/3 dose reduction in patients with  $\text{CrCL} < 50 \text{ mL/min}$ , and (bottom) 30 mg (fixed dose) to all patients and 1/3 dose reduction in  $50 < \text{CrCL} < 80 \text{ mL/min}$  and 1/2 dose reduction in  $\text{CrCL} < 50 \text{ mL/min}$ .

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### 3.7.2 Pharmacodynamic Analysis

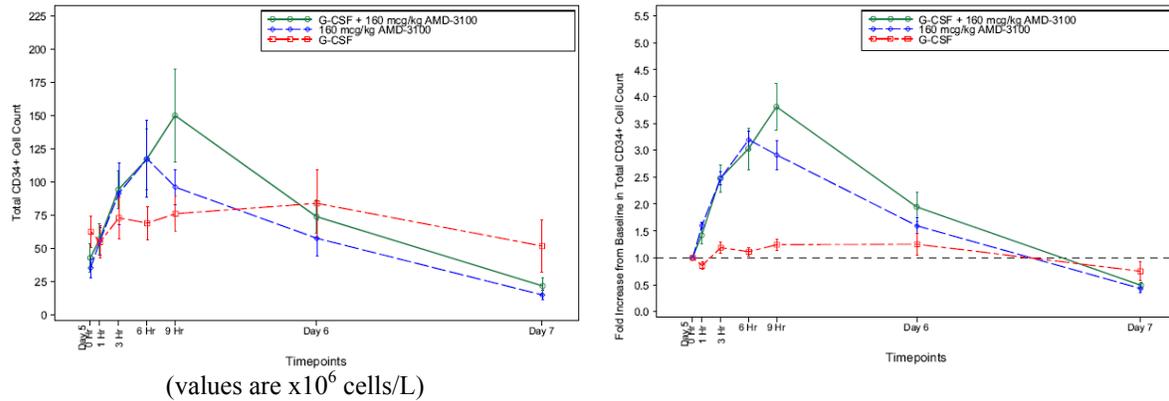
Peripheral blood CD34+ cell count has previously been demonstrated to correlate positively with apheresis yield with peak mobilization after G-CSF alone usually occurring 4 to 5 days after initiation of G-CSF.

A dose-proportional increase in CD34+ cells was observed when plerixafor alone was given at doses from 40 mcg/kg to 240 mcg/kg in healthy subjects (study AMD3100-1002) (see **Figure 8**).



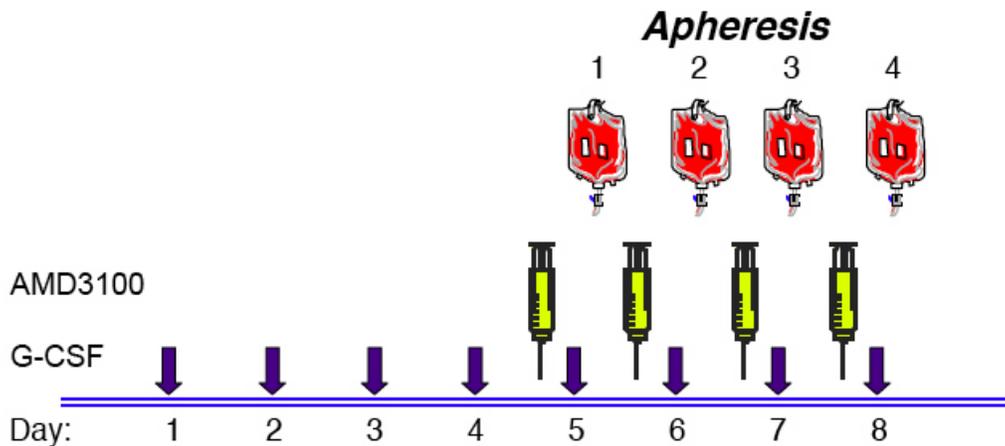
**Figure 8:** Mean CD34+ cell count following plerixafor doses of 40 (green), 80 (red), 160 (blue), and 240 (black) mcg/kg (Source: Figure 1 in sponsors AMD3100-1002 CSR on page 34).

When given to healthy subjects after a 4-day regimen of G-CSF, administration of plerixafor and G-CSF produced higher CD34+ cell counts than treatment with either plerixafor alone or G-CSF alone on the 5<sup>th</sup> day (study AMD3100-1003) (see Figure 9).



**Figure 9:** Mean (left) total and (right) fold increase in CD34+ cell count (Source: Figure 1-2 in sponsors AMD3100-1003 CSR on page 36-37).

The proposed dosing regimen is therefore to use plerixafor in conjunction with G-CSF rather than plerixafor alone. Taken together, the results from Phase 1 and early Phase 2 studies established the dose and administration schedule of plerixafor as a 4-day regimen of G-CSF, followed by plerixafor at 240 mcg/kg starting (b) (4) to 11 hours prior to the first apheresis on the 5<sup>th</sup> day. Patients continue to receive daily doses of G-CSF and plerixafor prior to each subsequent apheresis session (see Figure 10).

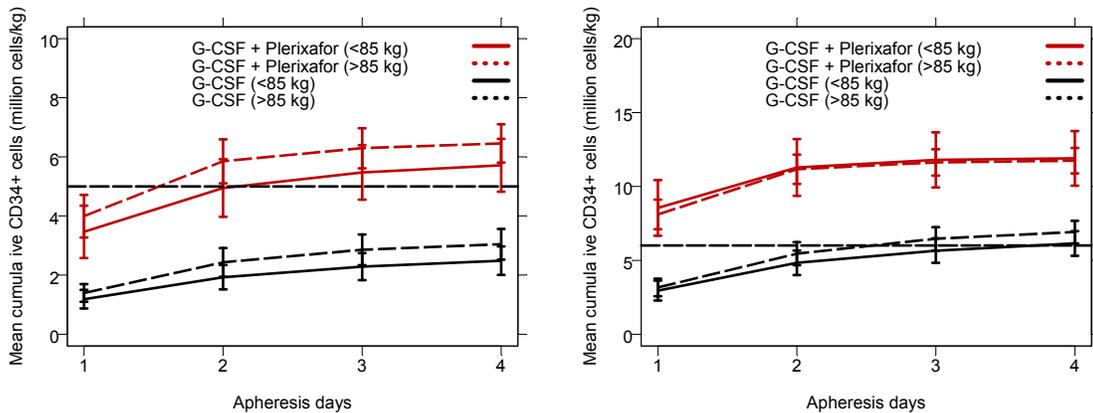


**Figure 10:** Mobilization/apheresis regimen used for phase 3 studies.

Source: Sponsor's FDA meeting slides on August 5, 2008.

The primary endpoint in the phase 3 studies was defined as the number of patients reaching a target of  $\geq 5/6 \times 10^6$  CD34+ cells/kg in 4/2 or less days of apheresis for NHL and MM patients, respectively.

The mean cumulative CD34+ cells/kg collected in the phase 3 studies in NHL (study 3101) and MM (study 3102) patients following a plerixafor dose of 240 mcg/kg and 10 mcg/kg G-CSF are shown in Figure 11. It is observed that the mean CD34+ cells/kg is lower for lighter NHL patients weighing less than the median body weight of 85 kg compared to heavier patients. This is not seen for MM patients since the endpoint of  $\geq 6 \times 10^6$  CD34+ cells/kg in 2 or less apheresis days appears to be easier to reach compared to NHL patients.

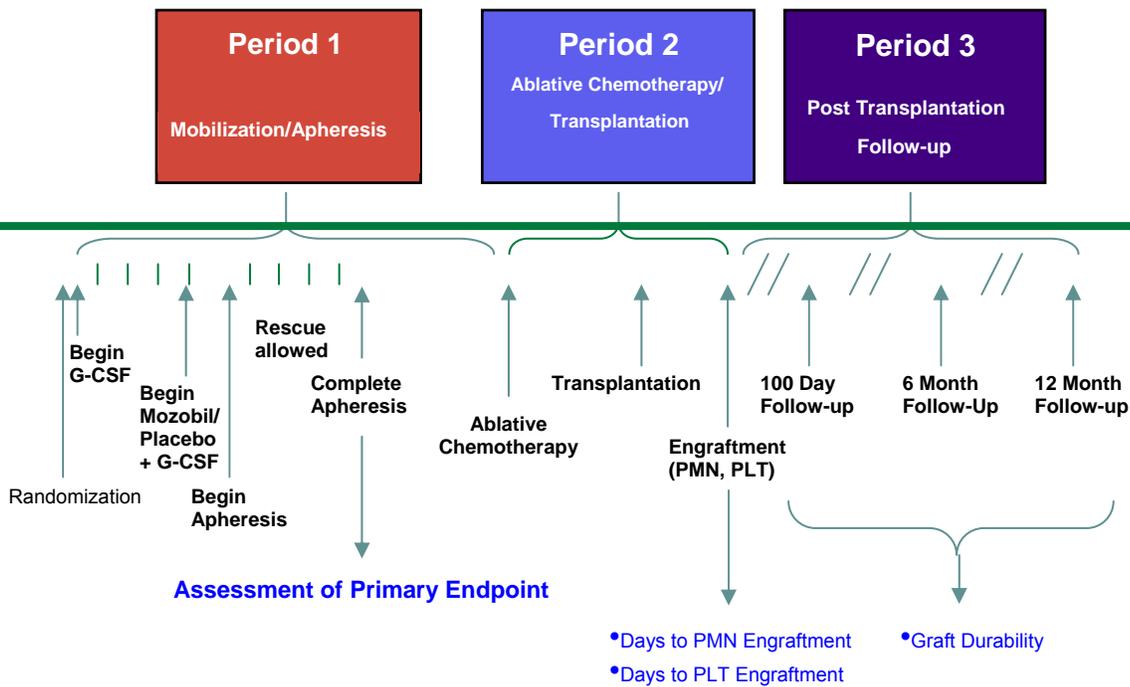


**Figure 11:** Mean (95% CI) cumulative CD34+ cells/kg collected in the phase 3 studies in (Left) NHL and (Right) MM patients following a plerixafor dose of 240 mcg/kg and 10 mcg/kg G-CSF. The horizontal dashed line represents the clinical response line of  $5/6 \times 10^6$  cells/kg in 4/2 or less days of apheresis for NHL and MM patients, respectively.

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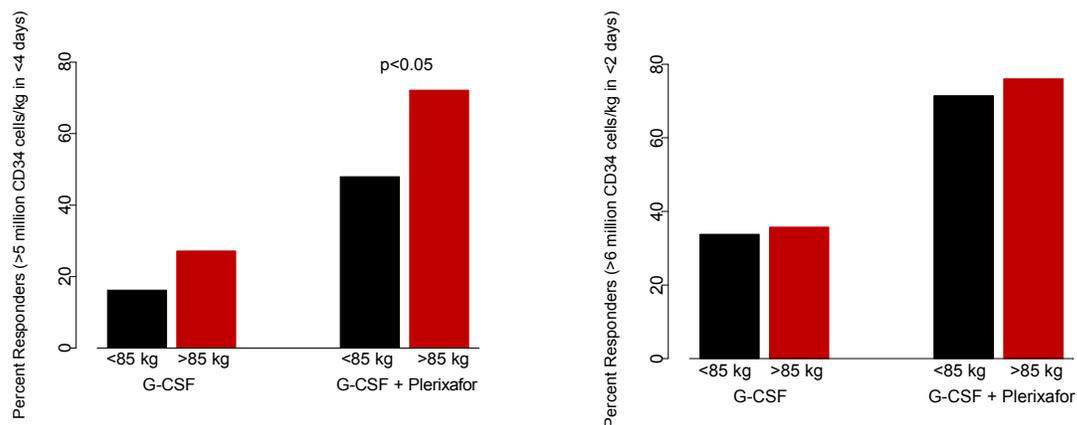
### 3.7.3 Responder Analysis (Mobilization/Apheresis)

A flow diagram of the phase 3 study design is provided in **Figure 12**. The reviewer's responder analysis only focuses on Period 1 (Mobilization/Apheresis) since that is where the CD34+ cells are being mobilized.



**Figure 12:** Flow diagram of Phase 3 study design (Source: Sponsor's FDA meeting slides on August 5, 2008).

The response rates for G-CSF + Plerixafor treated patients were found to be significantly lower in patients weighing less than 85 kg (48% (95% CI 36-60%)) compared to patients  $\geq 85$  kg (72% (95% CI 61-82%)) in non-Hodgkin's lymphoma (NHL) patients (study 3101) (see Figure 4 Left). The same numerical trend was seen for G-CSF treated patients however not statistical significant. No differences in response rate between low and high body weight groups were observed for MM patients (study 3102) (see Figure 4 Right).

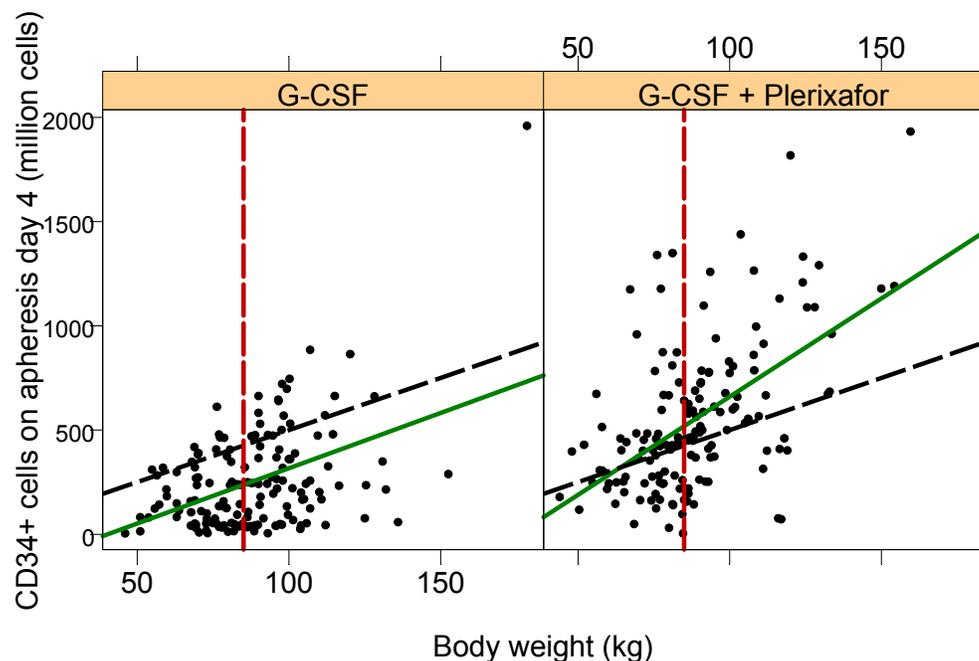


**Figure 13:** Percent responders for patients above or below the median body weight of 85 kg in (Left) non-Hodgkin's lymphoma patients (study 3101) and (Right) multiple myeloma patients (study 3102) receiving G-CSF (black bars) and G-CSF+Plerixafor (red bars).

The lower response rate in lighter patients (< 85 kg) could be due to the inadequacy of the proposed 240 mg/kg dose to match exposure across body weights (see Figure 6) or it might be because the responder status also depends on body weight ( $\geq 5/6 * 10^6$  CD34<sup>+</sup> cells/kg in 4/2 days of apheresis or less for NHL and MM patients, respectively).

As indicated in Figure 14 (left), it does not appear to be easier to achieve response ( $>5*10^6$  cells/kg on apheresis day 4) for lower body weight patients where the linear regression line of cumulative number of CD34<sup>+</sup> cells vs. body weight for G-CSF treated NHL patients is parallel to the responder line indicating similar probability of response across body weights. For G-CSF + plerixafor treated patients, the estimated regression line is steeper than the response line indicating patients with higher body weights are more likely to respond.

This finding suggest (assuming baseline CD34<sup>+</sup> cells is balanced between treatment arms on apheresis day 0) that it is not the response rate definition ( $>5*10^6$  cells/kg on apheresis day 4) that causes the observed differences in response rates between lighter and heavier patients but that it is the inadequacy of the 240 mg/kg plerixafor dose to achieve similar exposure across body weight that translates into significantly lower response rates for lighter patients.



**Figure 14:** Cumulative total number of CD34<sup>+</sup> cells on apheresis day 4 vs. body weight (surrogate for total dose) for G-CSF (Left) and G-CSF+Plerixafor (Right) treated NHL patients (study 3101). The dashed black line is the responder line ( $>5*10^6$  cells/kg) separating non-responders (below) from responders (above), the green line is the estimated linear regression line, and the dashed red line separates patients below and above the median body weight of 85 kg.

The probability of clinical response ( $>5 \cdot 10^6$  CD34+ cells/kg in 4 or less apheresis days) was modeled using a logistic regression model of the general form

$$\text{logit}(\text{Pr}(> 5 \cdot 10^6 \text{ CD34+ cells / kg})) = \alpha_{\text{Intercept}} + \beta \cdot \text{Cov}$$

where Cov is any potential categorical or continuous covariate.

The logistic regression analysis parameter estimates are shown in Table 3. Treatment with plerixafor was found to be the most important covariate with an odds ratio of 6.8. Higher baseline CD34+ concentration was also found to be a significant covariate for response with an odds ratio of 1.1 for an increase of 1 CD34+ cell/mL. Finally, body weight category (below or above 85 kg) was significant (after correcting for baseline CD34+ concentration) with an odds ratio of 2.1.

**Table 3:** Reviewer's Logistic Regression Analysis Parameter Estimates.

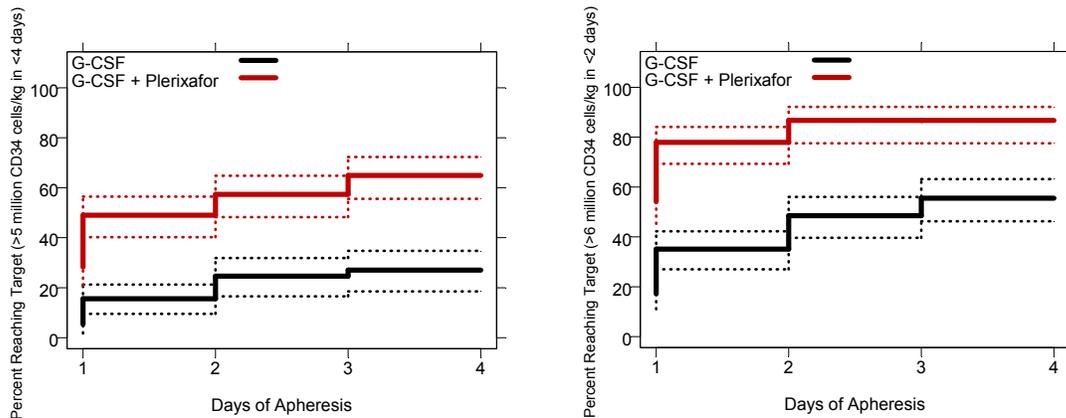
| Parameter                      | Covariate   | Estimate | RSE (%) | P-value | Odds Ratio (95% CI) |
|--------------------------------|---|----------|---------|---------|---------------------|
| $\alpha_{\text{Intercept}}$    | G-CSF, WT < 85kg<br>Median CD34+ concentration ( $7.8 \cdot 10^6$ cells/mL) | -2.12    | 21      | <0.0001 | -                   |
| $\beta_{\text{TRT}}$           | G-CSF + Plerixafor  | 1.92     | 17      | <0.0001 | 6.8 (3.6-12.8)      |
| $\beta_{\text{CD34 baseline}}$ | Baseline increase of 1 CD34+ cells/mL                                       | 0.10     | 18      | <0.0001 | 1.1 (1.07-1.14)     |
| $\beta_{\text{WT}}$            | WT > 85 kg  | 0.75     | 41      | 0.0155  | 2.1 (1.2-3.9)       |

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### 3.7.4 Time to Event Analysis (Mobilization/Apheresis)

The secondary endpoint in the phase 3 studies was the number of apheresis days to reach target number of cells/kg.

In NHL patients, 1 day of apheresis on G-CSF + plerixafor was more effective than 4 days on G-CSF in reaching target ( $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg) (see Figure 15 left). A 3 day improvement in reaching the target ( $\geq 6 \times 10^6$  CD34<sup>+</sup> cells/kg) for the median number of MM patients was seen with G-CSF + plerixafor over G-CSF (see Figure 15 right).



**Figure 15:** Number of apheresis days to reach target in (Left) non-Hodgkin’s lymphoma (study 3101) and (Right) multiple myeloma (study 3102) patients receiving G-CSF (black lines) and G-CSF+plerixafor (red lines). The solid lines represent the mean and the dotted lines illustrate the 95% confidence intervals.

Using Cox Proportional Hazards model, NHL patients treated with G-CSF + Plerixafor were 3.7 times more likely to reach the target number of CD34<sup>+</sup> cells compared to those receiving G-CSF alone (Hazard ratio of 3.69 (95% CI 2.48-5.50)) (see Figure 19 (Left) for checking the proportional hazard assumption in Cox regression).

Similarly for MM patients, the hazard ratio between G-CSF and G-CSF + Plerixafor was 3.24 (95% CI 2.39-4.40).

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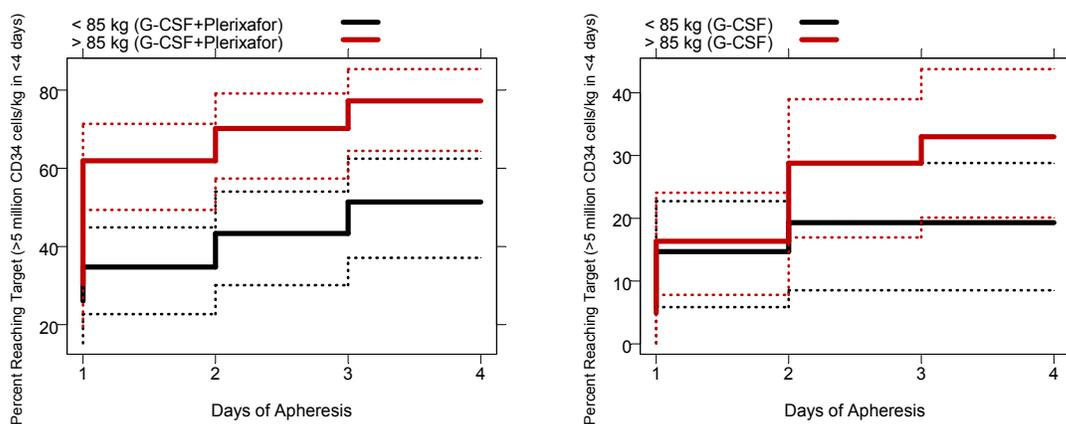
The probability of NHL patients treated with G-CSF + Plerixafor reaching the target number of CD34+ cells was found to be lower in lower body weight group as shown in the Kaplan-Meier plot (see Figure 16 (Left)). Univariate Cox regression showed that patients with body weight above 85 kg were twice as likely to respond (HR: 1.88 (95% CI 1.23-2.88),  $p=0.004$ ) compared to patients with low body weight (see Figure 19 (Right) for checking the proportional hazard assumption in Cox regression). However, a baseline imbalance for the light and heavy G-CSF+plerixafor treated patients was seen which can explain some of the differences seen in the time-to-event analysis.

The median estimated time to reach the target number of CD34+ cells in the high body weight group was 1 day of apheresis while patients weighing less than 85 kg took 3 days to reach target (see Figure 16 (Left)).

No significant difference between low and high body weight patients were found for G-CSF treated patients (HR: 1.70 (95% CI: 0.82-3.50),  $p=0.15$ ) (see Figure 16 (Right)).

This finding further together with the responder analysis (see 3.7.3) suggests that it is Plerixafor that is suboptimal for lighter patients since body weight category was not found to be a significant predictor for G-CSF treated patients.

Weight was not found to be a significant covariate for response in MM patients in study 3102. This might be because the 240 mg/kg dose is more than enough for MM patients to reach the target and it is therefore not possible to separate out the weight effect.



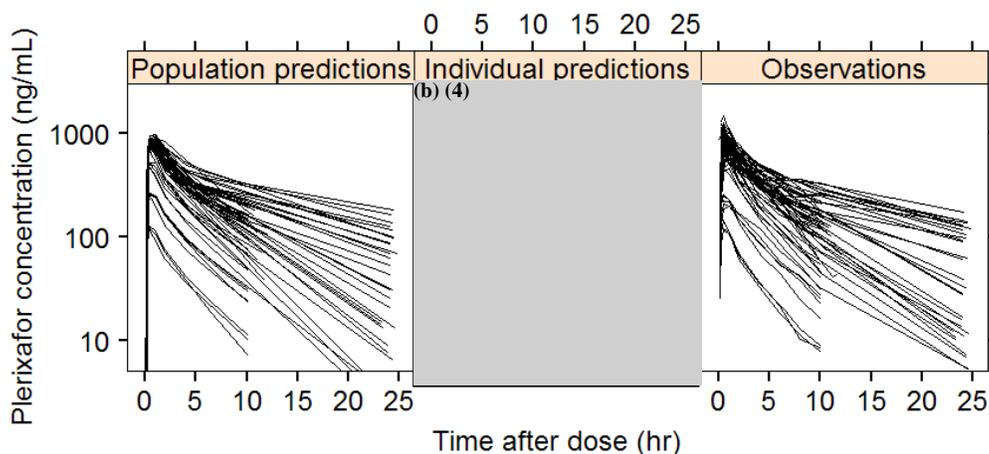
**Figure 16:** Number of apheresis days to reach target in non-Hodgkin's lymphoma patients (study 3101) weighing less than 85 kg (black lines) and above 85 kg (red line) receiving G-CSF+Plerixafor (Left) and G-CSF (Right). The solid lines represent the mean and the dotted lines illustrate the 95% confidence intervals.

#### 4 APPENDIX A: REVIEWER'S POPULATION PK ANALYSIS

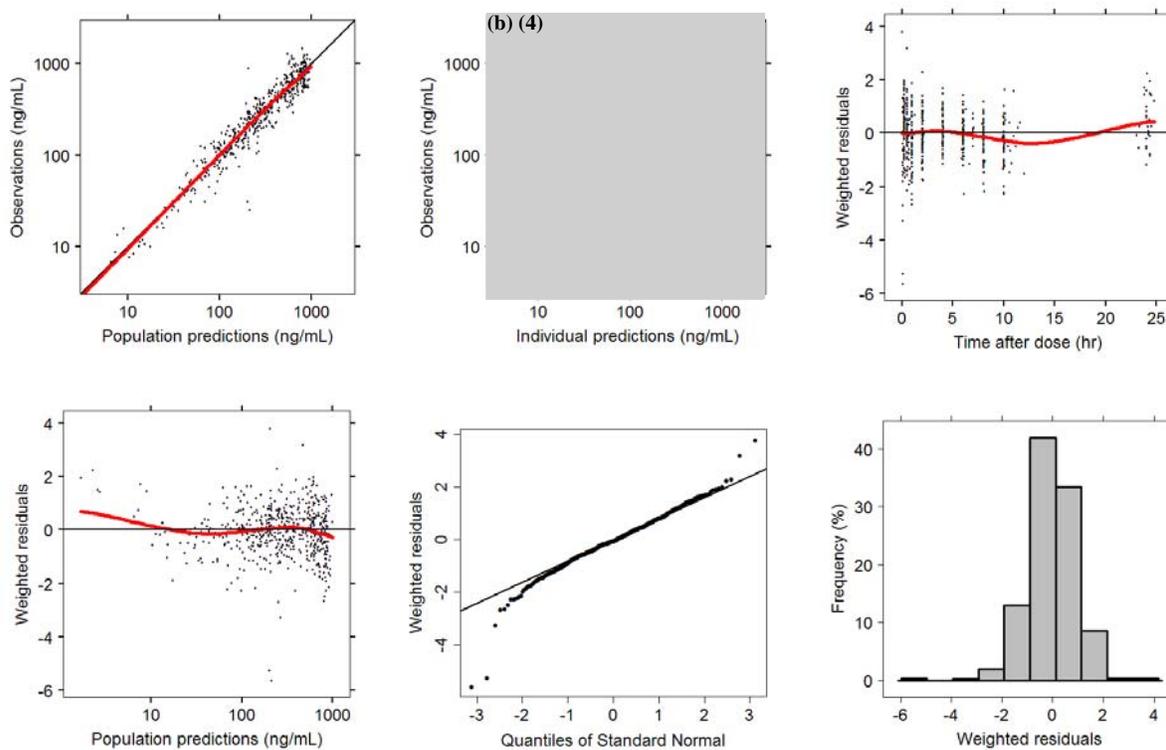
**Table 4** Reviewer's Final Plerixafor PK Model Parameter Estimates.

| Parameter                                  | Unit   | Population parameters |      | Inter-individual variability |         |
|--|--------|-----------------------|------|------------------------------|---------|
|  |        | Estimate              | %RSE | Estimate (CV%)               | %RSE    |
| <b><u>Fixed-Effects Parameters</u></b>     |        |                       |      |                              |         |
| $k_a$                                      | [1/hr] | 1.22                  | 9.34 | -                            | (b) (4) |
| CL/F (for subject with CrCL=100 mL/min)    | [L/hr] | 4.59                  | 3.03 | 18.7                         | (b) (4) |
| Q/F  | [L/hr] | 10.1                  | 7.22 | -                            | (b) (4) |
| $V_1/F$ (for 85 kg subject)                | [L]    | 6.84                  | 13.0 | 13.8                         | (b) (4) |
| $V_2/F$ (for 45 years old subject)         | [L]    | 20.9                  | 3.57 | 15.4                         | (b) (4) |
| <b><u>Covariate-relationships</u></b>      |        |                       |      |                              |         |
| CL-CrCL exponent                           | [-]    | 0.638                 | 16.3 | -                            | (b) (4) |
| $V_1$ -Weight exponent                     | [-]    | 1.72                  | 20.1 | -                            | (b) (4) |
| $V_2$ -Age exponent                        | [-]    | 0.638                 | 11.9 | -                            | (b) (4) |
| <b><u>Intra-Individual Variability</u></b> |        |                       |      |                              |         |
| Proportional error                         | [CV%]  | 16.7                  | 10.2 | -                            | (b) (4) |

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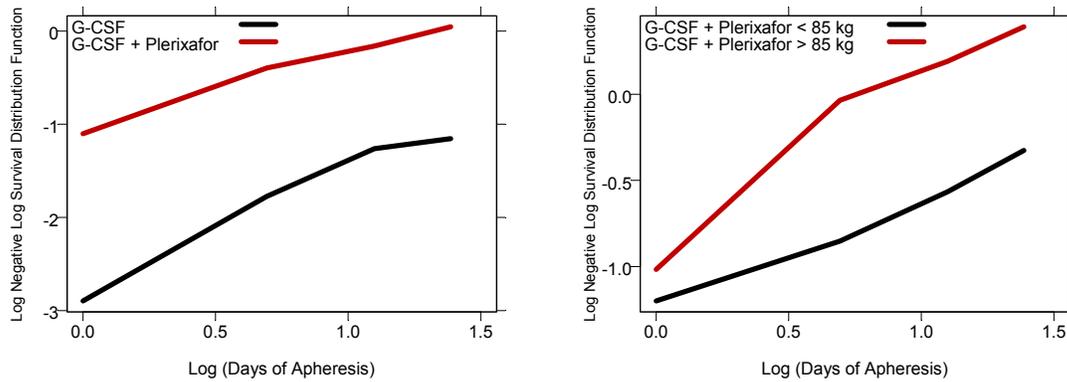


**Figure 17:** Plerixafor concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) clevidipine concentrations.



**Figure 18:** Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the red line is a local smoothing regression line.

## 5 APPENDIX B: REVIEWER'S TIME TO EVENT ANALYSIS



**Figure 19.** Log of the negative log of the survival distribution function vs log days of apheresis in non-Hodgkin's lymphoma (study 3101) receiving (Left) G-CSF (black line) and G-CSF+Plerixafor (red line) and (Right) for G-CSF + Plerixafor treated patients only weighing less than 85 kg (black line) and above 85 kg (red line). Parallel lines indicate that the assumption of proportional hazards is valid.

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## 4.5 PHARMACOGENOMICS REVIEW

**NDA: 22311**

**Sponsor:** Genzyme Corporation

**Drug:** Mozobil™ (Plerixafor)

**Formulation:** 20 mg/mL solution for injection

**Dosing regimen:** 240 µg/kg SC injection (b)(4) 11 hours prior to initiation of apheresis, repeat dose up to 7 consecutive days

**Proposed Indication:** Enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM).

**Review Due Date:** 11/13/2008

**Requested Genomic Review:** Jeanne Fourie, Ph.D.

**Material Submitted:** original NDA in EDR

**Genomic Reviewer:** Rosane Charlab Orbach, Ph.D.

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### Background:

Adult bone marrow is the primary source of stem cells that regenerate hematopoiesis. Most hematopoietic stem/progenitor cells (HSCs/HPCs) reside in the marrow, but HSCs/HPCs also circulate in peripheral blood at low frequency.

HSCs/HPCs can be forced into the blood in higher numbers, a process called mobilization. The proportion of mobilized hematopoietic immature cells can be assessed by the analysis of cells expressing CD34+ antigen. Human stem cell mobilization and positive selection of immature CD34+ cells have become the preferred source of repopulating stem cells for clinical transplantation (Experimental Hematology 30 (2002) 973–981; PMID: 12225788).

Recent findings indicate that the interaction between the homeostatic chemokine CXCL-12 (also known as SDF-1) and its major receptor CXCR4 is critical for HSC/HPC retention within the marrow. Once expressed on HSCs/HPCs, the interaction of CXCR4 with CXCL12 can activate a number of signalling pathways, which potentially could induce cell survival, proliferation, adhesion and/or migration. CXCL12 is also a ligand for the CXCR7 chemokine receptor, although it seems that this receptor does not make a significant contribution to HPCs migration and homing (Vox Sang. 2008 Jan;94(1):18-32, PMID: 18042197).

CXCR4 is also widely expressed in most cancers, although the effect(s) of CXCL12 on CXCR4-expressing tumor cells is unknown (*J Pathol* 2008; **215**: 211–213; PMID: 18523970). It is important to consider however that tumor cells or abnormal hematopoietic stem cells from bone marrow can be co-mobilized to contaminate mobilized peripheral blood progenitor cells, and proper cautionary measures should be placed.

Currently, G-CSF is the most commonly used mobilization agent. Evidence suggests that G-CSF induces neutrophil release from the bone marrow, in major part, by disrupting CXCL12/CXCR4 signaling (Curr Opin Hematol. 2007, PMID: 17133093). However, some patients, and also a minority of healthy individuals, are poor mobilizers. This led to the development of the of CXCR4 antagonists for use in patients refractory to G-CSF treatment as a HSCs/HPCs mobilizer.

Many variables have been previously reported to be associated with mobilization outcome including, but not limited to, peripheral blood white cell count, platelet count, peripheral blood CD34+ cell count prior to mobilization, the number of days after chemotherapy administration, and other patient factors (Biol Blood Marrow Transplant. 2008 Sep;14(9):1045-56; PMID: 18721768). Poor mobilization is also seen in heavily treated cancer patients and disorders, such as Fanconi's anemia and in aplastic anemia patients ([Curr Opin Hematol](#). 2008 Jul;15(4):285-92, PMID: 18536564).

Although genetic factors influencing HSC/HPC mobilization efficiency remain currently unknown, mutations/polymorphisms affecting either the CXCR4 or G-CSF signaling pathways have been reported. These sequence variations can potentially affect the release of bone marrow cells to the peripheral blood. Some examples are listed below.

- The CXCL12 polymorphism in the 3' untranslated region (G801A) has been associated with mobilization efficiency (Br J Haematol. 2001 Apr; 113 (1):247-50; PMID: 11328308). Results related to this polymorphism are not consistent.
- Activating mutations of CXCR4 in humans cause neutrophil retention in the bone marrow together with peripheral neutropenia (WHIM syndrome) (J Immunol. 2008 Oct 15;181(8):5183-8. Review; PMID: 18832668 )
- Neutrophil elastase gene (ELA2) mutations have been found in cyclic, sporadic and autosomal dominant neutropenia (Curr Opin Rheumatol. 2007 Nov;19(6):644-50 ; PMID: 17917547)
- Mutations that truncate the G-CSF receptor have also been reported in patients with severe congenital neutropenia (Blood. 2005 Jan 15;105(2):584-91; PMID: 15353486)

In addition, conditions such as "Benign ethnic neutropenia", characterized by a benign reduction in neutrophil counts, may affect mobilization efficiency. Benign ethnic neutropenia is considered to be more common at certain ages and in certain ethnic groups. In United States, neutropenia is more prevalent in African-Americans (J Immunol. 2008 Oct 15;181(8):5183-8. Review; PMID: 18832668). The clinical implication of this condition in regard to mobilization efficiency is not known.

Plerixafor (Mozobil, AMD3100) is a small-molecule bicyclam derivative antagonist of CXCR4. The current submission is the original NDA for plerixafor, in combination with G-CSF, to enhance the mobilization of CD34+ hematopoietic progenitor cells to the peripheral blood for collection and subsequent autologous bone marrow transplantation in patients with Multiple Myeloma and Lymphoma (or non-Hodgkin's lymphoma and Hodgkin's disease).

The current NDA submission does not include genetic/genomic data and associated analyses. In addition Plerixafor is not CYP-450-metabolized and does not inhibit or induces CYP450 enzymes. Transporter information is unknown. No formal genomic recommendations are made at this time.

#### **Potential Issues:**

1-Potential mobilization of tumor cells:

In order to determine whether mobilization of tumor cells occurred with Plerixafor the Sponsor designed the following protocols:

(b) (4)

(b) (4)

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#### 4.6 COVER SHEET & OCP FILING/REVIEW FORM

| Office of Clinical Pharmacology<br>New Drug Application Filing and Review Form |                           |                             |  |   |
|--|---------------------------|-----------------------------|--|---|
| General Information About the Submission                                       |                           |                             |  |   |
| NDA Number   | 22-311                    | Brand Name                  | Mozobil®   |   |
| DCP Division (I, II, III, IV, V)   | V                         | Generic Name                | Plerixafor   |   |
| Medical Division   | Oncology                  | Drug Class                  | Small molecule reversible CXCR4 inhibitor  |   |
| OCP Reviewer   | Jeanne Fourie, Ph.D.      | Indication(s)               | Lymphoma and multiple myeloma  |   |
| OCP Team Leader  | Brian Booth, Ph.D.        | Dosage Form                 | 20 mg/mL solution  |   |
| Date of Submission   | June 16, 2008             | Dosing Regimen              | 240 µg/kg 11 hours prior to initiation of apheresis, repeat dose up to 7 consecutive days. |   |
| Due Date of OCP Review   |                           | Route of Administration     | Subcutaneous injection   |   |
| Standard PDUFA Due Date  |                           | Sponsor                     | Genzyme Corporation  |   |
| Clinical Pharmacology Information  |                           |                             |  |   |
|  | "X" if included at filing | Number of studies submitted | Number of studies reviewed   | Critical Comments If any  |
| <b>STUDY TYPE</b>  |                           |                             |  |   |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                         |                             |  |   |
| Tabular Listing of All Human Studies   | X                         |                             |  |   |
| HPK Summary  | X                         |                             |  |   |
| Labeling   | X                         |                             |  |   |
| Reference Bioanalytical and Analytical Methods                                 | X                         | 6                           |  | 1 method for <sup>14</sup> CSDZ S D 791 in biological samples<br>1 method + validation for AMD3100 rat plasma<br>1 method + validation for ADM3100 dog plasma<br>1 validation for ADM3100 human plasma<br>1 validation for ADM3100 human samples<br>1 validation for ADM3100 human urine          |
| <b>I. Clinical Pharmacology</b>  |                           |                             |  |   |
| Mass balance   | X                         | 6                           |  | no human ADME/mass balance study<br>SDZ282-791: Rat ADME study with SC dose of 14C-SDZ 282-971<br>ADME study in dogs with 14CSDZ SID791-ch<br>7686-108 cms81280A: Mass Balance study in rats with 14C-AMD3100   |
| Isozyme characterization   | X                         | 5                           |  | AOM0038 metabolism in human microsomes<br>CT-249-PK-1 metabolic stability study human microsomes<br>AOM0067 and XT055036 inhibition studies human P450 isozymes<br>DMPK08-R001 induction study human P450 isozymes<br>GT-249-PK-2 metabolic stability study in human hepatocytes<br>No P-gp study |

|   |   |   |  |   |
|---|---|---|--|---|
| <b>Blood/plasma ratio:</b>                | X | 1 |  | GT-249-PK-4 Red blood cell partitioning in human whole blood  |
| <b>Plasma protein binding:</b>            | X | 2 |  | AOM0036 protein binding study to human plasma proteins<br>GT-249-PK-3 human whole blood stability/metabolism study  |
| <b>Pharmacokinetics (e.g., Phase I) -</b> |   |   |  |   |
| <i>Healthy Volunteers-</i>                |   |   |  |   |
| single dose:                              | X | 4 |  | AMD3100-98-01 safety, PK study; IV, SC, PO<br>AMD3100-1002 safety, PK, PD study; SC<br>AMD3100-1005 safety, PK, PD study; SC  |
| multiple dose:                            | X | 1 |  | AMD3100-1002 safety, PK, PD study; SC   |
| <i>Patients-</i>                          |   |   |  |   |
| single dose:                              | X | 3 |  | AMD3100-2106 with G-CSF in Hodgkin's Disease, Up to 5 SC doses, PK after first dose<br>AMD3100-C201 with G-CSF Phase 2 study in MM and NHL, Up to 5 CS doses, PK after first dose<br>AMD3100-CUP001 in all cancer except AML and CLL, SC dose, PK subset (ongoing) -PK subset report provided |
| multiple dose:                            | X | 1 |  | (b) (4)   |
| <b>Dose proportionality -</b>             |   |   |  |   |
| fasting / non-fasting single dose:        |   |   |  |   |
| fasting / non-fasting multiple dose:      |   |   |  |   |
| <b>Drug-drug interaction studies -</b>    |   |   |  |   |
| In-vivo effects on primary drug:          |   |   |  | Published manuscript showing synergy between G-CSF and AMD3100  |
| In-vivo effects of primary drug:          |   |   |  |   |
| In-vitro:                                 |   |   |  |   |
| <b>Subpopulation studies -</b>            |   |   |  |   |
| ethnicity:                                |   |   |  |   |
| gender:                                   |   |   |  |   |
| geriatrics:                               |   |   |  |   |
| renal impairment:                         | X | 1 |  | AMD3100-1101 Safety, PK, PD single dose study with mild, moderate and severe impairment   |
| hepatic impairment:                       |   |   |  |   |
| pediatrics:                               |   |   |  |   |
| <b>PD:</b>                                |   |   |  |   |

|                                     |   |    |   |
|-------------------------------------|---|----|---|
| Phase 2:                            | X | 11 | <p>AMD3100-1004 Phase 1B/2A open label safety and PD in MM and NHL</p> <p>AMD3100-2101 Phase 2 open-label cross-over safety and efficacy when given with G-CSF in MM and NHL</p> <p>AMD3100-2108 Phase 2 open-label single arm safety and preliminary efficacy in MM</p> <p>(b) (4)</p> <p>ISS –integrated summary of safety</p>  |
| Phase 3:                            |   |    |   |
| <b>PK/PD:</b>                       |   |    |   |
| Phase 1 and/or 2, proof of concept: | X | 4  | <p>AMD3100-1003 with G-CSF in healthy volunteers, single SC dose (160 and 240 µg/kg, safety and PD</p> <p>AMD3100-2106 Phase 2 single arm, safety, efficacy and PK in HD</p> <p>AMD3100-C201 Phase 2 open-label, single arm safety, PK and preliminary efficacy in MM and NHL</p> <p>AMD3100-CUP001 Open label safety and compassionate use study in all cancers except AML and CLL (ongoing) –PK report.</p> |

|   |                    |          |  |   |
|---|--------------------|----------|--|---|
| Phase 3 clinical trial:                                 | X                  | 2        |  | AMD3100-3101 Phase 3 double-blind placebo controlled safety and efficacy study in NHL<br>AMD3100-3102 Phase 3 double-blind placebo controlled safety and efficacy study in MM |
| <b>Population Analyses -</b>                            |                    |          |  |   |
| Data rich:  | X                  | 1        |  | Population PK analysis in 63 subjects (healthy volunteers, HD, NHL, MM and renal impaired non-cancer), single dose  |
| Data sparse:  |                    |          |  |   |
| <b>II. Biopharmaceutics</b>                             |                    |          |  |   |
| <b>Absolute bioavailability:</b>                        | X                  | 1        |  | AMD3100-98-01 safety, PK study; IV, SC, PO (note: deficiency in bioanalytical component limit validity of PK results).  |
| <b>Relative bioavailability -</b>                       |                    |          |  |   |
| solution as reference:                                  |                    |          |  |   |
| alternate formulation as reference:                     |                    |          |  |   |
| <b>Bioequivalence studies -</b>                         |                    |          |  |   |
| traditional design; single / multi dose:                |                    |          |  |   |
| replicate design; single / multi dose:                  |                    |          |  |   |
| <b>Food-drug interaction studies:</b>                   |                    |          |  |   |
| <b>QTC studies:</b>                                     | X                  | 1        |  | 06-H-0156 Phase 1 open-label QT/QTc and PK healthy volunteer study, 2 escalating doses  |
| <b>In-Vitro Release BE</b>                              | NA                 |          |  |   |
| <b>(IVIVC):</b>   |                    |          |  |   |
| <b>Bio-wavier request based on BCS</b>                  |                    |          |  |   |
| <b>BCS class</b>  |                    |          |  |   |
| <b>III. Other CPB Studies</b>                           |                    |          |  |   |
| <b>Biliary Elimination</b>                              | NA                 |          |  |   |
| <b>Pediatric development plan</b>                       | NA                 |          |  |   |
| <b>Literature References</b>                            |                    |          |  |   |
| <b>Total Number of Studies</b>                          |                    |          |  |   |
| <b>Filability and QBR comments</b>                      |                    |          |  |   |
|   | "X" if yes         | Comments |  |   |
| <b>Application filable?</b>                             | X                  |          |  |   |
| <b>Comments sent to firm?</b>                           | X                  |          |  |   |
| <b>QBR questions (key issues to be considered)</b>      |                    |          |  |   |
| <b>Other comments or information not included above</b> |                    |          |  |   |
| <b>Primary reviewer Signature and Date</b>              |                    |          |  |   |
| <b>Secondary reviewer Signature and Date</b>            | Brian Booth, Ph.D. |          |  |   |

CC: HFD-150 (CSO – S Jenney; MTL- A Farrell; MO –M Brave)  
HFD-860 (Reviewer –J Fourie and C Tornoe; DDD & Acting TL - B Booth; DD - A Rahman)

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