Australian Government

Department of Health and Ageing

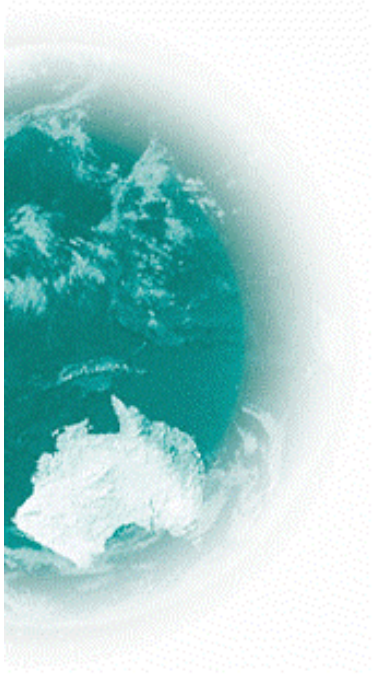
Therapeutic Goods Administration

Australian Public Assessment Report for Plerixafor

Proprietary Product Name: Mozobil

Submission No: SM- 2008-03602-4

Sponsor: Genzyme Australasia Pty Ltd



July 2010

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I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	18 May 2010
Active ingredient(s):	Plerixafor
Product Name(s):	Mozobil
Sponsor's Name and Address:	Genzyme Australasia Pty Ltd, PO Box 282, NORTH RYDE BC NSW 1670
Dose form(s):	Plerixafor in saline
Strength(s):	24 mg in 1.2 mL (20 mg/mL)
Container(s):	Vial
Pack size(s):	1 vial
Approved Therapeutic use:	Mozobil is indicated in combination with granulocyte-colony stimulation factor (G-CSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.
Route(s) of administration:	Subcutaneous injection
Dosage:	0.24 mg/kg to be administered 6 to 11 hours prior to initiation of apheresis.
ARTG number(s):	158423

Product Background

Genzyme Australasia Pty Ltd seeks to register plerixafor (Mozobil) subcutaneous injection for use (in combination with granulocyte-colony stimulating factor (G-CSF)) to mobilise hematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

The recommended dose is 0.24 mg/kg body weight by subcutaneous injection (for example, for 100 kg patient: 24 mg given as a 1.2 mL subcutaneous injection).

Regulatory Status

Mozobil has been designated an Orphan Drug in Australia.

Currently, Mozobil has received marketing authorisation in 33 countries worldwide (United States of America, the 27 member states of the European Union (EU), Norway, Iceland, South Korea, Israel, and Brazil) and is commercially available in 12 countries.

The approved indication in the US, South Korea, and Brazil is as follows:

Mozobil (plerixafor injection) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

The approved indication in the 27 member states of the EU, Norway, Iceland, and Israel is as follows:

Mozobil is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.

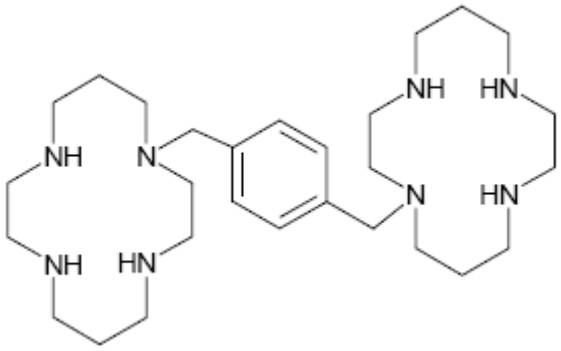
Product Information

The approved Product Information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Plerixafor is achiral and has no stereoisomers. Plerixafor is a crystalline solid, but it is in solution in the proposed dosage form.



plerixafor

$C_{28}H_{54}N_8$ MW 502.79

Company codes: AMD3100 (AnorMED/Genzyme), P104 (Patheon), FP0063 (Aptuit)

Plerixafor is 'freely soluble' (> 80 mg/mL) in water at all relevant pHs. Impurities are synthetic byproducts.

Drug Product

Mozobil is a clear, colourless to pale yellow, sterile, unpreserved, isotonic solution for subcutaneous injection. Clear glass vials contain 24 mg of plerixafor in 1.2 mL solution (there is an overfill to allow withdrawal of the labelled volume). The solution consists simply of plerixafor dissolved in saline with adjustment of pH (6.0 to 7.5). The filled vials are terminally sterilised.

Four different formulations were used in clinical trials. These differed in drug and salt (sodium chloride) concentration and presentation (vials and ampoules). The proposed formulation has a higher concentration than initially chosen, reducing the subcutaneous injection volume. These differences are unlikely to be clinically significant; the sponsor claims that a population pharmacokinetic analysis shows "no apparent differences" in pharmacokinetics.

Manufacturing and quality control aspects are conventional.

Bioavailability

One study was conducted which included a pharmacokinetic comparison of subcutaneous (SC) and intravenous (IV) (and oral) doses. Study AMD3100-98-01 compared 10, 20, 40, and

80 μg/kg IV; 40 and 80 μg/kg SC; and 80 and 160 μg/kg oral doses in 13 healthy subjects (analysable). Unfortunately, the sponsor's audits of the site where study samples were analysed found deficiencies in the conduct and reporting of results consistent with those identified by the FDA. The results of the study are thus unreliable. Because of these deficiencies, this study has not been reviewed in detail by the TGA.

Plerixafor is not metabolised. Urinary excretion after 240 μg/kg doses in healthy volunteers with normal renal function is reported to be approximately 70% within 24 hours of dosing.

The draft PI makes no recommendation about the site of subcutaneous injection. This can affect the bioavailability of some drugs, and in the absence of further data it might be prudent to recommend use in keeping with clinical trials.

Quality Summary and Conclusions

Registration is recommended with respect to chemistry and biopharmaceutics aspects.

III. Nonclinical Findings

Introduction

Similar submissions have been approved by the FDA and EMA (European Medicines Agency). The FDA pharmacology review is available on the FDA Website[1], and the following brief assessment is based on the FDA evaluation report.

The TGA evaluator commented that the nonclinical data package is considered adequate given the short duration of use (about 4 to 7 days) and the proposed indication. However, there are a number of deficiencies in the nonclinical data, in that no fertility or postnatal development data were submitted.

Pharmacology

Plerixafor is a haematopoietic stem cell mobiliser. It mobilised and repopulated haematopoietic stem cells in mice, dogs and monkeys. Such effects were due to the interruption of the interaction between chemokine receptor CXCR4 and its ligand SDF-1 (stromal cell-derived factor-1). Plerixafor enhanced granulocyte colony-stimulating factor (G-CSF)-induced mobilisation and engraftment of haematopoietic stem cells and haematopoietic progenitor cells in mice (irradiated prior to transplantation). Plerixafor induced mobilization and engraftment of haematopoietic stem cells and haematopoietic progenitor cells in dogs (autologous and allogeneic transplantation) and monkeys (autologous). The animal models were relevant and the nonclinical data support the efficacy of plerixafor for the proposed indication.

Pharmacokinetics

P-glycoprotein interactions

As part of the post-approval requirements, the FDA required the sponsor to conduct an *in vitro* p-glycoprotein interaction study. This report was completed in June 2009 and was sent to the TGA when requested. The study was adequately conducted with appropriate controls. Plerixafor did not act as a substrate or as an inhibitor of p-glycoprotein.

Relative Exposure

The area under the plasma concentration time curve from time zero to 24 hours ($AUC_{0\text{-}24\,h}$) values for subjects with healthy kidney function after a single dose of 240 μg/kg plerixafor

[1] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022311s000TOC.cfm

varied between 3817 and 5070 ng.h/mL. One trial (C201) investigated the pharmacokinetics in nine patients with non-Hodgkins lymphoma or multiple myeloma, the proposed indication group. The mean $AUC_{0\text{-}24\ h}$ value for this group of patients was 4500 ng.h/mL, and the maximal observed plasma concentration (C_{max}) was 0.93 μg/mL; these values are considered to be the most appropriate for relative exposure calculations. No pharmacokinetic parameters were determined in humans after repeat dosing.

Toxicology

The safety pharmacology studies in mouse, rat and dog, and general toxicology studies in rat, and dog identified liver, spleen, bone, respiratory, central nervous and cardiovascular systems and the injection sites as the target organs/tissues.

Haematopoietic/lymphoid system

The most prominent effect of plerixafor in rats following 4-week repeat-dose treatment was leukocytosis (increased total and differential white blood cell counts). The increase was dose-dependent (at doses ≥ 1.9 mg base/kg/day, AUC ≥ 5x the clinical value) and was reversible. Leukocytosis is at least partially due to an exaggerated pharmacological effect of plerixafor. In rats, increased hematopoiesis in spleen and liver and increased spleen weight were also observed (see discussion below). It was not certain whether lymphoid atrophy in spleen and thymus was a direct effect of plerixafor treatment. The haematological or lymphoid changes were not remarkable in dogs.

Effect on the spleen

In rat 2- and 4-week repeat dose studies there was a significant increase in relative and absolute spleen weights. This increase was statistically significant at ≥ 1.9 mg base/kg/day in both sexes in study 428r-tox. The $AUC_{0\text{-}24\ h}$ values at 1.9 mg base/kg/day in males and females after 30 days of exposure were 30.4 and 22.4 μg.h/mL respectively, giving an animal: human exposure ratio of 7 and 5 respectively, using a clinical $AUC_{0\text{-}24\ h}$ value of 4500 ng.h/mL.

In a two week preliminary rat study (189dfr) extramedullary haematopoiesis was observed in treated spleens more than control spleens. However, extramedullary haematopoiesis was not observed in the four week studies with larger numbers/group. It therefore does not seem appropriate to state that the increase in spleen weight was associated with extramedullary haematopoiesis.

Bone

Reduced bone mineral content of the tibia and humerus, and reduced bone volume in the humerus indicated increased bone mineral loss. This finding may be an exaggerated pharmacological effect of plerixafor. Disruption of CXCR4-related cellular activity was reported to enhance bone loss. The finding was recoverable. Consistent with the bone findings, elevated urinary calcium and magnesium levels were found in rats and dogs. Serum magnesium levels were decreased, but changes in calcium levels were inconsistent.

Central nervous system and respiratory system

In mice and rats, plerixafor treatment was associated with central nervous system (CNS) suppressive effects. These effects included decreased in-place and locomotor activity, alertness, startle response, dilated pupils and ptosis. In contrast, a CNS stimulant-like response was observed when animals were handled. The suppressive CNS effects may be the underlying mechanism of observed decreases in tidal volumes and respiratory rates in rats. Distribution studies showed that plerixafor or plerixafor-related compounds can cross the

blood-brain barrier in rats. In addition, small but measurable amounts of plerixafor were detected in the cerebro-spinal fluid of dogs in a toxicology study. Of note, plerixafor was shown to bind to adrenergic receptors as well as dopamine D_2 receptor at micromolar ranges. In dogs, clinical signs of salivation, pupil dilatation and non-sustained convulsion may also be a CNS-related phenomenon.

Cardiovascular system

Plerixafor did not inhibit hERG channel currents or induce electrocardiogram (ECG) changes in telemetered dogs. Histopathological findings in the cardiovascular system were limited to fibroid necrosis of the myocardial blood vessel wall found in one study conducted in dogs. However, in anesthetized rats, cardiodepression (that is, decreased blood pressure, heart rates and myocardial contractility) was fatal at 6 mg base/kg IV infusion, and was also observed at 12 mg base/kg SC. Deaths observed in repeat-dose studies at high doses (15 mg base/kg/day SC, C_{max}=32 μg/mL, 35 times the clinical value) may, in the nonclinical evaluator's opinion, also have been related to cardiosuppression. On the contrary, plerixafor treatment in conscious dogs induced tachycardia and hypertension. Plerixafor was shown to inhibit angiotensin II-induced vasoconstriction in cultured rat aortic smooth muscle cells and to bind to adrenergic receptors (rat and bovine). These findings provide additional mechanisms for cardiovascular dysfunction observed in animals treated with plerixafor.

Other toxicities

Plerixafor treatment in dogs caused gastrointestinal (GI) clinical signs, such as diarrhoea, emesis, increased defecation and salivation, with no histopathological correlate. Lesions at the injection sites (subcutaneous haemorrhage and inflammation, thickening of the skin) were attributable to repeated needle penetration and/or direct local irritation caused by plerixafor, and the SC injection of Mozobil is not expected to cause severe local irritation in patients.

Phototoxicity

Plerixafor distributed to melanin-containing tissues, such as the skin and the uveal tract, in rats. Phototoxicity might be an issue if plerixafor absorbed light. The sponsor provided the absorption spectrum of 20 mg/mL (40 mM) plerixafor (Figure 1). Plerixafor absorbed ultraviolet B light (wavelengths between 290 and 320 nm. The molar absorption coefficient of plerixafor at 290 nm can be calculated as 45 $M^{-1}cm^{-1}$, assuming that a 1 cm path length was used. In a recent paper[2] examining 35 molecules with known photosafety issues, it was established that all of these molecules had a molar absorption coefficient > 1000 $M^{-1}cm^{-1}$. Thus, although plerixafor absorbs UV-B light, the low molar absorption coefficient (45 $M^{-1}cm^{-1}$) gives some justification to the sponsor's statement that plerixafor "has no significant absorbance in the visible range." The sponsor also stated that plerixafor does not have the molecular characteristics (planar, polycyclic, and aromatic) of agents that interact strongly with light.

[2] Henry B, Foti C and K Alsante (2009) J Photochem Photobiol B: Biol 96: 57-62 "Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule?"

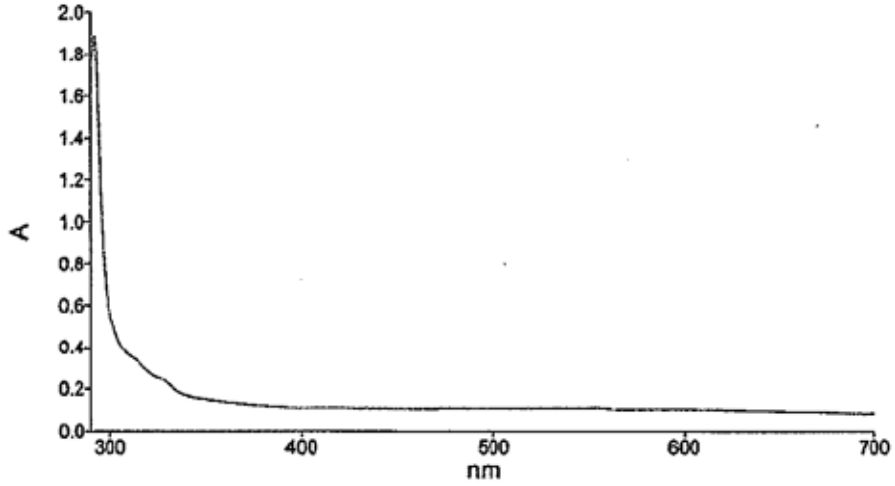


Figure 1 The absorption spectrum of 20 mg/mL plerixafor.

According to the sponsor's studies, plerixafor is photostable. In section 4 of the EU guidance document CPMP/SWP/398/01 (Note for Guidance on Photosafety Testing) it is stated that findings from photostability testing and consideration of structure-activity relationship may help to determine whether photosafety testing is warranted. In contrast, the US FDA "Guidance for Industry Photosafety Testing" May 2003 does not mention photostability as a consideration in determining whether phototoxicity testing is necessary. In addition, it has recently been demonstrated that some molecules with photosafety issues are photostable (for example, fluorouracil and acridine) (Henry *et al*, 2009). Henry *et al* concluded that photostability testing in physiological buffers is an inadequate predictor of photosafety. Thus the photostability of plerixafor is not considered to be a major factor in justifying the absence of photosafety testing.

In conclusion, the photosafety testing of plerixafor is considered to be unnecessary given the low molar absorption coefficient, the nature of the indication and the likelihood that most of the patients will not be exposed to significant amounts of sunshine during the treatment period.

Reproductive toxicity

No fertility or postnatal development studies were conducted. The potential effects on fertility are unknown. In studies conducted to measure the distribution of ^{14}C-plerixafor, there was no evidence of accumulation in rat testes. The staging of spermatogenesis measured in a 28-day repeat-dose toxicity study in rats revealed no abnormalities considered to be related to plerixafor. Using an $AUC_{0\text{-}24\ h}$ of 161.7 μg.h/mL, the rat: human exposure ratio in this study was 36. No histopathological evidence of toxicity to male or female reproductive organs was observed in repeated dose toxicity studies. The lack of fertility studies is acceptable because of the proposed indication and the absence of toxicity to reproductive organs at sufficiently high exposures.

A well-conducted, Good Laboratory Practice (GLP) embryofetal development study was conducted in rats, but only a small, non-GLP-compliant embryofetal study was conducted in rabbits. Both studies included toxicokinetic information.

Plerixafor administered to pregnant rats induced embryofetal toxicities including fetal death, increased resorptions and post-implantation loss, decreased fetal weights, anophthalmia, shortened digits, cardiac interventricular septal defect, ringed aorta, globular heart, hydrocephaly, dilatation of olfactory ventricles and retarded skeletal development. Embryofetal toxicities occurred mainly at 15 mg base/kg/day ($AUC_{0\text{-}24\ h}$ = 63,500 ng.h/mL

on gestation day (GD) 6, 81,300 ng/h/mL on GD 17), and were accompanied by maternal toxicity. However, there was a significant increase in common skeletal variations of the thoracic centrum at 3 mg base/kg/day ($AUC_{0\text{-}24\ h}$ = 14,100 ng.h/mL on GD 6, 16,750 ng.h/mL on GD 17). Therefore the No Observable Effect Level (NOEL) for rat embryofetal toxicity was 0.5 mg base/kg/day ($AUC_{0\text{-}24\ h}$ = 2100 ng.h/mL on GD 6, 4200 ng.h/mL on GD 17). Using a clinical $AUC_{0\text{-}24\ h}$ of 4500 ng.h/mL, the NOEL in rats was at an exposure ratio <1.

In the rabbit study (6 dams/group) maternal mortality occurred at ≥ 1.9 mg base/kg/day ($AUC_{0\text{-}6\ h}$ ≥ 11,100 ng.h/mL), and maternal toxicities occurred at all doses tested (≥ 0.6 mg base/kg/day, $AUC_{0\text{-}6\ h}$ ≥ 4882 ng.h/mL). At 6.3 mg base/kg/day there was an increase in post-implantation loss. There were external malformations in the fetuses at ≥ 1.9 mg base/kg/day, including aplasia of toes and head malformations. There was no mention of fetal weight or retarded skeletal development in the report, although these would be expected to have been affected by plerixafor. Given the small size of this study, it is inappropriate to set a NOEL using this study.

Pregnancy classification

The sponsor has proposed a pregnancy category of B3. The US has accepted a pregnancy category of D, which in the US means: "There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks." The Australian definition of category D is as follows: "Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details." Plerixafor was clearly teratogenic in rats and rabbits, and therefore may be expected to cause an increased incidence of human fetal malformations. It is therefore appropriate to classify plerixafor as pregnancy category D in Australia.

Nonclinical Summary and Conclusions

The nonclinical evaluation has relied primarily on the publicly available FDA Pharmacology Review. The nonclinical pharmacodynamic data support the proposed clinical use.

Plerixafor did not act as a substrate or as an inhibitor of p-glycoprotein in an *in vitro* study.

Safety pharmacology and repeat dose toxicity studies showed that the target organs of plerixafor are the liver, spleen, bone, injection sites and the respiratory, central nervous and cardiovascular systems. An increase in spleen weights was observed in rats at 5 times the anticipated clinical exposure.

Plerixafor was found not to be genotoxic in adequate studies. No carcinogenicity studies were conducted, which is acceptable for the proposed clinical use of a non-genotoxic compound.

Plerixafor was teratogenic in both rats and rabbits. The sponsor proposed a pregnancy category of B3. Given that plerixafor may be expected to cause an increased incidence of human fetal malformations, it is recommended that the pregnancy category should be D.

No nonclinical toxicity combination studies were conducted with plerixafor. The safety of concomitant use with G-CSF will need to be assessed by clinical data.

There are no nonclinical objections to the registration of plerixafor for the proposed indication.

IV. Clinical Findings

Introduction

In the clinical development programme, plerixafor has primarily been investigated in conjunction with G-CSF as a first-line mobilisation therapy regimen; however it has also been studied in poor mobiliser patients. The "poor mobiliser" population consists of 2 groups of patients: those who failed to collect enough cells in apheresis and those who are predicted to fail, either because of low peripheral blood (PB) hematopoietic progenitor cells expressing the CD34 antigen (PB CD34+ cells) counts or occasionally by the use of other surrogate markers such as total white blood cell (WBC) count, and thus do not even undergo apheresis. It is generally difficult to predict poor mobilisers, but PB CD34+ cell level may be used as an indicator.

The proposed target population for plerixafor is adult patients with lymphoma or multiple myeloma (MM), as these patient populations were studied in the Phase II and III studies. As of 29 February 2008, over 1400 subjects had received at least 1 dose of plerixafor in the clinical development programme and are used to establish the safety profile of plerixafor. Data from a total of 345 oncology patients (165 Non-Hodgkin's lymphoma (NHL), 158 MM and 22 Hodgkin's disease (HD)) treated with plerixafor in conjunction with G-CSF in 2 Phase II studies (AMD3100-2101 and -2106) and 2 Phase III studies (AMD3100-3101 and -3102) are used to demonstrate efficacy. All clinical studies were conducted in accordance with International Conference on Harmonization guidelines on Good Clinical Practice.

Clinical Pharmacology Studies

Data were submitted from the following clinical pharmacology studies:

- Pharmacokinetic (PK)/pharmacodynamic (PD) Phase I studies of plerixafor alone in healthy subjects: AMD3100-98-01#, -1002, and -1005#
- PD Phase I study of plerixafor in conjunction with G-CSF in healthy subjects: AMD3100-1003
- PD Phase I study of plerixafor alone in oncology patients: AMD3100-1004
- PK/PD Phase I study of plerixafor alone in renally impaired non-oncology patients: AMD3100-1101
- PK /PD Phase II studies of plerixafor in conjunction with G-CSF in oncology patients: AMD3100-C201* (NHL and MM), -2106* (HD)

*Ongoing studies, see further information below.

PK data in AMD3100-98-01 and -1005 were provided for informational use only due to audit issues of the testing laboratory.

Efficacy and Safety Data

Studies nominated as ***pivotal studies*** by the sponsor to demonstrate efficacy and safety included the following:

- Phase II efficacy and safety studies of plerixafor in conjunction with G-CSF in oncology patients: AMD3100-2101 (NHL and MM), -2106* (HD)
- Phase III placebo-controlled efficacy and safety studies of plerixafor in conjunction with G-CSF in oncology patients: AMD3100-3101* (NHL), -3102* (MM)

*Ongoing studies.

Supportive studies providing additional safety, efficacy and/or clinical pharmacology data included the following:

- Phase II studies of plerixafor in conjunction with G-CSF in oncology patients: AMD3100-2103 (NHL), -2105 (NHL and MM), -2109 (NHL and MM), -EU21 (NHL and MM)
- Phase II study of plerixafor alone in oncology patients: AMD3100-2108 (MM)
- Phase II study of plerixafor in conjunction with G-CSF and chemo-mobilisation in oncology patients: AMD3100-2104 (NHL and MM)
- Phase II study of plerixafor in conjunction with G-CSF and rituximab in oncology patients: AMD3100-2113* (NHL and HD)
- Phase II studies of plerixafor in conjunction with G-CSF in poor mobilisers: AMD3100-2102 (MM), -2112* (all cancers but amended to exclude acute myeloid leukaemia and chronic lymphocytic leukaemia)
- Phase II study of plerixafor alone in patients with HIV: AMD3100-2001
- Compassionate Use Programme (CUP)* of plerixafor in conjunction with G-CSF in oncology patients: all cancers (excluding leukaemia patients)

*Ongoing studies

Ongoing clinical studies at the time of submission included the following:

- Enrolment complete, patient follow up ongoing: AMD3100-C201, -2106, -3101, -3102
- Enrolment ongoing: AMD3100-2112, -2113, and CUP.

Other serious adverse event (SAE) data reported to 29 February 2008 from all available patients in the ongoing studies were included.

Pharmacokinetics

No PK data were collected in studies 1003 and 1004.

Study AMD3100-1002

Pharmacokinetic Results

A total of 26 subjects enrolled in this study with 18 sets of plasma samples available for PK analysis (40 μg/kg N=3; 80 μg/kg N=5; 160 μg/kg N=5; 240 μg/kg N=5). Based on individual subject PK modelling, observed concentrations of the drug were well described with a 2-compartment PK model, but estimations of PK parameters were similar between noncompartmental and compartmental analyses.

Mean values of AUC_{0-10} and C_{max} observed in this study suggest that plerixafor concentrations increased in a dose-proportional manner over the dosing range of 40 to 240 μg/kg after a single SC administration in normal healthy subjects (see Table 1). The mean C_{max} increased from 128 ng/mL at a dose of 40 μg/kg to 847 ng/mL at a dose of 240 μg/kg. In this study, the AUC was not extrapolated to 24 hours for subjects in the lower dose groups who had undetectable plerixafor concentrations by 24 hours post-dose. Therefore, the mean AUC_{0-24} is reported for the 240-μg/kg dose group only (3817 ng*hour/mL).

Table 1: Noncompartmental Pharmacokinetic Parameters From Individual Clinical Studies of Plerixafor, Excluding the CUP Programme.

Study AMD 3100-	**Dose level** μg/kg	**RF**	**C_{max}** ng/mL	**CL/F** L/h	**V_z/F** L	**T_{max}** h	**$t_{1/2}$** h	**AUC_{0-10h}** ng.h/mL	**AUC_{0-24h}** ng.h/mL
1002 (n=18)	40	N/A	128± 13.8	5.71± 0.900	25.6± 3.1	0.5 (0.5, 0.5)	3.1± 0.12	400± 11.2	ND
	80	N/A	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	N/A	565± 127.3	4.72± 1.049	24.9± 9.25	0.5 (0.5, 1.0)	3.6± 0.77	1932± 194.4	ND
	240	N/A	847± 95.6	4.53± 0.830	32.3± 9.11	0.5 (0.25, 1.0)	4.9± 0.71	3159± 343.6	3817± 384.2
C201 (n=13)	240	N/A	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
2106 (n=9)	240	N/A	831± 183	5.14± 2.03	25.5± 9.00	0.5 (0.3, 1.3)	3.5± 0.7	3572± 772	4072± 875
1101 (n=23)	240	Control	980± 196	4.38± 0.821	30.3± 3.62	0.56 (0.5, 1.02)	4.9± 0.56	3940± 637	5070± 979
	240	Mild	739± 76.1	3.50± 1.690	35.7± 5.58	0.5 (0.5, 1.0)	7.8± 2.15	3700± 493	5410± 1070
	240	Moderate	936± 280	2.42± 1.110	40.9± 13.50	0.5 (0.25, 1.0)	12.1± 2.06	4220± 1060	6780± 1660
	240	severe	861± 193	1.82± 0.380	40.6± 14.10	0.75 (0.5, 1.0)	15.8± 5.79	4160± 704	6990± 1010
06-H-0156 (n=6)	400	N/A	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 for T_{max} which is reported as median (min, max),.
ND=no done, N/A=not applicable, RF=renal function.

Study AMD3100-C201

Pharmacokinetic Results

PK data were available on 13 patients; 5 with NHL and 8 with MM, including 9 males and 4 females. Plerixafor was rapidly absorbed, with peak concentrations occurring 0.5 hours after dosing (see Table 2). Maximal plasma concentrations ranged from 585 to 1510 ng/mL, with a mean of 926.2 ng/mL. Plerixafor had a small apparent volume of distribution, with a median value of 28.6 L, suggesting that plerixafor is primarily confined to slightly less than the whole body fluid compartment. Plerixafor was rapidly cleared, with a mean half life ($t_{½}$) of 5.1 hours.

Additional analyses were performed to assess potential differences in the pharmacokinetics of plerixafor in patients with NHL and MM. Table 2 summarises select PK parameters by patient diagnosis. Systemic exposure to plerixafor was slightly higher in patients with MM compared with patients with NHL. However, the differences in parameters of exposure (that is, C_{max} and AUC) and mean plasma concentrations between the two disease groups are within the expected variability of the pharmacokinetics of plerixafor and are not likely to be clinically relevant.

Table 2: Summary of Select Plerixafor Pharmacokinetic Parameters By Patient Diagnosis in Study C201

Diagnosis	Statistic	C_{max} (ng/mL)	AUC_{0-10h} (ng.h/mL)	AUC_{0-24h} (ng.h/mL)	$t_{1/2}$ (h)
NHL	N	5	5	5	5
	Mean	761	3035	3686	4.4
	SD	101	412	625	1.1
	Min	585	2502	2678	2.7
	Median	799	3012	3907	4.5
	Max	831	3485	4280	5.4
	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	743	3424	4181	3.7
	Median	995	3866	4976	4.7
	Max	1510	5288	6515	11.7
	CV%	23.6	15.5	14.7	46.6

Study AMD3100-2106

Pharmacokinetic Results

PK data were available from 9 patients (4 males, 5 females) with HD.

Plerixafor was rapidly absorbed, with C_{max} occurring 30 minutes after dosing (see Table 1). Maximal plasma concentrations ranged from 622 to 1160 ng/mL. Plerixafor had a small apparent volume of distribution with a median value of 25.9 L, supporting that the drug is primarily confined to slightly less than the whole body fluid compartment. Plerixafor was rapidly cleared, with a terminal elimination half-life ($t_{1/2}$) ranging from 2.4 to 4.3 hours (mean $t_{1/2}$ of 3.5 hours). The percentage of AUC_{0-inf} due to extrapolation was less than 15% in all but 1 of 9 patients; hence estimated values of apparent clearance (CL/F) and apparent volume of distribution (VZ/F) can be considered reliable.

Study AMD3100-1101

Pharmacokinetic Results

23 subjects (17 with renal impairment and 6 healthy controls) were enrolled in this study, and the subjects were stratified into 4 cohorts as shown in Table 3. Plerixafor was rapidly absorbed in all cohorts. Peak concentrations were reached in 0.25 to 1 hour post-dose (see Table 1). PK parameters related to the absorption of plerixafor (for example, time to maximal observed plasma concentration, T_{max}, and the maximal observed plasma concentration, C_{max}) did not differ among cohorts.

Table 3: Stratification of Subjects According to Renal Clearance in Study 1101

Cohort	Number of subjects	Renal function	Average renal clearance (mL/min)[a]
Severe impairment	6	Severe	<31, not requiring dialysis
Moderate impairment	6	Moderate	31-50
Mild impairment	5	Mild	51-80
Control	6	normal	>90

[a]based on a screening 24-h urine collection

Table 4: Treatment Comparison for Dose-Normalised Parameters After Ln-Transformation in Study 1101

Parameter	Least-Square Means		Treatment Comparison	Ratio of Least-square Means(%)	90% Geometric C.I.	
	Control	Impaired Cohort			Lower	Upper
Ln C_{max}	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_{0-24}	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

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_{0-24} increased with decreasing renal function. Subjects with mild, moderate, and severe renal impairment had average increases in their ln-transformed least squares mean values of AUC_{0-24} of 7%, 32%, and 39%, respectively, in comparison to subjects with normal renal function (see Table 4). A statistically significant difference among cohorts for AUC_{0-24} was observed (p=0.0149).Consistent with the observed increase in systemic exposure with increasing renal dysfunction, mean CL/F and renal clearance over 24 hours (Clr_{0-24}) were reduced in subjects with renal impairment (see Tables 1 and 5). In the control cohort, approximately 71% of the parent compound was recovered in the urine by 24 hours post-dose compared to 40%, 27%, and 14% in the mild, moderate, and severe renal impairment cohorts, respectively. It was determined that approximately 4% of parent compound was excreted in urine during the period from 24 to 48 hours, for some subjects with mild and severe impairment.

The effect of reduced renal elimination resulted in an increase in the mean $t_{1/2}$, from 4.9 hours in subjects with normal renal function to 15.8 hours in those with severe impairment. Regression analyses showed a significant ($p<0.005$) negative correlation between AUC_{0-24} and Clr_{0-24} , however no such correlation was observed between C_{max} and Clr_{0-24}.

Table 5: Clearance and Excretion of Plerixafor in Healthy and Renally Impaired Subjects After a Single 240-µg/kg Dose in Study 1101 (Mean ± SD)

PK parameter	Control N=6	Mild N=6	Moderate N=6	Severe N=6
Clr_{0-24h} (mL/h)	3150±1700	1640±1060	827±404	346±134
Fe_{0-24h} (%)	71.09±42.78	40.46±9.62	26.52±5.29	13.57±6.58

Study AMD3100-CUP001

Pharmacokinetic Results

PK data were available for analysis from a total of 5 adult patients with renal dysfunction (creatinine clearance (CrCl)) values ranged from 19.0 to 48.0 mL/min). Four patients received 240 µg/kg plerixafor and 1 patient received 160 µg/kg on Day 1. Day 2 PK data were available for 2 adult patients, 1 who received 160 µg/kg and the other who received 240 µg/kg. Plerixafor was rapidly absorbed, with peak concentrations recorded 30 to 60 minutes after dosing. Day 1 C_{max} values ranged from 773 to 879 ng/mL in adult patients with renal dysfunction following a 240-µg/kg dose.

Study 06-H-0156

Pharmacokinetic Results

Plerixafor was rapidly absorbed by 6 healthy subjects following a 400-µg/kg dose, reaching peak concentrations approximately 30 minutes to 1 hour post-dose. The mean $t_{1/2}$ was 5.3 ± 1.1 hours. Mean values of C_{max}, AUC_{0-10}, and AUC_{0-24} were 1368 ± 169 ng/mL, 5930 ± 726 hour*ng/mL, and 7670 ± 1280 hour*ng/mL, respectively.

Drug Interactions

There were no specific Drug Interaction studies submitted with this application.

Pharmacodynamics

The clinical studies that contribute to PK and PD analyses of plerixafor in healthy subjects and oncology patients (including multiple myeloma (MM), Non-Hodgkin's lymphoma (NHL), and Hodgkin's disease (HD)) are:

- PK data from Studies AMD3100-1002, AMD3100-C201, AMD3100-2106, and AMD3100-1101.
- PK data from the United States (US) compassionate use programme (CUP) (AMD3100-CUP001) and an Investigator-sponsored study (06-H-0156) at the National Institutes of Health, Bethesda, MD, US (United States).

Three additional studies (AMD3100-98-01, AMD3100-2001, and AMD3100-1005) included PK analyses. In recognition of some deficiencies in the conduct and reporting of results, the sponsor stated that PK results from these studies are not used to support statements concerning the pharmacokinetics of plerixafor. Results from these studies will not be discussed in this evaluation report.

All official protocol and study numbers in the clinical programme were prefixed with 'AMD3100'.

Studies in Healthy Subjects

Study AMD3100-1002

Study Design and Objectives

This was an open-label, single-centre study designed to examine the safety, pharmacokinetics, and haematological activity of plerixafor in healthy subjects. The study

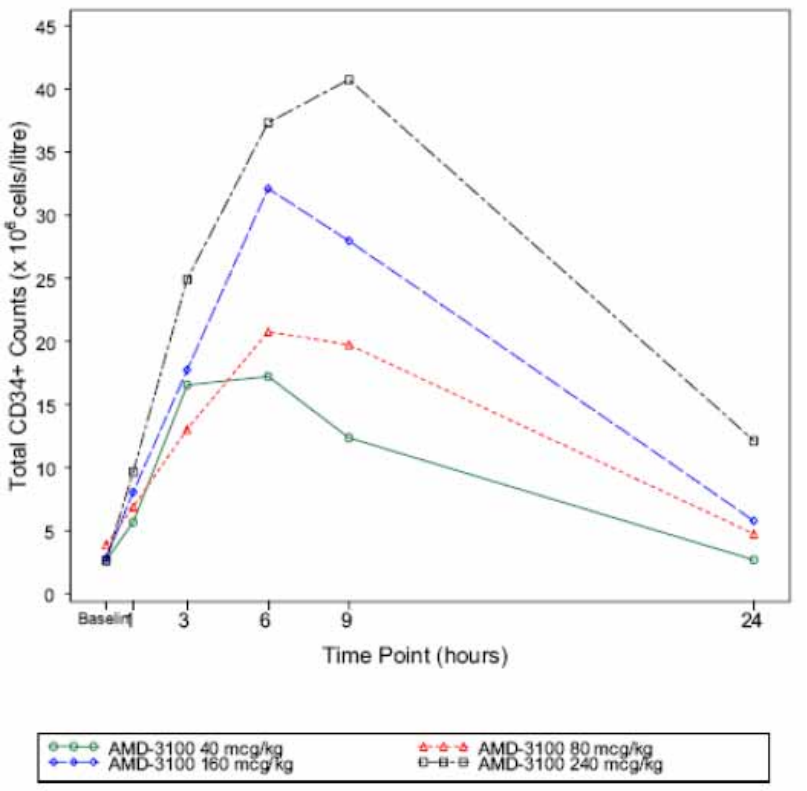
evaluated effects of a single subcutaneous (SC) injection of 4 different doses (40, 80, 160, or 240 µg/kg of plerixafor) on pharmacodynamics, pharmacokinetics, and safety parameters. PK parameters were estimated using compartmental and non-compartmental methods. Dose proportionality was assessed using the following PK parameters: area under the curve from time 0 to 10 hours post-dose (AUC_{0-10}), C_{max}, apparent volume of distribution ($V_{area/F,}$), apparent total volume of distribution ($V_{SS/F}$), and apparent clearance (CL/F). T_{max} and $t_{1/2}$ were also assessed.

The PD activity of plerixafor was assessed by measuring the functionality of mobilised cells (that is, assessing the number of colony forming units (CFUs)) and counting the number of PB CD34+ cells (using Fluorescence Activated Cell Sorter (FACS) analysis).

Pharmacodynamic Results

Single-dose administration of plerixafor injection produced increases in mean absolute PB CD34+ cell counts in all dose groups (40 µg/kg N=3; 80 µg/kg N=10; 160 µg/kg N=5; 240 µg/kg N=5). The changes from baseline were clinically significant and dose dependent, as shown in Figure 2. Peak absolute responses were observed at 6 to 9 hours post-dose for all dose levels. Values returned to approximately baseline levels at 24 hours post-dose in all dose groups, with the exception of the 240-µg/kg dose. The PB CD34+ cell response to 240 µg/kg plerixafor was greater than the response to 40, 80, and 160 µg/kg at 3, 6, and 9 hours post-dose. It is possible that the peak responses may have occurred later than 9 hours and before the 24-hour blood draw.

Figure 2: Mean Absolute PB CD34+ Cell Counts in Healthy Subjects After a Single Subcutaneous Dose of Plerixafor in Study 1002



Study AMD3100-1003

Study Design and Objectives

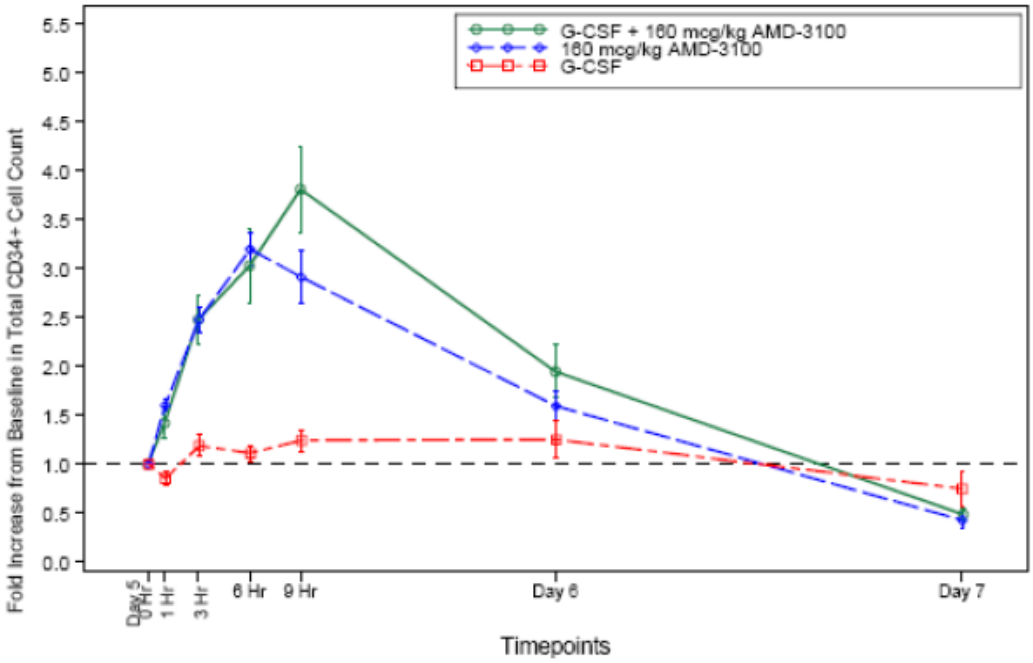
This was a randomised, open-label, single-centre study designed to examine the safety and efficacy (that is, haematological activity) of 7 regimens of plerixafor with G-CSF (10µg/kg) or G-CSF alone in healthy subjects. PD analyses were performed on samples from 5 of the 7 regimens. All subjects received 4 days of G-CSF prior to any plerixafor. Two doses of plerixafor were assessed in combination with G-CSF on Day 5 – a single SC injection of either 160 or 240 µg/kg. In addition, PD analyses of 160 µg/kg plerixafor alone and G-CSF alone were performed on Day 5.

Pharmacodynamic Results

Twenty nine subjects participated in this study. As the protocol did not prohibit re-enrolment, 2 subjects were enrolled in 2 treatment groups. Therefore, 29 subjects received a total of 31 doses of study drug. 25 subjects had samples for PD evaluation in study 1003 (G-CSF alone N=6; 160 µg/kg N=6; G-CSF and 160 µg/kg N=6; G-CSF and 240 µg/kg N=7), although only the 240-µg/kg dose level was sampled after 9 hours post-dose.

An initial comparison was performed in patients treated with 5 days of G-CSF alone, plerixafor 160 µg/kg alone after 4 days of G-CSF, and plerixafor 160 µg/kg given with G-CSF on Day 5. The greatest PD response, measured by either mean change in absolute CD34+ levels or fold-increase in PB CD34+ cells occurred when plerixafor 160 µg/kg was given with G-CSF on Day 5, as shown in Figure 3. After a 4-day regimen of G-CSF, similar mean change in absolute CD34+ levels and mean fold- were noted when 160-µg/kg and 240-µg/kg plerixafor were administered with G-CSF on Day 5. The peak response in the 240-µg/kg dose level was from 10 to 14 hours post-dose. At this dose level, plerixafor increased absolute PB CD34+ cells counts (following G-CSF administration) from a baseline cell count of ~50 cells/L to a peak cell count of 200 cells/µL.

Figure 3: Mean Fold-Change in PB CD34+ Cell Counts From Baseline in Healthy Subjects After an Injection of G-CSF alone, 160 µg/kg Plerixafor, or G-CSF with 160 µg/kg Plerixafor After 5 Days of G-CSF in Study 1003



Note: Error bars are standard errors.

Study AMD3100-1005

Study Design and Objectives

This open-label, single-centre study assessed the safety and haematological activity (efficacy) of plerixafor when administered as a single SC injection of 240 or 320 µg/kg in healthy subjects. The PD activity of plerixafor was assessed (in the 320-µg/kg group only) by measuring the number of PB CD34+ cells using fluorescence activated cell sorter (FACS) analysis.

Pharmacodynamic Results

Mean absolute PB CD34+ cell counts increased from 1.9 cells/µl (baseline) to 24.1 cells/µl at 8 hours after administration of 320 µg/kg plerixafor. The peak mean PB CD34+ cell count occurred from 8 to 10 hours and remained elevated at 14 hours after administration. Five of 6 subjects achieved peak PB CD34+ cell counts of > 20 cells/µl, while the remaining subject achieved a peak PB CD34+ cell count of 19.5 cells/µl.

Studies in Patients with NHL and MM

Study AMD3100-1004

Study Design and Objectives

This multi-centre, open-label study was designed primarily to determine the effectiveness of 160, 240 and 320 µg/kg plerixafor by its ability to increase PB CD34+ cells in patients with NHL and MM. There were 2 disease groups of patients enrolled into the study: patients with NHL and patients with MM. Each disease group was divided into dose cohorts that received 1 dose of either 160 µg/kg or 240 µg/kg plerixafor. Subsequently, a third dose cohort (1 dose of 320 µg/kg plerixafor) was added to each disease group. Some members of the 320-µg/kg dose cohort returned after a 7-day rest period to receive a mobilisation regimen of G-CSF and 320 µg/kg plerixafor.

Pharmacodynamic Results

A total of 21 patients had data available for evaluation of PD of plerixafor after a single 160- (N=6), 240- (N=7), or 320-µg/kg (N=7) SC injection. The PD activity was assessed by PB CD34+ counts over time in 3 dose cohorts for the NHL and MM disease groups.

During the first 6 hours post-dose, mean absolute PB CD34+ counts increased in all cohorts and disease groups. The short (6-hour) sampling period and small sample size at each dose level (N=3 or N=4) limit the conclusions that can be reached about a dose response. When subjects who received 320 µg/kg plerixafor were followed for 24 hours, there was a broad prolonged response to plerixafor, and sometimes a slight increase at 8 hours post-dose. In general, patients with MM had higher responses than patients with NHL. In addition, in the NHL group, patients with higher baseline concentrations of PB CD34+ cell counts (cells/µL) had more robust responses than those with lower baseline PB CD34+ cell counts.

Study AMD3100-C201

Study Design and Objectives

This open-label, single-arm, multi-centre study evaluated the safety and efficacy of plerixafor at 240 µg/kg, used in addition to a standard G-CSF mobilisation regimen, for the collection of PB hematopoietic stem cells (HSCs) for autologous stem cell transplantation in patients with NHL and MM. The primary objective of the study was to determine if plerixafor was generally safe, especially when used in combination with the G-CSF for HSC mobilisation.

The pharmacokinetics and pharmacodynamics of a single dose of 240 μg/kg plerixafor administered after 4 days of G-CSF was also examined.

Patients were initially given a mobilising regimen of G-CSF (10 μg/kg QD) for 4 days in the morning, as per local practice guidelines. On the evening prior to each day of apheresis (beginning on the evening of Day 4), plerixafor was administered at a dose of 240 μg/kg. The dosing regimen of G-CSF (10 μg/kg QD) in the morning and plerixafor (240 μg/kg) in the evening followed by apheresis (10 to 11 hours later) was repeated for up to 5 consecutive days. The number of days of apheresis depended on the time required to reach the target number (that is, 5 x 10^6 cells/kg) of CD34+ cells.

Pharmacodynamic Results

Absolute PB CD34+ cell counts were evaluated at multiple time points following the first dose of plerixafor in a subset of 5 patients. One patient had samples that could not be analysed. In the remaining 4 patients, the absolute maximum increases in PB CD34+ counts occurred at the pre-apheresis time point (approximately 10 hours post-plerixafor injection) and ranged from 33 to 59 cells/μL. The median maximum increase from baseline in the number of circulating cells was approximately 4.2-fold (range 3.0 to 5.5-fold), with the time of the maximal fold-change occurring at the pre-apheresis time point for all patients.

Study AMD3100-2106

Study Design and Objectives

This was a single-centre, open-label study of patients with Hodgkin's disease (HD). The primary objective of the study was to determine the proportion of patients with HD who mobilised ≥ 5x 10^6 CD34+ cells/kg after stem cell mobilisation with G-CSF plus plerixafor. One of the secondary objectives was to examine the pharmacokinetics and pharmacodynamics of a single dose of 240 μg/kg plerixafor administered after 4 days of G-CSF mobilisation.

As in study C201, patients in 2106 were initially given a mobilising regimen of G-CSF (10 μg/kg every day (QD)) for 4 days in the morning, as per local practice guidelines, and then on the evening prior to each day of apheresis, plerixafor was administered at a dose of 240 μg/kg. The dosing regimen of G CSF (10 μg/kg QD) in the morning and plerixafor (240 μg/kg) in the evening followed by apheresis (10 to 11 hours later) was repeated for up to 5 consecutive days. The number of days of apheresis depended on how many were required to reach the target number (that is, 5 x 10^6 cells/kg) of CD34+ cells.

Pharmacodynamic Results

PB CD34+ cell counts were evaluated at multiple time points following the first dose of plerixafor in a subset of 7 patients. For 2 of 7 patients, the absolute change from baseline and fold-change from baseline could not be calculated (1 patient had a missing baseline value and another had a PB CD34+ count of 0 cells/μL). PD activity could not be evaluated in a third patient because they had samples collected only at baseline and prior to apheresis. In the subset of the 4 remaining patients, the absolute maximum increases in PB CD34+ counts ranged from 37 to 62 cells/μL, which occurred from 2 to 10 hours after the first SC injection. The median maximum change from baseline in the number of PB CD34+ cells was 5.8-fold (from 1.7- to 9.65-fold), with the median time of the maximal change from baseline occurring 6 hours (from 2 to 10 hours) after the first SC injection.

Studies in Renally Impaired Subjects

Study AMD3100-1101

Study Design and Objectives

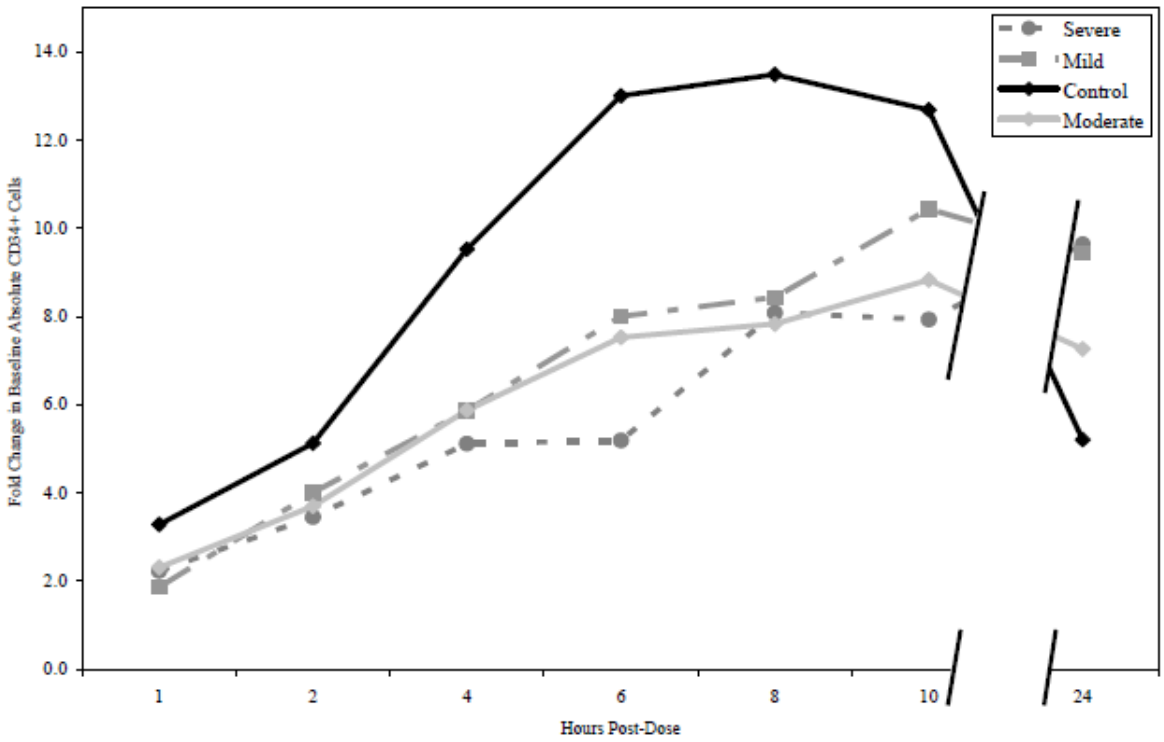
This Phase 1, open-label, multi-centre study evaluated the safety, PK parameters and haematological activity of plerixafor in subjects with renal impairment. The study evaluated the effects of a single dose of 240 μg/kg of plerixafor on pharmacodynamics, pharmacokinetics and safety parameters. Each subject received a single SC injection. Subjects were stratified into 4 cohorts with various degrees of renal impairment (Control, Mild Impairment, Moderate Impairment, and Severe Impairment) based on their measured creatinine clearance (CrCL) values determined by a screening 24-hour urine collection.

PK parameters were determined for plasma and urine samples that were collected after a single SC dose. PK evaluations were performed using noncompartmental 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_{0-24}; the limits were 70% and 143% for C_{max}.

Pharmacodynamic Results

After treatment with plerixafor, the level of PB CD34+ cells increased in all cohorts. Results for fold changes are shown in Figure 4. In the control cohort, numbers of PB CD34+ cells peaked at 8 hours post-dose. At baseline, the level of PB CD34+ cells was lower in the mild cohort (1.4 cells/μL) than in the control, moderate, and severe cohorts (2.5 cells/μL, 2.3 cells/μL, and 2.7 cells/μL, respectively). This discrepancy was most likely due to variability associated with small sample sizes.

Figure 4: Mean Fold-Change from Baseline in Absolute PB CD34+ Cell Counts over Time by Cohort in Study 1101



Note: Fold-change from baseline from 0 to 24 hours was calculated by dividing the value at a particular time point by the baseline value.

PB CD34+ levels appeared to increase more slowly in the renal impairment cohorts and, because no samples were collected between 10 and 24 hours post-dose, it appears as if the peak in PB CD34+ levels may have been missed in these cohorts. At 24 hours post-dose PB CD34+ levels were higher in the renal impairment cohorts than the control, which may suggest that the increase in PB CD34+ levels progressed more slowly post-dose in the renal impairment cohorts. In the mild and moderate cohorts, PB CD34+ levels had declined only 10% and 18%, respectively, from 10 to 24 hours post-dose. In the severe cohort, the levels of PB CD34+ cells increased from 10 to 24 hours post-dose, however since the peak level may have been missed completely, it is possible that the perceived increase at 24 hours may have been part of a declining PB CD34+ count.

Compassionate Use Programme (CUP) in Oncology Patients who Failed Conventional Therapy

Study AMD3100-CUP001

Study Design and Objectives

The purpose of this programme is to provide plerixafor to patients who have failed previous conventional therapies for HSC collection or, based on a low PB CD34+ count following conventional therapy, are not considered to have a reasonable chance of mobilising enough cells for transplant. Patients enrolled in the CUP receive 240 µg/kg plerixafor per protocol, but some patients with renal dysfunction received a dose of 160 µg/kg. The only change to the standard of care is the administration of plerixafor on the evening prior to each day of apheresis. Patients receive a mobilising regimen of the standard dose of G-CSF, typically 10 µg/kg. It is recommended in CUP that G-CSF be administered in the morning, preferably 1 hour prior to apheresis. Plerixafor should be administered in the evening and apheresis should

begin 10 to 11 hours later. Although not stipulated in the protocol, PK data were collected on a small subset of patients who were either renally insufficient or paediatric.

No PD data were collected in study CUP001.

Investigator-Sponsored Studies

Study 06-H-0156

Study Design and Objectives

This is an ongoing, single-centre, investigator-sponsored study of the safety and tolerability of plerixafor when administered in escalating doses. Doses are escalated once within patients (that is, from 240 to 320 µg/kg; from 320 to 400 µg/kg; and from 400 to 480 µg/kg plerixafor). Other objectives are to determine the peak CD34+ cell mobilisation kinetics in patients who receive 2 different doses of plerixafor. PK data from the 400-µg/kg dose level were available at the time of submission.

No PD data were collected in study 06-H-0156.

Comments: Overall the PK and PD data submitted for evaluation demonstrated the following:

- The pharmacokinetic profile of plerixafor is similar whether in healthy subjects given plerixafor alone or oncology patients given plerixafor plus G-CSF.
- Plerixafor pharmacokinetics are dose-proportional in the studied dose range.
- The pharmacodynamic response to plerixafor 240 µg/kg (no G-CSF) in healthy subjects occurs 6 to 10 hours after dosing. The median peak fold-increase was 15.8 over baseline.
- In healthy subjects, the pharmacodynamic response to 240 µg/kg plerixafor alone was higher than the response to 160 µg/kg plerixafor alone.
- The pharmacodynamic response to plerixafor with G-CSF administration in oncology patients occurs over a broad peak, with maximum PB CD34+ levels occurring 10 to 14 hours after dosing. Median peak PB CD34+ levels were 2.9-fold higher than baseline levels after treatment with G-CSF. The mean improvement in total cells collected in apheresis product was 2.9 $\pm$ 3.47 x 10^6cells/kg compared to G-CSF alone (Study 2101).
- In renally impaired subjects, systemic exposure (AUC_{0-24}), but not C_{max}, increased with increasing severity of impairment.

Efficacy

The main efficacy data to support the proposed efficacy claims for plerixafor were from 4 studies (N=647 patients): 2 Phase III studies (AMD3100-3101 (NHL patients) and AMD3100-3102 (MM patients)) and 2 Phase II studies (AMD3100-2101 (NHL and MM patients) and AMD3100-2106 (HD patients)). Study AMD3100-2101 was the Phase II proof-of-principle study that demonstrated the increased efficacy of G-CSF + plerixafor 240 µg/kg (G + plerixafor) compared with G-CSF-alone. Study AMD3100-2106 was a study in patients with HD that demonstrated the efficacy of G-CSF + plerixafor as compared to historical controls treated with G-CSF alone. The Phase III studies were specifically designed to demonstrate the efficacy and safety of plerixafor to support the registration.

The primary efficacy endpoint for the 4 studies was assessed at the end of the apheresis phase. Follow-up for the Phase III studies and 1 of the Phase II studies (AMD3100-2106) was ongoing at the time of submission of the application; AMD3100-2101 was completed. Patient data up to and including the last enrolled patient's 3-month post-transplant follow-up visit

(also referred to as 100 days) were provided for evaluation in this marketing application. In addition to data for the 100-day follow-up, 6-month durability data were available in the Phase III studies for 69% of patients (413/600), and the 12-month data were available for 34% (204/600).

Phase III Studies

Study Designs

The 2 Phase III studies were randomised, double-blind, placebo-controlled, parallel-group, multicentre studies designed to assess the efficacy and safety of G + plerixafor 240 μg/kg compared to G + placebo in mobilising and transplanting CD34+ cells. ***Study 3101*** was conducted in patients with NHL (N=298) and ***Study 3102*** was conducted in patients with MM (N=302). In Study 3101 patients were randomised in a 1:1 ratio, stratified by study centre. In Study 3102 eligible patients were stratified by study centre, platelet count ($< 0.2 \times 10^6$/dL versus $\geq 0.2 \times 10^6$/dL), and type of transplant planned (single or tandem) prior to randomisation.

The studies were divided into the following protocol-defined phases to summarise disposition:

1. - G-CSF Mobilisation (up to 8 days in duration)
   - Treatment/Apheresis (up to 4 days in duration) up to the day prior to chemotherapy ablation
2. - Chemotherapy Ablation
   - Transplantation (cell transplantation within 5 weeks of last apheresis) ending with engraftment (day of the latter of polymorphonuclear (PMN) cell and platelet (PLT) engraftment following transplantation)
3. - Post- engraftment follow-up (100 days, 6 and 12 months).

These protocol-defined phases are different from the adverse event (AE) evaluation periods. The AE evaluation periods were based on the patients' actual dosing, chemotherapy, transplantation, engraftment, and follow-up dates.

Tandem Transplant Patients: In contrast to Study 3101, patients with MM in Study 3102 were eligible to receive tandem transplants. The first transplantation was to have occurred within 5 weeks after the last apheresis session and the subsequent transplant must have occurred within 6 months of the first transplantation. For all patients receiving tandem transplants, only 1 transplant contributed to the evaluation of transplant-related efficacy endpoints. For tandem patients who received their second transplant within the 6 month window, the second transplant was used for the summary of efficacy. For those whose second transplant occurred beyond 6 months, the first transplant was used.

Rescue Patients: In both studies, patients who failed to mobilise (that is, did not collect $\geq 0.8 \times 10^6$ CD34+ cells/kg after 2 days of apheresis; or who did not achieve at least 2×10^6 CD34+ cells/kg in 4 or fewer days of apheresis; or did not achieve at least 4×10^6 CD34+ cells/kg in 4 or fewer days for tandem transplant in patients with MM) were eligible to enter an open-label rescue procedure where, after a minimum 7-day rest period, they received another course of treatment (G-CSF mobilisation followed by G + plerixafor) and cells were collected. Original treatment assignment was not unblinded.

Rituxan Patients: In Study 3101, up to 20 NHL patients per treatment arm could be enrolled in the study if they received Rituxan (rituximab) prior to and post-apheresis. Data from these

patients were prospectively planned to be excluded from the intent-to-treat (ITT) population and evaluated as a separate population.

Cytoreductive Chemotherapy Patients: Only 1 patient was planned to be treated with cytoreductive therapy.

Patient Populations

Inclusion and Exclusion Criteria

Patients included in both studies were 18- to 78-years old with a diagnosis of NHL (Study 3101) or MM (Study 3102) confirmed by bone marrow biopsy prior to the first mobilisation, who were eligible for autologous transplantation. Patients were in the first or second complete or partial remission, had ≥ 4 weeks since their last cycle of chemotherapy with recovery from all acute toxic effects of prior chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, met minimum lab values (that is, white blood cell (WBC) count > 2.5 x 10^9/L, absolute PMN cell count > 1.5 x 10^9/L, PLT count > 100 x 10^9/L, and serum creatinine ≤ 2.2 mg/dL), cardiac and pulmonary status sufficient to undergo apheresis and transplantation, and were negative for HIV.

The main exclusion criteria for both studies were: comorbid conditions that rendered the patient at high risk for treatment complications; previous failed stem cell collections; active central nervous system or bone marrow (>20%) involvement, active brain metastases or carcinomatous meningitis, active infection or fever (>38ºC); abnormal electrocardiogram; prior autologous or allogeneic transplant; previous radiation therapy to the pelvis, or having received G-CSF within 14 days prior to the first dose of G-CSF for mobilisation. Pregnant or lactating women were excluded from the studies.

Study 3101 – Patient Demographics and Disease Characteristics

The 2 treatment groups were similar to each other with respect to most demographic and baseline characteristics. The majority of patients were male (100/150, 66.7% in the G + plerixafor group and 102/148, 68.9% in the G + placebo group) and Caucasian (90.7% and 94.6% for the two groups, respectively).There was a difference in mean age that was statistically significant (55.1 years in the G + plerixafor group versus 57.5 years in the G + placebo group, p = 0.047); however the difference was not expected to have a major impact on the study results (analyses of the efficacy endpoints were performed by subgroups defined by patient age, gender and ethnic origin).

In each treatment group, the time from initial diagnosis to randomisation was approximately 24 months, and the time from most recent progression or relapse to randomisation was approximately 5 months. Current remission status was similar in the 2 treatment groups. All patients except 1 patient (in the G + plerixafor group) had prior surgery; 96.7% in the G + plerixafor group and 94.6% in the G + placebo group had prior chemotherapy; and 16.7% in the G + plerixafor group and 19.6% in the G + placebo group had prior radiotherapy.

There were significant differences between the treatment groups in stage of disease, both at initial diagnosis and current (p = 0.002 and p = 0.027, respectively). The percentage of patients with more advanced disease (Stage IV) was greater in the G + plerixafor group compared with the G + placebo group at both assessments.

Study 3102 – Patient Demographics and Disease Characteristics

The 2 treatment groups were similar with respect to age (mean age 58.2 years in the G + plerixafor group and 58.4 years in the G + placebo group) and sex (67.6% of the patients in the G + plerixafor group and 69.5% of the patients in the G + placebo group were male).

In each treatment group, mean time from initial diagnosis to randomisation was approximately 11 months, and the mean time from most recent progression or relapse to randomisation was similar (5.7 months in the G + plerixafor group and 7.4 months in the G + placebo group). Current remission status was similar in both groups, with the majority of the patients in their first partial remission. All patients except for 2 (one in each treatment group) had prior surgery, and all patients with available data had prior chemotherapy. Similar numbers of patients in each group had prior radiotherapy.

The difference between the treatment groups in stage of disease at study entry was statistically significant ($p = 0.017$). The percentage of patients with Stage I disease was higher in the G + plerixafor group, while the percentage of patients with Stage II disease was lower in the G + plerixafor group. In both cases, similar percentages of patients had Stage III disease.

Efficacy Parameters

Primary Endpoint: The primary measure of efficacy for the Phase III studies was the proportion of patients achieving a target number of CD34+ cells within a predefined number of apheresis sessions as defined for each study:

- Study 3101: 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 Mobilisation/ Treatment/ Apheresis period.
- Study 3102: 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 Mobilisation/Treatment/Apheresis period.

EMEA Composite Primary Endpoint: Following a meeting with the Committee for Medicinal Products for Human Use (CHMP) of the EMEA, an analysis of a composite endpoint of the proportion of patients achieving target number of cells and with successful engraftment was added to the Phase III studies.

Target cells and successful engraftment were defined as:

Target Number of Cells:

Study 3101

- $\geq 2 \times 10^6$ CD34+ cells/kg (minimum transplantable) in 4 or fewer days of apheresis
- $\geq 5 \times 10^6$ CD34+ cells/kg (target) in 4 or fewer days of apheresis.

Study 3102

- $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer days of apheresis.

Successful Engraftment:

Studies 3101 and 3102

- 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.

This analysis was added to meet requirements of the EU guidance document CPMP/EWP/197/99 (Points to Consider Concerning Endpoints in Clinical Studies with Haematopoietic Growth Factors for Mobilisation of Autologous Stem Cells, Sections 4.2.4-5).

Fold Increase

Fold increase was the ratio of the number of circulating CD34+ cells post-plerixafor treatment (numerator) compared to the number of CD34+ cells pre-treatment (denominator). For the Phase III studies, the measurement time period was a 24-hour window: from the morning of Day 4 (just prior to G-CSF dose) to the morning of Day 5 (prior to first apheresis), with the first dose of plerixafor or placebo administered approximately in the middle of the window (that is, administered on the evening of Day 4, 10 to 11 hours prior to first apheresis).

Graft Durability

In the protocol and statistical analysis plan (SAP), graft durability was defined as maintenance of acceptable blood counts at 100 days, 6 months, and 12 months post-transplantation according to at least 2 of the 3 following criteria:

1. PLT count > 50,000/μL (50 x 10^9/L) without transfusion for at least 2 weeks prior to the follow-up visit.
2. Haemoglobin level ≥ 10 g/dL with no erythropoietin or transfusions for at least 1 month prior to the follow-up visit.
3. PMN > 1,000/μL (1 x 10^9/L) with no G-CSF for at least 1 week prior to the follow-up visit.

Graft failure was defined as 1 or both of the following:

1. No durable graft in 2 of the 3 cell lines of red blood cells, leukocytes, and platelets (using definitions of durability above) at 100 days (and 6 and 12 months) post-transplantation.
2. For the purposes of the 100-day evaluation, an additional criterion was applied. If 100-day data were not available, and the patient's absolute neutrophil count (ANC) did not rise above 500/μL (0.5 x 10^9/L) by 28 days post-transplantation, the patient was considered not to have maintained a durable graft at the 100-day visit.

Statistical Analyses

Efficacy was evaluated using the Intent To Treat (ITT) and Per Protocol (PP) populations. The ITT population for the primary endpoints consisted of all randomised patients (excluding the 13 patients in Study 3101 who took rituximab as preplanned in the protocol and excluding the 1 patient in Study 3102 who was planned to receive cytoreductive chemotherapy post-transplant as planned in the protocol). The PP population consisted of all patients who received any fraction of study treatment (plerixafor or placebo), completed the apheresis phase, and did not have any major protocol violations. The PP population was used for the subpopulation analyses.

For Study 3101, the primary efficacy endpoints were analysed using Pearson's Chi-square test (unstratified). A supportive analysis was performed using Cochran-Mantel-Haenszel (CMH) statistic, blocked by study centre, to test treatment differences.

For Study 3102, the primary efficacy endpoints were analysed using a CMH statistic stratified by baseline PLT count. A supportive analysis was performed using the CMH statistic stratified by study centre. Another supportive analysis used the Pearson Chi-square test, uncorrected for continuity. This latter condition was imposed since the sample size was estimated using the non-corrected version of the test statistic.

All statistical tests were 2-sided and based on a significance criterion of $\alpha \leq 0.05$, unless stated otherwise. Statistical tests were based on the parametric form of the statistic (for example, 2-sample t-test).

Patient Disposition

Across the studies, the study phase and treatment group with the most significant drop in patient numbers (number that did not complete the phase) was in the G + placebo group following treatment/apheresis. In Study 3101 in patients with NHL, 39% of G + placebo patients failed mobilisation compared with 7% of G + plerixafor patients. In Study 3102 in patients with MM, 5% of G + placebo patients failed mobilisation compared with 0 patients in the G + plerixafor group.

Both studies were ongoing at the time of the submission; however, at this stage there has been no differential loss to follow-up between treatment groups, with >83% of patients in each study/treatment group either completing the study, entering rescue treatment, or still remaining on study in post-transplant follow-up. Of the patients entering rescue, 85% (59/69) were G + placebo patients.

Efficacy Results – Study 3101

Primary Efficacy Results

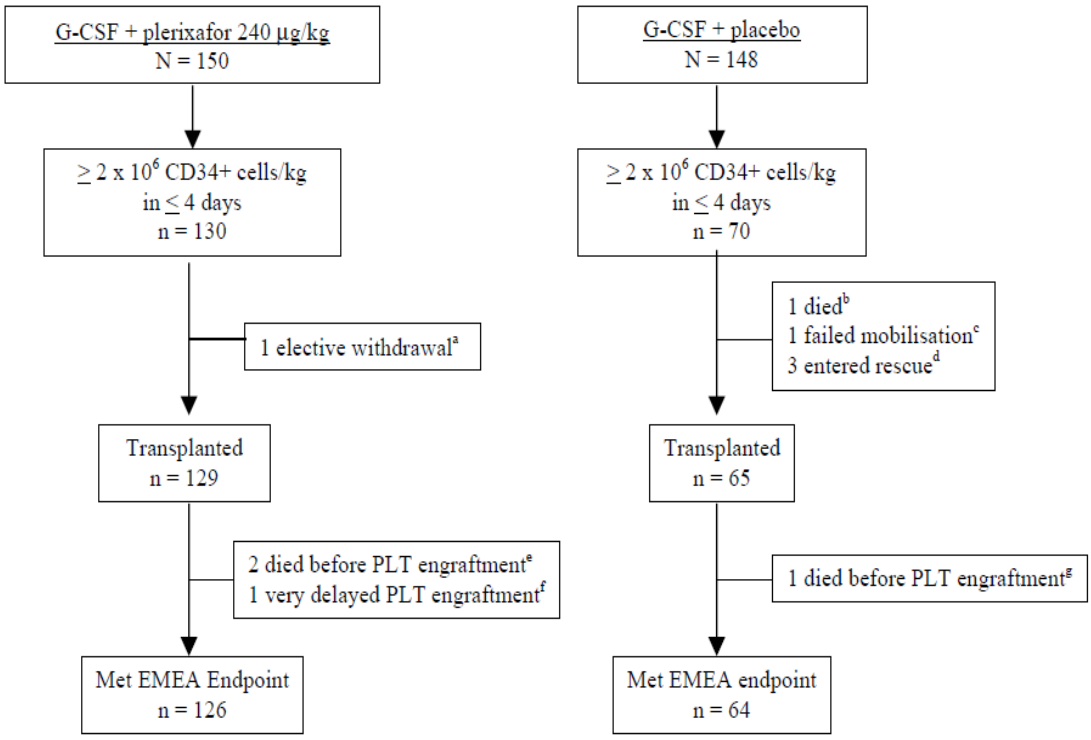
In Study 3101 the proportion of patients achieving treatment success (that is, mobilisation of $\geq 5 \times 10^6$ CD34+ cells/kg in 4 or fewer days of apheresis) was a primary efficacy endpoint. Approximately 3 times the proportion of patients in the G + plerixafor group achieved treatment success compared with the G + placebo group (59.3% versus 19.6%, respectively). The treatment effect (that is, the difference in proportions between the treatment arms) was 39.7% and statistically significant (95% confidence interval (CI) = 29.6% to 49.9%, $p < 0.001$).

For the EMEA composite primary endpoint, there were 2 composite endpoints for Study 3101:

(i) $\geq 2 \times 10^6$ CD34+ cells/kg in ≤ 4 apheresis and successful PMN and PLT engraftment.

Results for the EMEA composite primary endpoint are summarised in Figure 5. In the G + plerixafor group, 84.0% (126/150) of patients met the EMEA composite primary endpoint of collecting the minimum number of cells for transplantation ($\geq 2 \times 10^6$ CD34+ cells/kg) in 4 or fewer days of apheresis and successful PMN and PLT engraftment compared with 43.2% (64/148) of patients in the G + placebo group. The estimated treatment effect was 40.8%, which was statistically significant (95% CI = 30.9% to 50.7%, $p < 0.001$).

Figure 5: Summary of Patient Transplants, Engraftment, and EMEA Composite Primary Endpoint (≥ 2 x 10^6 CD34+ cells in ≤ 4 Days and Successful Engraftment) (Study 3101, NHL)

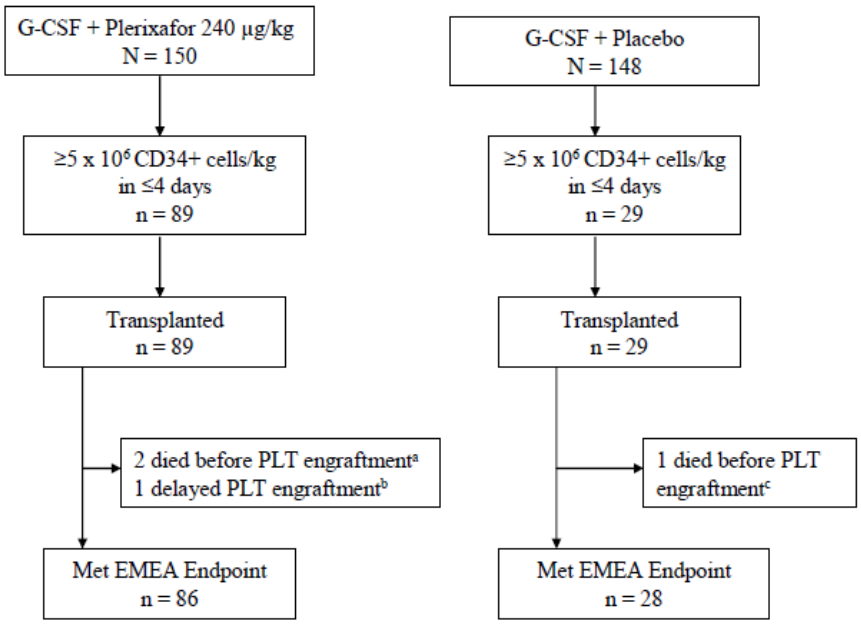


EMEA = European Agency for the Evaluation of Medicinal Products; G-CSF = granulocyte-colony stimulating factor; NA = not applicable; PLT = platelet; PMN = polymorphonuclear cell.

(ii) ≥ 5 x 10^6 CD34+ cells/kg in ≤ 4 apheresis and successful PMN and PLT engraftment

Results of the EMEA composite primary endpoint of the proportion of patients achieving a target number of ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis and having successful PMN and PLT engraftment are summarised in Figure 6. In the G + plerixafor group, 57.3% (86/150) of patients achieved ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis and had successful PMN and PLT engraftment compared with 18.9% (28/148) of patients in the G + placebo group. The estimated treatment effect was 38.4%, which was statistically significant (95% CI = 28.3% to 48.5%, $p < 0.001$).

Figure 6: Summary of Patient Transplants, Engraftment, and EMEA Composite Primary Endpoint (≥ 5 x 10^6 CD34+ cells in ≤ 4 Days and Successful Engraftment) (Study 3101, NHL)



Secondary Efficacy Results

Proportion of Patients Achieving Target Number of Cells

Target: ≥ 2 x 10^6 CD34+ cells/kg in 4 or Fewer Days of Apheresis

In the G + plerixafor group, 86.7% of the patients achieved ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis compared with 47.3% of the patients in the G + placebo group. The treatment effect was 39.4%, which was statistically significant (95% CI = 29.7% to 49.1%, p < 0.001).

Comparison of Time to Reach Target Number of Cells

Time (Days) to Reach Target of ≥ 5 x 10^6 CD34+ cells/kg

For Study 3101 a Kaplan-Meier analysis of the median time (days) to achieve a target of ≥ 5 x 10^6 CD34+ cells/kg was a secondary efficacy endpoint. Results are summarised in Table 6. The median time to reach the target CD34+ cell dose was 3.0 days in the G + plerixafor group but was not estimable in the G + placebo group since less than half of the patients in that group reached the target in 4 days of apheresis. For the estimated proportion of patients who achieved the target on each apheresis day, the proportion was greater in the G + plerixafor group at every time point compared with the G + placebo group. Patients in the G + plerixafor group were 3.6 times more likely to achieve the target CD34+ cell count over 4 days compared to the G + placebo group (hazard ratio = 3.6, 95% CI = 2.4 to 5.5, p < 0.001).

Table 6: Study AMD3100-3101 Efficacy Results – Proportion of Patients Who Achieved ≥ 5 x 10^6 CD34+ cells/kg by Apheresis Day in NHL Patients

Days	Proportion[a] in MOZOBIL and G-CSF (n=147[b])	Proportion[a] in Placebo and G-CSF (n=142[b])
1	27.9%	4.2%
2	49.1%	14.2%
3	57.7%	21.6%
4	65.6%	24.2%

[a]Percents determined by Kaplan Meier method

[b] n includes all patients who received at least one day of apheresis

Engraftment Success and Time to Engraftment

HSC Transplantation

In the G + plerixafor group, 90% (135/150) of patients underwent transplantation compared with 55% (82/148) of the G + placebo group. Among all patients receiving transplants, the majority collected ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis (129/135 G + plerixafor and 65/82 G + placebo patients). Twenty-two of the transplanted patients (6 in the G + plerixafor group and 16 in the G + placebo group) reached ≥ 2 x 10^6 CD34+ cells/kg but required more than 4 days of apheresis. Of these 22 patients, 10 patients (2 G + plerixafor and 8 G + placebo) received mobilisation regimens in addition to study treatment.

PMN Engraftment Success and Time to Engraftment

In Study 3101 engraftment was defined as PMN counts ≥ 0.5 x 10^9/L for 3 consecutive days or ≥ 1.0 x 10^9/L for 1 day. In both treatment groups, all of the patients who underwent transplantation, regardless of mobilisation regimen, achieved successful PMN engraftment. The median time to engraftment was 10.0 days in each treatment group.

PLT Engraftment Success and Time to Engraftment

Platelet engraftment was defined as PLT counts ≥ 20 x 10^9/L for the first of 7 consecutive days without receiving a transfusion in the prior 7 days. Results of PLT engraftment success and time to engraftment were similar between the 2 treatment groups. Among the patients who underwent transplantation, 132/135 (97.8%) in the G + plerixafor group achieved successful PLT engraftment compared with 81/82 (98.8%) in the G + placebo group. The median time to engraftment was 20.0 days in each treatment group.

Graft Durability

The Phase III studies are both ongoing studies in the follow-up phase where the assessment and collection of data for graft durability are performed at 100 days (3 months), 6 months, and 12 months. Results were provided for the protocol-specified analysis and the revised analysis.

Protocol-specified Analysis for Graft Durability

Since this is an ongoing study, there are still patients in follow-up and therefore the numbers of patients are fewer at 6- and 12-month follow-up than at 100 days. Using these criteria, the proportions of patients maintaining a durable graft in the G + plerixafor group were 107/135 (79.3%) at 100 days, 96/100 (96.0%) at 6 months, and 48/50 (96.0%) at 12 months. In the G + placebo group, the proportions were 61/82 (74.4%) at 100 days, 63/64 (98.4%) at 6 months, and 37/37 (100%) at 12 months. The differences between the treatment groups were not statistically significant at any of the assessment times.

Revised Analysis for Graft Durability

A revised analysis of graft durability considered as "durable" any patient who did not have haematology data to assess graft durability during the protocol-specified time period but had a durable graft at a later time. The proportions of patients maintaining a durable graft in the G + plerixafor group were 89.6% (121/135) at 100 days, 96.1% (99/103) at 6 months, and 96.0% (48/50) at 12 months. In the G + placebo group, the proportions were 91.5% (75/82) at 100 days, 98.5% (65/66) at 6 months, and 100.0% (37/37) at 12 months.

Exploratory Endpoints

(1) Proportion of Patients Maintaining a Durable Graft Using Modified Platelet Criteria for Graft Durability: The proportions of patients who maintained a durable graft using modified PLT criteria (PLT counts $\geq 20 \times 10^9$/L without transfusions for at least 2 weeks prior to the visit) were similar in both treatment groups at the 3 assessment times. Results were similar when compared with the revised analysis of graft durability.

(2) Peripheral Blood CD34+ Cells (cells/µl) and Fold Increase from Apheresis

Day 4 to 5: For the Phase III studies, the measurement time period for fold increase was a 24-hour window: from the morning of Day 4 (just prior to G-CSF dose) to the morning of Day 5 (prior to first apheresis), with the first dose of plerixafor or placebo administered on the evening of Day 4, 10 to 11 hours prior to first apheresis. On Day 4 prior to the first dose of plerixafor or placebo, the PB CD34+ cell count was similar in the 2 treatment groups. On Day 5, 10 to 11 hours after the first dose, the mean PB CD34+ cell count was significantly higher ($p < 0.001$) in the G + plerixafor group (53.5 cells/µL) compared with the G + placebo group (19.2 cells/µL). In addition, the mean fold-increase from Day 4 to Day 5 was significantly higher ($p < 0.001$) in the G + plerixafor group (6.2-fold increase) compared with the G + placebo group (1.9-fold increase).

(3) Peripheral Blood CD34+ Cells on Day 5:

On Day 5, the proportion of patients who had PB CD34+ cell counts < 10, < 15, and < 20 cells/µL in the G + plerixafor group were 10.2%, 20.3%, and 27.3%, respectively, compared with 42.6%, 54.9%, and 61.5% in the G + placebo group.

Covariate-adjusted Time to PMN Cell Engraftment and Time to PLT Engraftment

There was no difference in time to PMN or PLT engraftment between the 2 treatment groups.

Overall Survival

There were no statistically significant differences in survival between the 2 treatment groups.

Post hoc Analysis of Engraftment: Patients With Lower Cell Dose for Transplantation

Following study completion, a post hoc analysis was performed for both Phase III studies of PMN and PLT engraftment for those patients transplanted with lower cell doses ($<3.5 \times 10^6$ µg/kg cells). Results showed that the time to cell engraftment (PMNs and PLTs) was similar

between patients mobilised with G-CSF alone or G + plerixafor. The results suggested that the G + plerixafor mobilised CD34+ cells were functionally similar to cells mobilised with G-CSF alone.

Rescue Patients from Study 3101

Patients who fail to reach the minimum number of cells required for transplantation are considered to be poor mobilisers and therefore may receive multiple procedures and apheresis sessions in order to collect sufficient cells. In Study 3101, a total of 62 patients (6.7% (10/150) G + plerixafor, and 35.1% (52/148 patients) G + placebo) failed to collect 2 x 10^6 CD34+ cells/kg in the initial treatment/apheresis period and subsequently entered the open-label Rescue procedure.

Proportion of Rescue Patients Achieving Target Number of Cells (Rescue, Study 3101)

After entering Rescue, 63.5% (33/52) of the previously-treated G + placebo patients collected the minimum number of target cells for transplantation (≥ 2 x 10^6 CD34+ cells/kg) in 4 or fewer days of apheresis and 40% (4/10) of the G + plerixafor group collected the minimum target in 4 or fewer days. 7 patients (all from the G + placebo group) collected ≥ 5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis.

Proportion of Rescue Patients who Underwent HSC Transplantation (Rescue, Study 3101)

Ten of the 62 Rescue patients did not undergo transplantation, including 4 G + plerixafor patients (1 died, 2 failed mobilisation, 1 refused transplant) and 6 G + placebo patients (4 failed mobilisation, 1 had reason of 'other', 1 died). Of the 6 G + plerixafor patients who underwent transplantation, 3 collected ≥ 2 x 10^6 CD34+ cells/kg, and 3 collected < 2 x 10^6 CD34+ cells/kg. In the G + placebo group, 32/46 patients who underwent transplantation collected ≥ 2 x 10^6 CD34+ cells/kg and 14 collected < 2 x 10^6 CD34+ cells/kg.

Proportion of Patients with PMN and PLT Engraftment (Rescue, Study 3101)

All of the Rescue patients who underwent transplantation achieved successful PMN engraftment, and 50/52 (96.2%) of the transplanted patients achieved successful PLT engraftment. The median time to PMN engraftment was 11.0 days and to PLT engraftment was 20.0 days.

EMEA Composite Primary Endpoint (Rescue, Study 3101)

34/62 (54.8%) of the Rescue patients collected the minimum number of cells for transplantation (≥ 2 x 10^6 CD34+ cells/kg) in ≤ 4 days of apheresis and had successful PMN and PLT engraftment: 3/10 (30.0%) from the G + plerixafor group and 31/52 (59.6%) from the G + placebo group. Of the 34 patients meeting EMEA composite primary endpoint criteria with the minimum number of cells collected for transplantation, 6 (all from the G + placebo group) also met the criteria of collecting ≥ 5 x 10^6 CD34+ cells/kg in ≤ 4 days of apheresis and had successful PMN and PLT engraftment.

Graft Durability for Rescue Patients (Rescue, Study 3101)

Since Study 3101 is an ongoing study in the follow-up phase where the assessment and collection of data for graft durability are performed at 100 days, 6 months, and 12 months, graft durability data are incomplete. In the post hoc analysis of graft durability patients who did not have haematology data to assess graft durability during the specified time period but had a durable graft at a later time (but prior to the cut-off date) were considered “durable”. In this analysis of graft durability (using data from prior to the cut-off date), 47 of the 52 (90.4%) patients who received a transplant maintained a durable graft at 100 days, 35 of 38

(92.1%) patients with data at 6 months maintained a durable graft at 6 months, and 17 of 18 (94.4%) patients with data at 12 months maintained a durable graft at 12 months.

Fold Increase of PB CD34+ Cells and Survival of Rescue Patients (Rescue, Study 3101)

For the Rescue patients, the mean (± standard deviation (SD)) number of PB CD34+ cells on Day 4 (prior to the first dose of plerixafor in the rescue procedure) was similar: 4.5 ± 5.2 cells/μL for the patients from the previously-treated G + plerixafor group and 4.1 ± 11.6 cells/μL for the patients from the previously-treated G + placebo group. On Day 5 (10 to 11 hours after the first plerixafor dose), the number of PB CD34+ cells was 6.8 ± 8.5 cells/μL for the G + plerixafor group and 16.5 ± 18.9 for the G + placebo group.

The mean fold increase over the 24-hour period from the day prior to the first apheresis to just before the first apheresis (that is, Day 4 to Day 5, before the morning G-CSF doses) was 1.4 ± 0.6 for the G + plerixafor group and 7.9 ± 5.6 for the G + placebo group. As of the data cut-off date for this report, 53/62 (85.5%) of the Rescue patients were alive.

Rituximab Patients from Study 3101

As planned in the protocol, a small number of patients could be enrolled in the study if they received rituximab. The size of the rituximab population in Study 3101 was small (13 patients: 6 in the G + plerixafor and 7 in the G + placebo group), which limited the conclusions that could be made from this population.

Efficacy Results – Study 3102

Primary Efficacy Results

The proportion of patients achieving treatment success (that is, mobilisation of $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer days of apheresis) was a primary efficacy endpoint in Study 3102. The proportion of patients with success in the G + plerixafor group was significantly greater compared to the G + placebo group (71.6% versus 34.4%, respectively). The treatment effect was 37.2% (95% CI = 26.8% to 47.6%, $p < 0.001$).

≥ 6 x 10^6 CD34+ cells/kg in ≤ 2 Days and Successful PLT and PMN Engraftment

Results of the EMEA composite primary endpoint of the proportion of patients achieving a target number of $\geq 6 \times 10^6$ CD34+ cells/kg in ≤ 2 days of apheresis and having successful PMN and PLT engraftment showed that in the G + plerixafor group, 70.3% (104/148) of patients met the composite endpoint compared with 34.4% (53/154) of patients in the G + placebo group. The estimated treatment effect was 35.9% (95% CI = 25.3% to 46.4%, $p < 0.001$), which was statistically significant and similar to the results seen in Study 3101.

Secondary Efficacy Results

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

In the G + plerixafor group 95.3% of the patients achieved treatment success compared with 88.3% of the patients in the G + placebo group. The statistically significant estimated treatment effect was 7.0% (95% CI = 0.8% to 13.1%; $p = 0.031$).

Target: ≥ 6 x 10^6 CD34+ Cells/kg in 4 or Fewer Days of Apheresis Study 3102 (not an endpoint in Study 3101)

The proportion of patients achieving $\geq 6 \times 10^6$ CD34+ cells/kg in 4 or fewer days of apheresis was a secondary efficacy endpoint in Study 3102. In the G + plerixafor group, 75.7% of the patients achieved treatment success compared with 51.3% of the patients in the G + placebo

group. The statistically significant estimated treatment effect was 24.4%, which was highly statistically significant (95% CI = 13.9% to 34.9%; p < 0.001).

Comparison of Time to Reach Target Number of Cells

Time (Days) to Reach Target of ≥ 6 x 10^6 CD34+ cells/kg

A Kaplan-Meier analysis of the time (days) to reach the target of ≥ 6 x 10^6 CD34+ cells/kg was a secondary efficacy endpoint for Study 3102. The median time to reach the target CD34+ cell dose was 1.0 day in the G + plerixafor group and 4.0 days in the G + placebo group (see Table 7). As in Study 3101, for the estimated proportion of patients who achieved the target on each apheresis day, the proportion was greater at every time point in the G + plerixafor group compared with the G + placebo group. In a Cox proportional hazards model adjusted for treatment, patients who received G + plerixafor were 2.5 times more likely to achieve the target CD34+ cell count over 4 days compared to G + placebo patients (hazard ratio = 2.5, 95% CI = 1.87 to 3.44, p < 0.001).

Table 7: Study AMD3100-3102 – Proportion of Patients Who Achieved ≥ 6 x 10^6 CD34+ cells/kg by Apheresis Day in MM Patients

Days	Proportion[a] in Mozobil and G-CSF (n=144[b])	Proportion[a] in Placebo and G-CSF (n=150[b])
1	54.2%	17.3%
2	77.9%	35.3%
3	86.8%	48.9%
4	86.8%	55.9%

[a]Percents determined by Kaplan Meier method

[b] n includes all patients who received at least one day of apheresis

Engraftment Success and Time to Engraftment

HSC Transplantation

In the G + plerixafor group, 96% (142/148) of patients underwent transplantation compared with 88% (136/154) of the G + placebo group. Among all patients receiving transplants, the majority collected ≥ 2 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis (139/148 G + plerixafor and 127/154 G + placebo patients). Twelve additional patients who did not meet the criteria of minimum cell collection in ≤ 4 days underwent transplant. These patients either reached ≥ 2 x 10^6 CD34+ cells/kg by receiving additional mobilisation regimens (5 G + placebo patients), were transplanted with < 2 x 10^6 CD34+ cells/kg at the discretion of the Investigator (2 G + plerixafor patients and 3 G + placebo patients), or both (1 G + plerixafor and 1 G + placebo patient).

PMN Engraftment Success and Time to Engraftment

In the G + plerixafor group, 141/142 (99.3%) patients who underwent transplantation achieved successful PMN engraftment, and in the G + placebo group, 136/136 (100%) patients who underwent transplantation achieved successful PMN engraftment. The single patient in the G + plerixafor group who did not engraft died 10 days post-transplant. The median time to PMN engraftment was 11.0 days in each treatment group.

PLT Engraftment Success and Time to Engraftment

Among the patients who underwent transplantation, 141/142 (99.3%) in the G + plerixafor group achieved successful PLT engraftment compared with 135/136 (99.3%) in the G + placebo group. The 2 patients who did not engraft both died (1 at 10 days and 1 at 13 days post-transplant). The median time to engraftment was 18.0 days in each treatment group.

Graft Durability

Protocol-specified Analysis for Graft Durability

As in Study 3101, there were no statistically significant differences between the treatment groups in the proportion of patients maintaining a durable graft at 100-day, 6-month, or 12-month follow-up. The proportions of patients maintaining a durable graft in the G + plerixafor group were 110/142 (77.5%) at 100 days, 118/120 (98.3%) at 6 months, and 60/60 (100.0%) at 12 months. In the G + placebo group, the proportions were 99/136 (72.8%) at 100 days, 106/112 (94.6%) at 6 months, and 57/57 (100.0%) at 12 months.

Revised Analysis for Graft Durability

In the revised analysis the proportions of patients maintaining a durable graft in the G + plerixafor group were 97.2% (138/142) at 100 days, 98.4% (124/126) at 6 months, and 100.0% (60/60) at 12 months. In the G + placebo group, the proportions were 93.4% (127/136) at 100 days, 97.5% (115/118) at 6 months, and 100.0% (57/57) at 12 months. The differences between the treatment groups were not statistically significant at the 3 assessment times.

Exploratory Endpoints

(1) Proportion of Patients Maintaining a Durable Graft Using Modified Platelet Criteria for Graft Durability: Exploratory results for Study 3102 were similar to those seen in Study 3101.

(2) Proportion of Patients Maintaining a Durable Graft Using Modified Platelet Criteria for Graft Durability: The proportions of patients who maintained a durable graft using modified PLT criteria (PLT counts $\geq 20 \times 10^9$/L without transfusions for at least 2 weeks prior to the visit) were similar in both treatment groups at the 3 assessment times. The differences between treatment groups were not statistically significant, using the modified definition of graft durability. The results were similar to the revised analysis of graft durability.

(***3) Peripheral Blood CD34+ Cells (cells/µl) and Fold Increase from Apheresis Day 4 to Day 5:*** The measurement time period for fold increase was a 24-hour window: from the morning of Day 4 (just prior to G-CSF dose) to the morning of Day 5 (prior to first apheresis), with the first dose of plerixafor or placebo administered on the evening of Day 4, 10 to 11 hours prior to first apheresis. In Study 3102, on Day 4 prior to the first dose of plerixafor or placebo, the PB CD34+ cell count was similar in the 2 treatment groups. On Day 5, 10 to 11 hours after the first dose, the mean PB CD34+ cell count was significantly higher ($p < 0.001$) in the G + plerixafor group (143.3 cells/µL) compared with the G + placebo group (67.3 cells/µL). In addition, the mean fold increase from Day 4 to Day 5 was significantly higher ($p < 0.001$) in the G + plerixafor group (6.4-fold increase) compared with the G + placebo group (2.4-fold increase).

(4) Peripheral Blood CD34+ Cells on Day 5: An ad hoc analysis of PB CD34+ cell count on Day 5 (10 to 11 hours after the first dose) was performed for patients who had CD34+ cell data on both Days 4 and 5 (that is, 121 patients in the G + plerixafor group and 122 patients

in the G + placebo group). On Day 5, the proportion of patients who had PB CD34+ cell counts < 10, < 15, and < 20 cells/μL in the G + plerixafor group were 1.6% at each cut point, compared with 9.2%, 16.4%, and 24.6% in the G + placebo group.

Covariate-adjusted Time to PMN Cell Engraftment and Time to PLT Engraftment

There was no difference in time to PMN or PLT engraftment between the 2 treatment groups.

Overall Survival

As in Study 3101, there were no statistically significant differences in survival between the 2 treatment groups.

Proportion of Rescue Patients Achieving Target Number of Cells (Rescue, Study 3102)

In Study 3102, 7 patients entered the open-label Rescue procedure, with all 7 being from the G + placebo group. During the Rescue procedure, 7/7 (100%) of Rescue patients achieved a minimum target of $\geq 2 \times 10^6$ cells/kg in 4 or fewer apheresis days. Of the 7 patients, 2 (28.6%) achieved the primary endpoint of $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer apheresis days. Three of 7 patients (42.9%) met the endpoint of $\geq 6 \times 10^6$ CD34+ cells/kg in 4 or fewer apheresis days. Of the Rescue patients, 6/7 were planned to receive tandem transplant, and in the rescue procedure 4/6 of these (5/7 overall) collected $\geq 4 \times 10^6$ cells/kg in 4 days of apheresis (above the minimum needed for tandem transplant). The median time to reach the target dose was 3.0 days.

Proportion of Rescue Patients who Underwent HSC Transplantation (Rescue, Study 3102)

All 7 patients underwent transplantation and 4/7 underwent tandem transplant.

Proportion of Rescue Patients with Successful PMN and PLT Engraftment (Rescue, Study 3102)

All 7 patients achieved PMN and PLT engraftment. Median time to PMN engraftment was 11.0 days and to PLT engraftment was 18.0 days.

EMEA Composite Primary Endpoint (Rescue, Study 3102)

With respect to the EMEA composite primary endpoint, 2/7 (28.6%) of the Rescue patients collected $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer days of apheresis and had successful PMN and PLT engraftment. All of the Rescue patients collected $\geq 2 \times 10^6$ cells/kg in 4 or fewer apheresis days and achieved PMN and PLT engraftment, which is a clinically important target for these patients who initially had poor mobilisation.

Graft Durability for Rescue Patients (Rescue, Study 3102)

The proportion of Rescue patients maintaining a durable graft was 85.7% (6/7) at 100 days and 100% (4/4) at 6 months. No 12-month data were available as of the data cut-off date, since some patients are still in the study.

Fold Increase of PB CD34+ Cells and Survival of Rescue Patients (Rescue, Study 3102)

The mean ± SD number of PB CD34+ cells was 3.7 ± 5.0 cells/μL on Day 4 and 43.7 ± 48.7 on Day 5. The mean fold-increase from Day 4 to Day 5 was 12.6 ± 2.5. 7/7 (100%) of the Rescue patients were alive as of the data cut-off date.

Phase II Studies

Study Designs

The 2 Phase II studies were open label. ***Study 2101*** was a multicentre, crossover study in 25 patients with NHL (N=15) or MM (N=10). Originally, patients were randomly assigned to

receive G + plerixafor or G-CSF alone as their initial mobilising regimen, followed by a 2-week washout and remobilisation with the alternate regimen. After the first 8 patients had received plerixafor at a dose of 160 μg/kg, the dose was increased to 240 μg/kg because studies in healthy volunteers, and 1 study with oncology patients, demonstrated equal or better CD34+ cell mobilisation at the higher dose. In addition, the day to start plerixafor dose was changed from Day 4 to Day 5. A second protocol amendment discontinued the randomisation due to a concern that a first apheresis post plerixafor would reduce the yield of the second mobilisation with G-CSF alone (that is, have a sequence effect).

Study 2106 was conducted at a single centre and was designed to assess the efficacy and safety of G + plerixafor 240 μg/kg in patients with HD (N=22). The number of cells collected and the rate of failure to collect a minimum number of cells ($\geq 2 \times 10^6$ CD34+ cells/kg) were compared to historical controls that had mobilisation with G-CSF alone treated at the same site. No statistical analyses were performed for the comparison. The study phases in both of the Phase II studies were similar to those described for the Phase III studies.

Patient Populations

Inclusion and Exclusion Criteria

Patients in Study 2101 were 18 to 70 years old with a diagnosis of MM or NHL. Patients in Study 2106 were 18 to 70 years old with a diagnosis of HD. All other inclusion and exclusion criteria for these studies were similar to those used in the Phase III studies, with the exception of the waiting periods for chemotherapeutics (established as at least 1 week from last dose of Velcade and dexamethasone in the Phase III studies) and the exclusion of the use of bone-seeking therapeutic radionuclides in the Phase III studies (not excluded in Phase II). .

Patient Demographics and Disease Characteristics

In Study 2101 there were 15 patients with NHL and 10 patients with MM enrolled. Mean ages of patients in Study 2101 were similar to those in the Phase III studies. The ratio of males: females was also similar to the Phase III studies in patients with MM (approximately 2:1), while the ratio of males to females with NHL was approximately 1:1. At study entry, most patients with NHL had Stage IV disease; most patients with MM had Stage II (40%) or III (40%) disease. All NHL and MM patients had received prior chemotherapy.

In Study 2106, patients with HD were younger than patients in the other 3 studies, and the ratio of females to males was approximately 1.5:1. The majority of patients in Study 2106 had Stage III (32%) or IV (36%) disease at study entry.

Efficacy Parameters

Primary Objectives: Study 2101 was the proof-of-principle study. The primary objective was to evaluate the difference in the number of CD34+ cells/kg collected after mobilisation with G + plerixafor compared with that collected after mobilisation of G-CSF alone (G-alone). Secondary objectives of the study were:

- To evaluate, for each of the mobilisation regimens, the number of apheresis days required to collect the target total number of cells for transplantation of $\geq 5 \times 10^6$ CD34+ cells/kg.
- To estimate the rate of successful engraftment of PMN cells and to estimate the number of days post-transplant that engraftment occurred.

The primary objective of Study 2106 was to determine the proportion of HD patients who had $\geq 5 \times 10^6$ CD34+ cells/kg after HSC mobilisation with G + plerixafor. The number of PB HSCs collected and the rate of failure to collect $\geq 2 \times 10^6$ CD34+ cells/kg were compared to 2 sets of data generated from historical controls that had mobilisation with G-CSF alone.

Patients in the historical control group had been treated at the same site and samples were analysed at the same local laboratory as the study trial. No statistical analyses were performed for the comparison.

Secondary objectives of Study 2106 included evaluation of the:

- Proportion of patients with a total apheresis yield of $\geq 2 \times 10^6$ CD34+ cells/kg after stem cell mobilisation with G + plerixafor.
- Increase in CD34+ cells after plerixafor administration.
- Number of apheresis days to reach a total apheresis yield of $\geq 5 \times 10^6$ CD34+ cells/kg.
- Number of days to successful PMN and PLT engraftment.
- Graft durability at 3, 6, and 12 months after stem cell transplantation.
- Pharmacokinetics and pharmacodynamics of a single dose of 240 μg/kg plerixafor administered after 4 days of G-CSF mobilisation.

Fold Increase for Studies 2101 and 2106

As in the Phase III studies, fold increase was the ratio of the number of circulating CD34+ cells post-plerixafor treatment (numerator) compared to the number of CD34+ cells pre-treatment (denominator); however, the timing of CD34+ measurements was different in the Phase II studies. For Study 2101, the measurement time period was a 6-hour window: from just prior to plerixafor dose to 6 hours post-plerixafor dose. For Study 2106, the time period was an 11-hour window: from just prior to plerixafor dose to 11 hours post-plerixafor dose.

Graft Durability for Studies 2101 and 2106

For Study 2101, the criteria for graft durability and graft failure were based on current clinical practice as well as ongoing consultations with the study's Data Safety Monitoring Board and other experts in the field of PB HSC transplants (HSCT). Graft durability for Study 2106 was determined by the study investigator at the site. As a guideline, the 2106 protocol defined graft durability as maintenance of acceptable blood counts at 3, 6, and 12 months post-transplantation. For Study 2106, since this was an ongoing study at the time of this submission, not all patient data were available for the assessment of durability at the time of data cut-off (05 April 2007). Results beyond the cut-off date for graft durability analysis were obtained, whenever possible, to determine true failures.

Graft failure was determined by the study investigator at each site. As a guideline, graft failure was defined in the protocol as blood counts chronically below acceptable values in 2 cell lines (of red blood cells, leukocytes, and PLTs) with no evidence of other causes, such as recurrent progressive HD, renal failure, chronic bleeding, severe infection, drug-induced cytopenias, or development of new haematologic problems.

Patient Disposition

Study 2101:

Of the 25 total patients in Study 2101, 6 patients did not complete study treatment procedures up to the final visit at the end of the crossover treatment, including 5 patients who missed the final visit that was scheduled 24 hours after the last apheresis, and 1 patient who missed the last crossover treatment (G + plerixafor).

Study 2106:

All 22 patients completed study treatment procedures and, at the time of interim data cut-off for this submission (05 April 2007), 15 patients had 12-month follow-up data recorded in the

database. In addition, 6 patients had 12-month follow-up information sent by the site after the interim cut-off date of 05 April 2007, and 1 patient withdrew during the follow-up phase because of insufficient collection of cells (therefore there was no report of graft durability at 12-months for this patient).

Efficacy Results

Results – Study 2101

In Study 2101 in both the NHL and MM patient groups and overall, the G + plerixafor regimen resulted in a significantly greater total CD34+ cell collection by apheresis than the G-alone regimen, as well as significantly greater total (cumulative) CD34+ cell collection by apheresis and higher daily CD34+ collection by apheresis day.

Proportion of Patients Achieving Target Transplantable CD34+ Cell Doses

In Study 2101 approximately 3 times the proportion of patients in the G + plerixafor regimen (67%) achieved a target of $\geq 5 \times 10^6$ CD34+ cells/kg compared to the G-alone regimen (20%).

In patients with MM, approximately 2 times the proportion of patients in the G + plerixafor regimen (100%) achieved a target of $\geq 5 \times 10^6$ CD34+ cells/kg compared to the G-alone regimen (50%). Among all patients, with the G + plerixafor regimen all 25 patients (100%) achieved the minimum transplantable cell dose of $\geq 2 \times 10^6$ CD34+ cells/kg compared with 16 (64%) with the G-alone regimen.

Of note, in 9 patients whose CD34+ cells were difficult to mobilise with G-CSF alone ($< 2 \times 10^6$ CD34+ cells/kg collected in 4 days of treatment/apheresis), the G + plerixafor regimen enabled these patients to achieve a transplantable dose of CD34+ cells for haematopoietic stem cell transplant. After 2 days of apheresis, 15/25 patients (60.0%; 8/15 NHL, 53.5%; 7/10 MM, 70.0%) in the G + plerixafor regimen versus 4/25 patients (16.0%; 1/15 NHL, 6.7%; 3/10 MM, 30.0%) in the G-CSF alone regimen reached the target cell dose. Transplantation with G + plerixafor mobilised apheresis product resulted in 100% (20/20) successful PMN cells engraftment (11/11 NHL and 9/9 MM), with a median time to PMN engraftment of 10.5 days. 95% (19/20) had successful PLT engraftment (10/11 NHL and 9/9 MM), with a median time to PLT engraftment of 17 days. One NHL patient died of sepsis after PMN engraftment and before PLT engraftment. All 14 patients who were followed through 12 months had durable grafts.

In all patients, treatment with G + plerixafor resulted in a median 2.9-fold increase in peripheral blood (PB) CD34+ cell count from the time just prior to plerixafor administration to the time just prior to apheresis on the first treatment day (3.7-fold in NHL; 2.3-fold in MM).

Clinical Information Relevant to Dosing Recommendations

The 240-μg/kg dose was selected based on the PD and safety profile observed in early studies that enrolled healthy subjects and oncology patients with NHL and MM.

Study 2101 was the proof-of-principle study with a primary objective designed to evaluate the difference in the number of PB CD34+ cells/kg collected by apheresis after mobilisation with plerixafor and G-CSF compared with that collected after mobilisation of G-CSF alone in patients with NHL or MM. There was a dose-dependent increase to the dose of plerixafor (added to G-CSF) in the CD34+ cell yield per apheresis session compared to G-CSF alone.. These data (N=16) exclude patients who were poor mobilisers (defined in this study as those patients who failed to collect the minimum number of cells for transplantation with G-CSF alone).

Results – Study 2106

Primary Efficacy Results

Proportion of Patients Achieving Target Transplantable CD34+ Cell Dose

The proportion of patients achieving treatment success (collection of ≥ 5 x 10^6 CD34+ cells/kg) was the primary efficacy endpoint for Study 2106. Similar to the results seen in patients with NHL in Study 2101, 68% (15/22) of patients with HD in Study 2106 achieved a target of ≥ 5 x 10^6 CD34+ cells/kg and 91% (20/22) achieved the minimum transplantable cell dose of ≥ 2 x 10^6 CD34+ cells/kg. A review of the data in the locked interim database showed that 1 additional patient did have the minimum cells collected in the first collection; however, they underwent mobilisation procedures a second time due to a problem with cell processing of the first collection. Including the first collection for this patient, 95% (21/22) of patients collected ≥ 2 x 10^6 cells/kg and the observed failure rate was 4.5% (1/22) compared to a 26% failure rate in a retrospective analysis of 130 patients with HD who were mobilised with G-CSF alone (DiPersio *et al*, 2006, Blood), and a failure rate of 22% in an earlier study of 98 patients at the same institution (Cashen, 2006, Biol Blood Marrow Transplantation). The median number of cells collected for the 22 patients was 6.6 x 10^6 CD34+ cells/kg.

Secondary Efficacy Results

Time (Days) to Reach Target CD34+ Cell Dose (Study 2106)

For the 20 patients who had CD34+ results from the central laboratory, the median number of apheresis days was 2.0. For the 18 of these patients with a minimum transplantable cell dose of ≥ 2 x 10^6 CD34+ cells/kg, the median number of days to reach target was 1.0 day. For the 13 of these patients who reached the target dose of ≥ 5 x 10^6 CD34+ cells/kg, the median number of days to reach target was 1.0 day.

Peripheral Blood CD34+ Cell Count (cells/µl) (Study 2106)

The PB CD34+ cell counts pre- and post- first plerixafor administration were analysed in Study 2106. The time period for measurement of fold increase was an 11-hour window: from just prior to plerixafor dose to 11 hours post-plerixafor dose. The median fold increase after the first plerixafor administration was 3.0. Patients had a median pre-dose PB CD34+ count of 13.0 cells/µl, which increased to 40.0 cells/µl at 10 to 11 hours post-dose prior to the first apheresis.

Engraftment Success and Time to Engraftment (Study 2106)

Proportion of Patients who Underwent HSCT

Twenty-one patients (95.5%) in Study 2106 were able to proceed to transplantation. Of these, only 1 patient had ≤ 2 x 10^6 cells/kg by central laboratory; however, this patient had 2.33 x 10^6 cells/kg by local laboratory and proceeded to transplantation.

PMN and PLT Engraftment Success and Time to Engraftment

There was a 100% success rate in PMN engraftment and PLT engraftment for the 21 patients who underwent transplantation. The median time to engraftment was 9.0 days. Twenty patients had prompt and stable PMN engraftment by 12 days post-transplantation, and 1 patient had PMN engraftment on Day 14 post-transplantation. Nineteen patients had prompt and stable PLT engraftment within 22 days post-transplantation. One patient engrafted by Day 29. The date of PLT engraftment for the remaining patient was unknown. In all, a total of 21 patients had successful PLT engraftment.

Graft Durability (Study 2106)

For Study 2106, a study protocol amendment was made during the study to add visits at 3 and 6 months; therefore, not all patients had 3- and 6-month evaluations. In addition, since Study 2106 is an ongoing study, not all patient data were available by the cut-off date for the assessment of durability and inclusion of data in the database.

Overall, 21 of the 21 patients who had transplants were evaluable for durability. As of the data cut-off of 05 April 2007, 12-month post-transplant follow-up data were available for 15 of the 21 patients. All 15 (100.0%) of the evaluable patients reported durable grafts at the 12-month time period. Preliminary information was available for 6 patients whose 12-month results were not available as of the cut-off date. These 6 patients also reported durable grafts at their 12-month follow-up.

Additional Clinical Data Relevant to Dosing Recommendations

Efficacy

Plerixafor alone:

Study 1002: There was a dose-dependent mean fold-increase of PB CD34+ cell counts in the 40-µg/kg (4-fold), 80-µg/kg (5-fold), 160-µg/kg (12-fold), and 240-µg/kg (16-fold) plerixafor dose groups. In addition, there was a clinically important dose-dependent increase from baseline in mean absolute PB CD34+ cell counts (±SD) in the 40-µg/kg (10 ± 8.3), 80-µg/kg (16 ± 7.9), 160-µg/kg (25 ± 10.6), and 240-µg/kg (38 ± 10.8) dose groups, respectively. The time to peak mobilisation was 6 to 9 hours post-administration of plerixafor.

Plerixafor + G-CSF:

Study 1003: There were similar mean peak fold-increases of PB CD34+ cell counts in the 160-µg/kg (3.8-fold) and 240-µg/kg (4.0-fold) dose groups over the baseline PB CD34+ cell count elicited by G-CSF alone. There were also similar mean peak absolute changes from baseline PB CD34+ cell counts (±SD), which were elicited by G-CSF alone, in the 160-µg/kg (107 ± 68.0) and 240-µg/kg (161 ± 72.1) dose groups. There was a later and broader peak response in the 240-µg/kg dose group compared to the 160-µg/kg dose group. The time to peak mobilisation in the 240-µg/kg dose group was broad; from 10 to 14 hours post-administration of plerixafor.

Dose Interval

A dosing schedule for plerixafor administration of 6 to 11 hours prior to apheresis was established based on PD data from Studies 1002 and 1003. Results from Study 1002 showed peak mobilisation of CD34+ cells at 6 to 9 hours after dose of plerixafor alone. Results from Study 1003 showed peak mobilisation of CD34+ cells at 10 to 14 hours after dose of G + plerixafor.

Conclusion for Dose Selection

Together the studies showed that in healthy subjects, the plerixafor dose of 240 µg/kg elicited a higher and later peak response compared with the 160-µg/kg dose.160 µg/kg and 240 µg/kg plerixafor, added to a dosing regimen of G-CSF, had similar magnitudes of mean peak absolute and fold-increases in PB CD34+ cells; the absolute values in the plerixafor plus G-CSF dose groups were higher than with plerixafor alone.

In patients with MM and NHL, the 240-µg/kg dose with G-CSF elicited a greater response (greater fold-increase in apheresis yields) than the 160-µg/kg dose with G-CSF. In the studies, the 160- and 240-µg/kg dose groups had a similar safety profile when plerixafor was

administered alone or following G-CSF administration. There appeared to be a dose-related trend in AE intensity when comparing the 240-µg/kg and 320-µg/kg plerixafor doses in healthy subjects. Based on the safety and efficacy observed in the Phase I studies and 1 Phase II study, the 240-µg/kg dose was chosen as the dose to go forward in the clinical development programme for plerixafor. In addition, given the difference in response rates of patients with MM and NHL, the higher of the 2 doses (240 µg/kg) was chosen to account for potential lower response rates (achievement of target levels of PB CD34+ cells for transplantation and engraftment) in a wider population of patients.

Summary of Efficacy Data

The efficacy data presented for evaluation support the following conclusions:

Treatment with G + plerixafor (compared to treatment with G + placebo):

- significantly increased the proportion of patients who collected sufficient numbers of CD34+ cells (≥ 2 million cells/kg) for subsequent HSCT (that is, significantly reduced mobilisation failures)
- significantly increased the proportion of patients who achieved a target number of CD34+ cells for transplantation
- significantly increased the proportion of patients who met a composite endpoint (EMEA composite primary endpoint) of achieving target number of CD34+ cells for transplantation and successful PMN cell and PLT engraftment
- significantly decreased the number of apheresis sessions required to collect a target number of CD34+ cells for transplantation
- resulted in a greater than 6-fold increase in mean peripheral blood CD34+ cell count over the 24-hour period from the day prior to the first apheresis to just before the first apheresis (that is, Day 4 to Day 5, before the morning G-CSF doses). During that 24-hour period, the first dose of plerixafor or placebo was administered (10 - 11 hours prior to apheresis). G + placebo resulted in a 2-fold increase in mean peripheral blood CD34+ cell count over the same time period (that is, G + plerixafor resulted in an additional 4-fold increase in mean peripheral blood CD34+ cell count relative to G + placebo)
- was similar to G + placebo with respect to time to PMN and PLT engraftment and graft durability
- resulted in fewer patients going into a Rescue procedure for further mobilisation to collect the minimum number of CD34+ cells for transplantation (10 total G + plerixafor patients in the 2 Phase III studies went into Rescue compared with 59 patients total in the G + placebo group). Of patients who entered open-label treatment with plerixafor in the Rescue procedure, most (59/69) underwent transplantation, resulting in a successful and durable engraftment.

The two Phase II open-label studies support MM and NHL as a claim, and support the general conclusions that treatment with G + plerixafor results in a greater proportion of patients who reach a target number of cells for transplantation, and who reach the target in fewer apheresis days when compared to patients treated with G-CSF alone.

Comment: In the Phase III studies, patients with NHL and MM received plerixafor in combination with G-CSF. Efficacy data indicated responses in the overall population and in patients who were poor mobilisers and entered the Rescue period.

Overall the evaluator considered that the data presented for evaluation do support efficacy of plerixafor in combination with G-CSF to mobilise HSCs. The sponsor has not stipulated that

plerixafor should be used in combination with G-CSF; however the evaluator considered that this should be included in the indication. This would align the Australian approved indication with the indication approved in the US.

"Mozobil, a haemopoietic stem cell mobiliser, is indicated in combination with granulocyte colony stimulating factor (G-CSF) to mobilise haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma."

Safety

Extent of Exposure

Safety data were presented from all 21 clinical studies and 1 CUP (2 Phase III, 13 Phase II, 6 Phase I and 1 CUP). As of the data cut-off dates for ongoing studies and the safety database, a total of 1426 patients were enrolled and treated in the 21 studies plus the CUP; 1161 patients had received plerixafor and 239 received G + placebo. A total of 26 patients received G-CSF but never received plerixafor or placebo.

In this evaluation report safety data from the Phase III studies and the oncology studies (All Oncology population) are presented.

Exposure for Phase III Placebo-Controlled Studies in Patients With NHL and MM

For G-CSF mobilisation, the mean (± SD) cumulative dose of G-CSF/body weight was 59.9 μg/kg (± 13.2) and the mean number of administrations was 6.1 in the G + plerixafor group compared with 68.1 μg/kg (± 14.1) and a mean number of administrations of 7.0 in the G + placebo group. For study treatment (plerixafor or placebo), the mean (± SD) cumulative dose of study drug/body weight was 543.8 μg/kg (± 263.0) with an average of 2.3 administrations in the G + plerixafor group compared with an average of 3.1 administrations in the G + placebo group. The mean (± SD) number of days of exposure from first G-CSF mobilisation to the last G-CSF, plerixafor, or placebo treatment was 6.1 (± 1.2) days for patients in the G + plerixafor group compared with 7.0 (± 1.1) days for patients in the G + placebo group. More than 97% of patients in both treatment groups had an average daily dose of study drug/body weight of 240 μg/kg.

Exposure for All Oncology Studies in Patients With Lymphoma and MM Using G + Plerixafor

For analyses a pooled Phase III placebo group was the comparator for the All Oncology group as only the Phase III studies were placebo controlled. In the G + placebo there were 295 patients (145 NHL; 150 MM) and in the G + Plerixafor group there were 540 patients (244 NHL; 255 MM; 39 HD). For G-CSF mobilisation, the mean (± SD) cumulative dose of G-CSF/body weight was 65.3 μg/kg (± 26.2) and the mean number of administrations was 6.5 in the G + plerixafor group compared with 68.1 μg/kg (± 14.1) and a mean number of administrations of 7.0 in the G + placebo group. For study treatment (plerixafor or placebo), the mean (± SD) cumulative dose of study drug/body weight was 603.9 μg/kg (± 366.5) with an average of 2.5 administrations in the G + plerixafor group compared with an average of 3.1 administrations in the G + placebo group. The mean (± SD) number of days of exposure from the first G-CSF mobilisation to the last G-CSF, plerixafor, or placebo treatment was 6.6 (± 2.5) days for patients in the G + plerixafor group compared with 7.0 (± 1.1) days for patients in the G + placebo group.

Exposure for Poor Mobilisers

A poor mobiliser was defined as a patient who did not achieve collection of enough CD34+ cells for a single transplant using 1 mobilisation regimen. For the safety analyses, patients

who achieved < 2×10^6 CD34+ cells/kg were considered poor mobilisers. The poor mobiliser analysis group includes patients from Studies 3101 (n = 52), 3102 (n = 7), 2101 (n = 9), 2102 (n = 20), 2103 (n = 3), and 2112 (n = 40). For G-CSF mobilisation, the mean (± SD) cumulative dose of G-CSF/body weight was 82.6 µg/kg (± 41.7) and the mean number of administrations was 8.3. For study treatment (plerixafor), the mean (± SD) cumulative dose of study drug/body weight was 906.0 µg/kg (± 441.7) with an average of 3.8 administrations. The mean (± SD) number of days of exposure was 8.5 (± 4.2) days. More than 97% of patients had an average daily dose of study drug/body weight of 240 µg/kg/day.

Overview of Adverse Events (AEs)

Overview of AEs in the Phase III Placebo-controlled Studies

During Period 1 (from the first dose of G-CSF for mobilization to 30 days after the last apheresis or to the day before starting the first dose of ablative chemotherapy), when all AEs that occurred were recorded regardless of relationship or severity, 287/298 (96.3%) of patients in the G + plerixafor group experienced at least 1 adverse event (AE), and 194/298 (65.1%) experienced at least 1 AE considered by the investigator to be related to study treatment (possibly, probably, definitely related or not filled out/unknown). In the G + placebo group, 277/295 (93.9%) of patients experienced an AE in Period 1 and 126/295 (42.7%) experienced an AE related to study treatment.

The proportion of patients with at least 1 serious adverse event (SAE) in Period 1 was low and was similar for the 2 treatment groups (4.0% 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). The incidence of SAEs was (in the G + plerixafor versus G + placebo groups, respectively): 22.3% versus 20.3% in Period 2 (from the first pre-transplant chemotherapy to the day before PMN/PLT engraftment) and 16.2% versus 15.7% in Period 3 (during the study period from PMN/PLT engraftment through the follow-up period).

Twelve patients experienced AEs that resulted in study or treatment discontinuation from the Phase III studies: 6 patients in the G + plerixafor group and 6 patients in the G + placebo group. A total of 37 patients in the Phase III studies died prior to the data cut-off date (18 in the G + plerixafor group and 19 in the G + placebo group). The majority of deaths (32/37) occurred in Period 3.

Overview of AEs in the All Oncology Studies

AEs observed in the All Oncology studies were similar to those seen in the pooled Phase III placebo-controlled studies. During Period 1, 504/540 (93.3%) of patients in the G + plerixafor group experienced at least 1 AE, and 338/540 (62.6%) experienced at least 1 AE considered by the Investigator to be related to study treatment. In the G + placebo group, 277/295 (93.9%) of patients experienced an AE in Period 1 and 126/295 (42.7%) experienced an AE related to study treatment. When analysed by cancer type (NHL, MM, and HD), there were no meaningful differences in the incidences and types of AEs across the NHL and MM subgroups. The incidence of AEs was generally lowest in the HD subgroup compared with the NHL and MM subgroups.

The proportion of patients with at least 1 SAE in Period 1 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. The incidence of SAEs was (in the G + plerixafor versus G + placebo groups, respectively): 18.4% versus 20.3% in Period 2 and 15.8% versus 15.7% in Period 3.

Seventeen patients experienced AEs that resulted in study discontinuation, treatment discontinuation or modification in the All Oncology studies: 11 (2.0%) in the G + plerixafor group and 6 (2.0%) in the G + placebo group. In Period 1, 15 patients experienced AEs that resulted in study discontinuation or treatment discontinuation, interruption or modification in the All Oncology studies: 9 patients in the G + plerixafor group and 6 patients in the G + placebo group.

A total of 54 patients in the All Oncology studies died prior to the cut-off dates for the safety database and the individual studies: 35 (6.5%) in the G + plerixafor group and 19 (6.4%) in the G + placebo group. There were no notable differences between treatment groups in the timing or cause of deaths. All of the deaths occurred after transplantation with the exception of 4 patients in the G + placebo group, and the most common cause of death after transplantation was disease progression.

Overview of AEs for Poor Mobilisers

The AEs occurring in the poor mobiliser population were similar to those observed in the pooled Phase III placebo-controlled studies. During Period 1, 126/131 (96.2%) of patients experienced at least 1 AE, and 87/131 (66.4%) experienced at least 1 AE considered by the Investigator to be related to study treatment.

Forty-seven of 131 poor mobilisers (35.9%) experienced an SAE, but only 7/131 patients (5.3%) experienced an SAE during Period 1. The majority of the SAEs occurred in Periods 2 and 3. Four patients in the poor mobiliser population experienced AEs that resulted in study discontinuation; treatment discontinuation or modification. A total of 16 poor mobilisers died prior to the data cut-off, and the majority of these deaths (13) occurred during Period 3.

Common Adverse Events

Common Adverse Events for Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma

The number of patients in the treatment groups changed considerably over the course of the studies, primarily due to the difference in the number of patients who failed mobilisation and entered the rescue phase of the study. In addition, study treatment (plerixafor or placebo) was only administered in Period 1, while other procedures such as ablative chemotherapy and transplantation were administered in later study periods, and AE collection was limited by the study protocols in the later periods.

Period 1: Common Adverse Events During Mobilisation and Treatment/Apheresis (Phase 3 Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma)

Period 1 was from the first dose of G-CSF for mobilization to 30 days after the last apheresis or to the day before starting the first dose of ablative chemotherapy. Table 8 summarises the common AEs (occurring in ≥ 5% of patients in either treatment group) that were reported in the placebo-controlled Phase III studies. Of these events, the most frequently occurring (> 10% in either treatment group) were diarrhoea, nausea, bone pain, fatigue, injection site erythema, headache, paresthesia, back pain, hypokalaemia, arthralgia, catheter site pain and dizziness.

Events occurring more frequently in the G + plerixafor group were diarrhoea, nausea, vomiting, flatulence, injection site erythema, injection site pruritus and dizziness. Common AEs reported more frequently in the G + placebo group included bone pain, back pain, pain in extremity and catheter site pain. The majority of patients with AEs in Period 1 had events reported by the Investigator as either mild or moderate in severity.

Table 8: Period 1: Most Common Adverse Events (Occurring in ≥ 5% of Patients) by System Organ Class (SOC) and Preferred Term During Mobilisation and Treatment/Apheresis (Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma).

	G+Plerixafor Period 1 (N=298)	**G+Placebo Period 1** (N=295)
SOC Preferred Term	N (%)	N (%)
Any AE in Period 1	287 (96.3)	277 (93.9)
Gastrointestinal disorders		
Diarrhoea	112 (37.6)	49 (16.6)
Nausea	102 (34.2)	64 (21.7)
Vomiting	29 (9.7)	18 (6.1)
Paresthesia oral	22 (7.4)	25 (8.5)
Flatulence	20 (6.7)	11 (3.7)
General disorders and administration site conditions		
Fatigue	80 (26.8)	74 (25.1)
Injection site erythema	78 (26.2)	14 (4.7)
Catheter site pain	32 (10.7)	40 (13.6)
Edema peripheral	27 (9.1)	28 (9.5)
Pain	24 (8.1)	26 (8.8)
Pyrexia	18 (6.0)	19 (6.4)
Injection site pruritus	17 (5.7)	2 (0.7)
Metabolism and connective tissue disorders		
Hypokalemia	45 (15.1)	49 (16.6)
Hypomagnesemia	26 (8.7)	28 (9.5)
Musculoskeletal and connective tissue disorders		
Bone pain	95 (31.9)	105 (35.6)
Back pain	54 (18.1)	64 (21.7)
Arthralgia	39 (13.1)	36 (12.2)
Pain in extremity	15 (5.0)	21 (7.1)
Nervous system disorders		
Headache	67 (22.5)	62 (21.0)
Paresthesia	60 (20.1)	64 (21.7)
Dizziness	31 (10.4)	18 (6.1)
Psychiatric disorders		
Insomnia	21 (7.0)	15 (5.1)
Anxiety	16 (5.4)	13 (4.4)

This analysis group includes patients from the 3101 and 3102 studies. It excludes all patients who received rituximab, excludes one patient from study 3102 in the G+placebo group who received post-transplant cytoreductive chemotherapy and excludes the rescue experience for the patients who entered the rescue arm of the studies.
"n" equals the number of all randomised patients receiving ≥1 dose of treatment. Percentages were calculated as the number of patients with ≥1 AE (n) divided by the total number of patients available for the analysis (N): n/Nx100%). A patient experiencing more than 1 AE within a SOC or preferred term was counted once within that SOC or preferred term.

In the G + plerixafor group severe events occurring in more than one patient were bone pain and nausea. In the G + placebo group severe events occurring in more than one patient were hypokalaemia, headache, back pain and hypomagnesaemia.

The most frequently occurring AEs (> 10% in either treatment group) reported as related to treatment were diarrhoea, nausea, bone pain and injection site erythema. Common treatment-related AEs (≥ 5% of patients in either treatment group) occurring more frequently in the G + plerixafor group during Period 1 were diarrhoea, nausea, injection site erythema, fatigue, injection site pruritus, bone pain, headache and paresthesia.

Other AEs occurring more frequently with plerixafor than placebo and considered related in ≥ 1% and < 5% of patients treated with G + plerixafor during Period 1 were flatulence, abdominal pain, vomiting, dizziness, injection site irritation, hyperhidrosis, injection site reaction, abdominal distension, dry mouth, stomach discomfort, arthralgia, erythema, malaise, constipation, dyspepsia, hypoesthesia oral, injection site rash, and insomnia.

Period 2: Common Adverse Events From Chemotherapy to Engraftment (Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma)

In Period 2 (from the first pre-transplant chemotherapy to the day before PMN/PLT engraftment), only AEs Grade 3 or greater were required to be collected. Febrile neutropenia and haemorrhage were collected if Grades 4 or 5; neutropenia, thrombocytopenia, and anaemia were collected if the outcome was death and all SAEs were required to be collected.

The proportion of patients with AEs in Period 2 for the placebo-controlled Phase III studies was similar for the 2 treatment groups (46.4% for G + plerixafor compared with 43.8% for G + placebo). Common AEs (occurring in ≥ 5% of patients in either treatment group) during Period 2 in the placebo-controlled Phase III studies were mucosal inflammation, febrile neutropenia, nausea, vomiting and diarrhoea. The incidence of these events was similar for the 2 treatment groups. These AEs are consistent with the known side effects of ablative chemotherapy.

Period 3: Common Adverse Events From Engraftment Through Follow-up (Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma)

During the study period from PMN/PLT engraftment through the Follow-up period (Period 3), all SAEs within 6 months post-transplantation or until relapse, whichever occurred first, were required to be reported (or within 30 days after last dose of study treatment or until relapse, if the patient did not undergo transplant), and graft failures within 12 months post transplantation and MDS after 6 months post transplantation were required to be recorded.

In Period 3, 52/277 (18.8%) of patients in the G + plerixafor group and 36/217 (16.6%) of patients in the G + placebo group had AEs. None of the AEs in Period 3 occurred in ≥ 5% of patients in either treatment group.

Period 4: Common Adverse Events From Chemotherapy to Engraftment for Second Transplant (Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma)

In Period 4 (from second chemotherapy to the day before PMN/PLT engraftment following second transplant), only SAEs were collected. In Period 4, 13/32 (40.6%) in the G + plerixafor group and 4/24 (16.7%) patients in the G + placebo group had at least one AE.

Events reported in more than 1 patient in the G + plerixafor group included mucosal inflammation, febrile neutropenia, nausea and vomiting. Events reported in more than one patient in the G + placebo group included neutropenia and pyrexia. None of these events were considered related to study treatment.

Period 5: Common Adverse Events From Engraftment Through Follow-up for Second Transplant (Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma)

In Period 5 (from PMN/PLT engraftment after the second transplant through the Follow-up period), all SAEs within 6 months post-transplantation or until relapse, whichever occurred first, were to be reported (or within 30 days after last dose of study treatment or until relapse, if the patient did not undergo transplant), and graft failure within 12 months post transplantation and MDS after 6 months post transplantation were required to be reported.

During Period 5, 4/32 (12.5%) of the patients in the G + plerixafor group and 1/24 (4.2%) of the patients in the G + placebo had at least 1 AE. Only 1 event occurred in ≥ 5% of patients in either treatment group: pyrexia in 2/32 (6.3%) patients in the G + plerixafor group. No AEs in Period 5 were considered related to study treatment.

Common Adverse Events for All Oncology Studies in Patients With Lymphoma and Multiple Myeloma

The overall incidence of AEs in Period 1 was similar in the 2 treatment groups. In addition, the overall incidence of AEs among patients with NHL was similar for both treatment groups as was the overall incidence of AEs among patients with MM.

The most common AEs (≥ 5% of patients in either treatment group) occurring in the All Oncology studies in Period 1 were the same as those noted in the pooled Phase III placebo-controlled studies with the exception of muscles spasms and thrombocytopenia which occurred in 6.7% and 6.1% of patients, respectively in the G + plerixafor group. Thrombocytopenia, a known complication of apheresis, was observed in 2.7% of patients in the G + plerixafor group and 3.1% of patients in the G + placebo group in the pooled Phase III studies.

The most frequently occurring AEs (> 10% in either treatment group) in Period 1 were diarrhoea, nausea, injection site erythema, fatigue, catheter site pain, hypokalaemia, hypomagnesaemia, bone pain, back pain, arthralgia, headache, and paresthesia. Diarrhoea, nausea, fatigue, bone pain, back pain, headache, and paresthesia were reported by > 10% of NHL and MM patients, regardless of treatment group, as well as by > 10% of HD patients.

Within the G + plerixafor group, the most frequently occurring (> 10%) AEs in Period 1 among patients with NHL or MM were diarrhoea, nausea, and injection site erythema. When analysed by cancer type (NHL, MM, and HD), there were no meaningful differences in the incidences and types of AEs across the NHL and MM subgroups.

The majority of patients with AEs in Period 1 had events reported by the investigator as either mild or moderate in severity. In the G + plerixafor group, 9.6% of patients had severe events and in the G + placebo group, 8.5% of patients had severe events. In general, the incidence of severe AEs was similar in the All Oncology studies and the pooled Phase III placebo-controlled studies with the exception of thrombocytopenia which occurred in a higher incidence of patients (2.2% versus 1.0%, respectively) in the G + plerixafor group in the All Oncology studies compared with the pooled Phase III studies.

The most frequently occurring (> 10% in either treatment group) related AEs in Period 1 were diarrhoea, nausea, and injection site erythema. Related events occurring more frequently

in the G + plerixafor group during Period 1 were thrombocytopenia, diarrhoea, nausea, flatulence, vomiting, injection site erythema, fatigue, injection site pruritus, pyrexia, oedema peripheral, catheter site pain, hypokalaemia, hypomagnesaemia, insomnia, and anxiety.

Common Adverse Events for Poor Mobilisers

The most common AEs occurring in the poor mobilisers were similar to those observed in the pooled Phase III placebo-controlled studies. The most frequently occurring (> 10%) were diarrhoea, injection site erythema, bone pain, fatigue, nausea, hypokalaemia, hypomagnesaemia, headache, paresthesia, vomiting, arthralgia, back pain, thrombocytopenia, anaemia, anxiety, and oral paresthesia.

The majority of poor mobiliser patients with AEs in Period 1 had events reported by the Investigator as either mild or moderate in severity. A total of 13.0% of poor mobiliser patients had severe or life-threatening events. Severe or life-threatening events occurring in more than 1 patient were thrombocytopenia and anaemia.

In Period 1, 66.4% of poor mobilisers had AEs considered related to study treatment. The most frequently occurring (> 10%) related AEs were diarrhoea, injection site erythema and nausea.

Serious Adverse Events (SAEs)

Deaths

As of the data cut-off dates for ongoing studies and the safety database, a total of 1426 patients were enrolled and treated in the 21 studies plus the CUP. A total of 108 patients have died in the 21 studies plus the CUP (based on all data sources); 88 (7.6%) who received plerixafor and 20 (8.4%) who received G + placebo. There were no notable differences between treatment groups in the timing or cause of deaths. The most common cause of death was disease progression after transplantation.

Deaths in Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma

As of the cut-off date for the Phase III studies, a total of 37 patients have died: 18 in the G + plerixafor group and 19 in the G + placebo group. There were no notable differences between treatment groups in the number, timing, or cause of deaths. The most common cause of death after transplantation was disease progression.

Deaths in All Oncology Studies in Patients With Lymphoma and Multiple Myeloma Using G + Plerixafor

As of the data cut-off dates for ongoing studies and the safety database, a total of 54 patients have died in the All Oncology studies: 35 (6.5%) in the G + plerixafor group and 19 (6.4%) in the G + placebo group. Once again, there were no notable differences between treatment groups in the timing or cause of deaths. All of the deaths occurred after transplantation with the exception of 4 patients in the G + placebo group. The most common cause of death after transplantation was disease progression.

Deaths in Poor Mobilisers

As of the safety data cut-off date, a total of 16 patients in the poor mobiliser subset have died: 9 in the G + plerixafor group and 7 who received G + placebo initially in Study 3101 and subsequently received G + plerixafor in the rescue procedure. There were no notable differences between treatment groups in the number, timing, or cause of deaths. All of the deaths occurred after transplantation with the exception of 1 patient who died in Period 1 of rescue following initial treatment with G + placebo in Study 3101. The most common cause of death after transplantation was disease progression or relapse.

Serious Adverse Events other than Death

Other Serious Adverse Events for Phase III Placebo-Controlled Studies in Patients With Non-Hodgkin's Lymphoma and Multiple Myeloma

Overall, the proportion of patients with at least 1 SAE was higher for G + plerixafor than for G + placebo (37.2% compared with 28.8%); however these results should be interpreted with caution because the number of patients in the treatment groups changed considerably over the course of the studies. The higher incidences of SAEs in the G + plerixafor group primarily reflected higher incidences of SAEs in the SOCs of blood and lymphatic system disorders (11.4% and 6.8%, respectively), and infections and infestations (13.8% and 9.5%, respectively). The difference between treatment groups in the incidences of SAEs in the SOC of blood and lymphatic system disorders was largely due to the difference in incidences of febrile neutropenia (10.1% and 5.8%, respectively). Both febrile neutropenia and infections are common following haematopoietic stem cell transplantation. None of the SAEs of febrile neutropenia or SAEs of infection were considered by the investigator as related to the study treatment.

Graft failure occurring within 12 months after transplantation was to be reported as an SAE. Among the Phase 3 studies, there have been 2 cases of graft failure, both of which occurred in single-transplant patients treated with G + plerixafor in Study 3101, but only one of which was reported as an SAE. Neither of the cases of graft failure was considered by the Investigator as related to the study treatment.

Clinical Laboratory Data and Physical Findings

Safety laboratory parameter findings in the pooled Phase III analysis were similar in the G + plerixafor and G + placebo treatment groups with no clinically meaningful differences between groups. The majority of patients in each group had normal white blood cell (WBC) and neutrophil values at baseline that shifted to above the normal range at 24 hours after the last apheresis. A generalised leukocytosis has been observed in healthy subjects after a single SC injection of plerixafor and leukocytosis has also been reported with G-CSF alone.

In both treatment groups, the majority of patients had a shift in platelet values from normal to below the normal range at 24 hours after the last apheresis, although a higher proportion of patients experienced this in the G + placebo group (80.7%) than in the G + plerixafor group (71.9%).

There were no clinically significant differences observed between the G + plerixafor and G + placebo treatment groups with regards to clinical chemistry laboratory parameters. There were also no clinically meaningful changes observed in either treatment group during Period 1 in the Phase III studies with respect to vital signs (including cardiovascular assessments) and physical examination findings.

Special Adverse Events

Potential Systemic Reactions

In all, there were 6 plerixafor-treated patients with systemic reactions, which included urticaria (n = 2), periorbital swelling (n = 2), dyspnoea (n = 1) or hypoxia (n = 1). These events were mild to moderate and most occurred within approximately 30 minutes after plerixafor administration. In general, symptoms responded to treatments (for example, antihistamine, corticosteroid, hydration, or supplemental oxygen) or resolved spontaneously. Patients should be monitored for systemic reactions following administration of plerixafor.

Vasovagal reactions

In plerixafor oncology and healthy volunteer clinical studies, fewer than 1% of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following subcutaneous administration of plerixafor doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of Mozobil administration.

Tumour Cell Mobilisation

Contamination of autologous transplants by the initial tumour is a recognised phenomenon, whether the grafts are obtained from peripheral blood or bone marrow. In the case of peripheral blood HSC transplants, all methods of mobilisation, including G-CSF, can result in tumour cell contamination of the graft. It has been hypothesised that the disruption of the binding of CXCR4 to SDF-1 by plerixafor in the bone marrow microenvironment could potentially result in the release and mobilisation of tumour cells from the bone marrow in patients receiving plerixafor for HSC mobilisation. However, based on laboratory investigations conducted in clinical studies (2101, 2102, 2103, 3101, and EU21), enhanced mobilisation of tumour cells has not been observed with plerixafor in patients with lymphoma and MM.

In contrast, plerixafor and G-CSF administered to patients with acute myeloid leukaemia and MM in transition to plasma cell leukaemia in the CUP were associated, in some instances, with an increase in the number of circulating leukaemia cells. The CUP protocol was subsequently amended to exclude patients with a diagnosis of leukaemia. As G + plerixafor may cause mobilisation of leukemic cells and subsequent contamination of the apheresis product, plerixafor is not intended for HSC mobilisation and harvest in patients with leukaemia.

Cardiovascular Events

Myocardial infarction has been noted following G-CSF administration, although the mechanism, frequency and temporal relationship to G-CSF remain somewhat uncertain. The half life of plerixafor is approximately 3-5 hours, and plerixafor-mediated changes in total peripheral blood WBC and CD34+ cell count wane by 24 hours. Based on these data, plerixafor would not be expected to increase myocardial infarction risk following mobilisation. One event of myocardial infarction was reported as possibly related to study treatment in the safety database; therefore a further investigation of AEs of myocardial infarction was conducted.

In clinical studies, 7 of 679 oncology patients experienced myocardial infarction after HSC mobilisation with plerixafor and G-CSF. All events occurred at least 14 days after last plerixafor administration. In addition, 2 oncology patients in the CUP experienced myocardial infarction following HSC mobilisation with plerixafor and G-CSF. One of these events occurred 4 days after last plerixafor administration. The lack of temporal relationship in 8 of the 9 patients with myocardial infarction, together with the other risk factors in these

patients, suggests that it is unlikely that plerixafor confers an independent risk for myocardial infarction in patients who also receive G-CSF.

Overdose, Withdrawal and Rebound

The recommended daily dose of plerixafor is 240 μg/kg SC. During clinical studies in oncology patients, 4 patients were known to have received inadvertent administration of doses larger than those specified in the study protocol: 3 patients in the CUP received doses of 480 μg/kg SC and 1 patient in EU21 received a dose of 606 μg/kg SC. Reported AEs in patients who received the higher doses were similar to those in patients who received the recommended dose of 240 μg/kg SC. No data were provided in relation to withdrawal and rebound effects.

Comment: Data from across the clinical programme indicate that plerixafor is reasonably well tolerated. The incidence of AEs following administration of plerixafor in conjunction with G-CSF was similar to that after G-CSF alone with the exception of gastrointestinal disorders such as diarrhoea and nausea, administration site conditions such as injection site erythema, and dizziness, which occurred more frequently in patients receiving plerixafor. In the clinical studies, from the time of chemotherapy/ablative treatment in preparation of transplantation through 12 months post-transplantation, no clinically meaningful differences in the AE profiles were observed between treatment groups. The frequency of related SAEs was low and no deaths in the clinical programme were considered by the investigators to be related to plerixafor treatment.

Clinical Summary and Conclusions

In this application the sponsor is seeking to register a new chemical entity, Mozobil (plerixafor) 20 mg/ml solution for injection, to mobilise haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation. The target population studied in the Phase III clinical trials of plerixafor was adult patients with non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM). Data from 21 clinical studies and 1 Compassionate Use Programme (CUP) were submitted in this dossier.

The PK and PD data submitted for evaluation demonstrated the following:

- The PK profile of plerixafor is similar whether in healthy subjects given plerixafor alone or oncology patients given plerixafor plus G-CSF
- Plerixafor pharmacokinetics are dose-proportional in the studied dose range.
- The maximum PD response to plerixafor 240 μg/kg (no G-CSF) in healthy subjects occurs 6 to 10 hours after dosing. The median peak fold-increase was 15.8 over baseline
- In healthy subjects, the PD response to 240 μg/kg plerixafor alone was higher than the response to 160 μg/kg plerixafor alone
- The PD response to plerixafor with G-CSF administration in oncology patients occurs over a broad peak, with maximum PB CD34+ levels occurring 10 to 14 hours after dosing. Median peak PB CD34+ levels were 2.9-fold higher than baseline levels after 6 hours treatment with G-CSF. The mean improvement in total cells collected in apheresis product was 2.9 ± 3.47 x 10^6cells/kg compared to G-CSF alone (Study 2101)
- In renally impaired subjects, systemic exposure (AUC_{0-24}), but not C_{max}, increased with increasing severity of impairment

The efficacy data presented for evaluation supported that treatment with G + plerixafor (compared to treatment with G + placebo):

- significantly increased the proportion of patients who collected sufficient numbers of CD34+ cells (≥ 2 million cells/kg) for subsequent HSCT (that is, significantly reduced mobilisation failures)
- significantly increased the proportion of patients who achieved a target number of CD34+ cells for transplantation
- significantly increased the proportion of patients who met a composite endpoint (EMEA composite primary endpoint) of achieving target number of CD34+ cells for transplantation and successful PMN cell and PLT engraftment
- significantly decreased the number of apheresis sessions required to collect a target number of CD34+ cells for transplantation
- resulted in a greater than 6-fold increase in mean peripheral blood CD34+ cell count over the 24-hour period from the day prior to the first apheresis to just before the first apheresis (that is, Day 4 to Day 5, before the morning G-CSF doses). During that 24-hour period, the first dose of plerixafor or placebo was administered (10 - 11 hours prior to apheresis). G + placebo resulted in a 2-fold increase in mean peripheral blood CD34+ cell count over the same time period (that is, G + plerixafor resulted in an additional 4-fold increase in mean peripheral blood CD34+ cell count relative to G + placebo)
- was similar to G + placebo with respect to time to PMN and PLT engraftment and graft durability
- resulted in fewer patients going into a Rescue procedure for further mobilisation to collect the minimum number of CD34+ cells for transplantation (10 total G + plerixafor patients in the 2 Phase 3 studies went into Rescue compared with 59 patients total in the G + placebo group). Of patients who entered open-label treatment with plerixafor in the Rescue procedure, most (59/69) underwent transplantation, resulting in a successful and durable engraftment.

Data from the two Phase II open-label studies in patients with NHL, MM and HD support the indication in MM and NHL patients when used in combination with G-CSF.

In the Phase III studies patients with NHL and MM received plerixafor in combination with G-CSF. Efficacy data indicated responses in the overall population and in patients who were poor mobilisers and entered the Rescue period.

Data from across the clinical programme indicate that plerixafor is reasonably well tolerated. The incidence of AEs following administration of plerixafor in conjunction with G-CSF was similar to that after G-CSF alone with the exception of gastrointestinal disorders such as diarrhoea and nausea, administration site conditions such as injection site erythema, and dizziness, which occurred more frequently in patients receiving plerixafor.

Overall this evaluator considers that the data presented for evaluation adequately support efficacy of plerixafor in combination with G-CSF to mobilise HSCs.

Clinical Evaluator's recommendations

At present, and on the basis of the data evaluated, it was recommended that:

1. The application to register plerixafor for use as a haemopoietic stem cell mobiliser should be approved. The following indication would be appropriate:

"MOZOBIL, a haemopoietic stem cell mobiliser, is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilise haematopoietic stem cells to the

peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkins lymphoma and multiple myeloma."

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no Quality objections to registration. The application is to be considered by the Pharmaceutical Subcommittee (PSC) at its meeting directly before the Advisory Committee on Prescription Medicines (ACPM; which has succeeded ADEC) meeting.

Nonclinical

There are no Nonclinical objections to registration. The FDA's evaluation of the preclinical data was used and is included in the agenda papers. Toxicological findings included:

- Leukocytosis
- Increased haematopoiesis in liver and spleen;
- Bone mineral loss;
- CNS depression;
- Cardiovascular dysfunction;
- Gastrointestinal toxicity;
- Injection site reactions.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacodynamics

The effect of plerixafor on peripheral blood CD34+ cell counts was studied in healthy volunteers and in patients. In healthy volunteers, CD34+ cell counts were increased in a dose-dependant manner after single doses of plerixafor, and the peak effect was seen at 6-9 hours. When plerixafor was administered in conjunction with G-CSF, the effects on CD34+ cell count were additive.

In patients with myeloma or non-Hodgkin's lymphoma (NHL), plerixafor again produced elevations in CD34+ cell counts, with peak effect being seen at 8-10 hours. In patients with renal impairment, cell mobilisation appeared to be delayed.

Pharmacokinetics

Following SC administration the drug is absorbed rapidly with a T_{max} of 30 minutes. Following SC administration to healthy volunteers (n=6), approximately 71% of the administered dose was recovered unchanged in the urine within 24 hours, suggesting high bioavailability. In healthy volunteers, C_{max} and AUC increased in a dose proportional manner.

PK data for IV administration are unavailable, hence true values for volume of distribution and clearance are unknown. Apparent volume (Vz/F) was approximately 25 – 35 L and apparent clearance (CL/F) was approximately 4 – 5 L/hr. Half-life was approximately 3 – 5 hours.

The drug is predominately cleared renally. *In vitro* studies indicated that plerixafor is not metabolised by human hepatocytes. In patients with impaired renal function AUC increased by up to 39%).

In vitro data indicate that plerixafor does not inhibit or induce CYP450 enzymes in human hepatocytes. No studies have been conducted to examine potential renal interactions.

Efficacy

Evidence for efficacy comes from two randomised, double-blind, placebo-controlled trials. In each study, plerixafor and placebo were administered in conjunction with G-CSF:

- G-CSF was administered in the morning on days 1 to 5;
- Plerixafor or placebo was commenced in the evening on day 4;
- Apheresis was commenced on day 5.
- Plerixafor or placebo in the evening prior to, and G-CSF in the morning prior to, each daily apheresis session were continued for up to four days or until sufficient HSC's were collected.

Study 3101 enrolled subjects with NHL (n=298). The primary endpoint was the proportion of patients able to mobilise ≥ 5 x 10^6 CD34+ cells / kg in ≤ 4 apheresis days. The proportion was significantly increased in the plerixafor arm (59.3% versus 19.6%; $p < 0.001$).

Multiple secondary endpoints were studied and notable findings included the following:

- The median time taken to reach the target of 5 x 10^6 CD34+ cells / kg was 3.0 days in the plerixafor group. By day 4, the median had yet to be reached in the placebo group.
- In those patients who actually received an autologous graft, there was no significant difference between treatment groups in the median time to engraftment, or the incidence of graft failure at 3, 6 or 12 months.

Study 3102 enrolled subjects with myeloma (n=302). The primary endpoint was the proportion of patients able to mobilise ≥ 6 x 10^6 CD34+ cells / kg in ≤ 2 apheresis days. The proportion was significantly increased in the plerixafor arm (71.6% versus 34.4%; $p < 0.001$).

Plerixafor was also superior to placebo on secondary endpoints studied.

- The median time taken to reach the target of 6 x 10^6 CD34+ cells / kg was 1.0 day in the plerixafor group and 4.0 days in the placebo group.
- In those patients who actually received an autologous graft, there was no significant difference between treatment groups in the median time to engraftment, or the incidence of graft failure at 3, 6 or 12 months.

In both studies, patients who failed to reach the minimum number of cells to enable grafting were enrolled in an open extension 'rescue' phase in which plerixafor was administered together with G-CSF.

- In the rescue phase of study 3101, 63.5% of subjects who had not achieved adequate mobilisation with G-CSF + placebo, and 40% of subjects who had not achieved adequate mobilisation with G-CSF + plerixafor, were able to achieve the minimum number.
- Only seven patients entered the rescue phase of study 3102, all of whom had received G-CSF + placebo. All of these patients were able to mobilise the minimum number of cells with the rescue treatment.

The evaluator has reviewed two supportive Phase II studies:

- **Study 2101** examined both NHL and myeloma patients and compared the combination of plerixafor with G-CSF to G-CSF alone. The combination was superior in terms of

the number of CD34+ cells able to be collected. The study also compared two doses of plerixafor (160 and 240 mcg / kg) with the higher dose demonstrating superior efficacy.

- **Study 2106** was an open uncontrolled study in patients with Hodgkin's disease. A total of 68% of subjects were able to mobilise ≥ 5 x 10^6 CD34+ cells / kg. This result is comparable to that seen in the pivotal study 3101 (59.3%) in patients with NHL.

Safety

In the submitted studies, a total of 1161 patients received plerixafor. Plerixafor is indicated for short-term use – in the pivotal studies, the median number of doses received was 2 (range 1-4).

In the pivotal studies, adverse events were analysed according to a set of time periods. Adverse events with an increased incidence in the plerixafor group in "Period 1" were:

- Diarrhoea 37.6% versus 16.6%
- Nausea 34.2% versus 21.7%
- Vomiting 9.7% versus 6.1%
- Flatulence 6.7% versus 3.7%
- Fatigue 26.8% versus 25.1%
- Arthralgia 13.1% versus 12.2%
- Headache 22.5% versus 21.0%
- Abdominal pain 4.4% versus 2.4%
- Injection site erythema 26.2% versus 4.7%
- Injection site pruritus 5.7% versus 0.7%
- Dizziness 10.4% versus 6.1%
- Insomnia 7.0% versus 5.1%

The incidence of bone pain was not increased.

There was no excess in the plerixafor group of discontinuations due to adverse events or deaths. There was an increased incidence of adverse events and serious adverse events (SAEs) in 'Period 4' and 'Period 5' (that is, in the group of patients who underwent tandem transplants). However none of these were considered related to study drug. There was no increase in SAEs in the active treatment period (Period 1).

Risk-Benefit Analysis

1. Overall risk benefit

   The pivotal studies have provided adequate evidence of efficacy with a substantial increase in the proportion of patients able to achieve a mobilisation target cell count with a reduced number of apheresis sessions required. There were no adverse effects on graft viability or time to engraftment.

   The safety profile of the drug appears acceptable, with a modest increase in the incidence of adverse events compared with placebo. Overall the Delegate considered the drug has an acceptable risk-benefit ratio and proposed to approve the application.

2. Indication

   The indication proposed by the sponsor is as follows:

   "..to enhance mobilisation of haematopoietic stem cells (HSC's) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma."

The clinical evaluator had recommended that the indication should specify that the drug is to be used in combination with G-CSF. The Delegate agreed with the clinical evaluator, as the pivotal studies did not examine the efficacy of plerixafor monotherapy.

The clinical evaluator has also recommended that in the indication the term *"lymphoma"* should be restricted to *"Non-Hodgkin's lymphoma"*, again reflecting the population enrolled in the pivotal studies. However, the submission did include one small phase II study in patients with Hodgkin's disease. If registration is recommended, the Committee's advice is sought as to whether approval for Hodgkin's disease is appropriate.

ACPM, having considered the evaluations, the advice of the Pharmaceutical subcommittee (of ACPM), the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission from Genzyme Australasia Pty Ltd to register a new chemical entity plerixafor (Mozobil) solution for injection 20 mg / mL for the indication:

> Mozobil is indicated in combination with granulocyte colony stimulating factor (GCSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

In making this recommendation the ACPM noted the low frequency and the modest increase over placebo in adverse events and the equal frequency of deaths compared with placebo. The ACPM agreed with the Delegate that the evidence supports the indication to include the requirement of combination therapy with G-CSF. As tumour cell mobilisation remains possible, the ACPM advised that long term follow-up of patients in the placebo-controlled studies is appropriate. The ACPM advised that although the submission included only one small phase II study in patients with Hodgkin's Disease, the evidence of the safety and efficacy of the product was sufficient to also include this indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Mozobil, as plerixafor 20 mg/mL, indicated:

> "*In combination with granulocyte-colony stimulation factor (G-CSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.*"

Attachment 1. Product Information

MOZOBIL®

(plerixafor) Injection, Solution for Subcutaneous use

PRODUCT INFORMATION

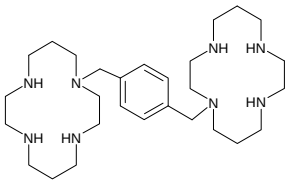
NAME OF THE MEDICINE

MOZOBIL® (plerixafor) 20 mg/mL Injection, Solution for Subcutaneous use

DESCRIPTION

Plerixafor is an antagonist of the CXCR4 chemokine receptor. Its chemical name is l, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane. The molecular weight of plerixafor is 502.79 g/mol. The structural formula is provided in Figure 1.

Figure 1: Structural Formula



Plerixafor is a white to off-white crystalline solid. MOZOBIL is supplied as a clear, colourless to pale yellow, sterile, preservative-free, isotonic solution in a 2.0 mL clear glass (Type I) vial, sealed with a rubber stopper and aluminium seal with a plastic flip-off cap. Each single-use vial contains 24 mg plerixafor and 5.9 mg 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.

PHARMACOLOGY

Mechanism of Action

Plerixafor is a reversible antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1 α), also known as CXCL12. SDF-1α and CXCR4 are involved in the trafficking and homing of human haematopoetic stem cells (HSCs) to the marrow compartment. Stem cells express CXCR4 and migrate to the bone marrow through a chemoattractant effect of SDF-1α that is produced locally by bone marrow stromal cells. Once in the marrow, it is postulated that stem cell CXCR4 can act to help "anchor" these cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules. Plerixafor-induced leukocytosis and elevations in circulating haematopoietic progenitor cell levels are thought to result from a disruption of CXCR4 binding to its cognate ligand, resulting in the appearance of both mature and pluripotent cells in the systemic circulation.

CD34+ cells mobilised by plerixafor were capable of engraftment with long-term repopulating capacity in dog and monkey transplantation models.

Pharmacodynamics
Data on the fold increase in peripheral blood CD34+ cell count (cells/mcL) by apheresis day were collected in two placebo-controlled clinical studies in patients with non-Hodgkin's lymphoma and multiple myeloma (MM) (AMD3100-3101 and AMD3100-3102, respectively). The fold increase in CD34+ cell count (cells/mcL) over the 24-hour period starting from the day prior to the first apheresis and ending the next morning ~~to~~ just before the first apheresis is summarised in Table 1. During that 24-hour period, the first dose of MOZOBIL 0.24 mg/kg or placebo was administered 10-11 hours prior to apheresis.

Table 1: Fold Increase in Peripheral Blood CD34+ Cell Count Following MOZOBIL Administration

Study	MOZOBIL and G-CSF		Placebo and G-CSF	
	Median	Mean (SD)	Median	Mean (SD)
AMD3100-3101	5.0	6.2 (5.4)	1.4	1.9 (1.5)
AMD3100-3102	4.8	6.4 (6.8)	1.7	2.4 (7.3)

In pharmacodynamic studies of MOZOBIL in healthy volunteers, peak mobilisation of CD34+ cells was observed between 6 and 9 hours after administration. In pharmacodynamic studies of MOZOBIL in conjunction with granulocyte-colony stimulating factor (G-CSF) in healthy volunteers, a sustained elevation in the peripheral blood CD34+ count was observed from 4 to 18 hours after MOZOBIL administration with peak response between 10 and 14 hours.

Pharmacokinetics
The pharmacokinetics of plerixafor have been evaluated in patients with lymphoma and MM at the clinical dose level of 0.24 mg/kg following pre-treatment with G-CSF (10 mcg/kg once daily for 4 consecutive days).

Absorption
Plerixafor is rapidly absorbed following subcutaneous (SC) injection with peak concentrations reached in approximately 30-60 minutes. Following subcutaneous administration of plerixafor the absolute bioavailability is at least 70%.

Distribution
Plerixafor is moderately bound to human plasma proteins (37-58%). 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.

Metabolism
Plerixafor was not metabolised *in vitro* using human liver microsomes or human primary hepatocytes and did not exhibit inhibitory activity *in vitro* towards the major drug metabolising CYP450 enzymes (1A2, 2C9, 2C19, 2D6, and 3A4/5). In *in vitro* studies with human hepatocytes, plerixafor does not induce CYP1A2, CYP2B6, or CYP3A4 enzymes. These findings indicate that plerixafor has a low potential for involvement in P450-dependent drug-drug interactions.

Elimination
The major route of elimination of plerixafor is urinary. Following a 0.24 mg/kg dose in healthy volunteers with normal renal function, approximately 70% of the dose was excreted in the urine as the parent drug during the first 24 hours following administration. The half-life in plasma is 3-5 hours.

Renal Impairment
Following a single 0.24 mg/kg dose of MOZOBIL, plerixafor clearance was reduced in subjects with varying degrees of renal dysfunction and was positively correlated with creatinine clearance (CrCl). The mean AUC_{0-24} of plerixafor in subjects with mild (CrCl 51-80 mL/min), moderate (CrCl 31-50 mL/min), and severe (CrCl < 31 mL/min) renal impairment was 7%, 32%, and 39% higher than healthy subjects with normal renal function, respectively. Renal impairment had no effect on C_{max}. (See DOSAGE AND ADMINISTRATION)]

CLINICAL TRIALS

The efficacy and safety of MOZOBIL in conjunction with G-CSF in lymphoma and MM were evaluated in two placebo-controlled Phase 3 studies (Studies AMD3100-3101 and AMD3100-3102). Patients were randomised to receive either MOZOBIL 0.24 mg/kg or placebo on each evening prior to apheresis. Patients received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of MOZOBIL or placebo and on each morning prior to apheresis. The primary endpoint was collection of a target number of CD34+ cells/kg within a given number of apheresis days. Two hundred and ninety-eight (298) NHL patients were included in the primary efficacy analyses for AMD3100-3101. The mean age was 55.1 years (29-75) and 57.5 years (22-75) in the MOZOBIL and placebo groups, respectively, and 93% of subjects were Caucasian. Three hundred and two (302) MM patients were included in the primary efficacy analyses for AMD3100-3102. The mean age was 58.2 years (28-75) and 58.5 years (28-75) in the MOZOBIL and placebo groups, respectively, and 81% of subjects were Caucasian.

In study AMD3100-3101, 59.3% of non-Hodgkin's lymphoma patients who were mobilised with MOZOBIL and G-CSF achieved the primary endpoint of collection of $\geq 5 \times 10^6$ CD34+cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 19.6% of patients who were mobilised with placebo and G-CSF ($p < 0.001$). Secondary CD34+ cell mobilisation outcomes were consistent with the primary endpoint (Table 2).

Table 2: Study AMD3100-3101 Efficacy Results - CD34+ Cell Mobilisation in Non-Hodgkin's Lymphoma Patients

Efficacy Endpoint	MOZOBIL and G-CSF (n = 150)	Placebo and G-CSF (n = 148)	p-value[a]
Patients achieving ≥ 5 X 10^6 cells/kg in ≤ 4 apheresis days	89 (59.3%)	29 (19.6%)	< 0.001
Patients achieving ≥ 2 X 10^6 cells/kg in ≤ 4 apheresis days	130 (86.7%)	70 (47.3%)	< 0.001

[a]p-value calculated using Pearson's Chi-Squared test

The median number of days to reach the primary endpoint of $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for the MOZOBIL group and not evaluable for the placebo group. Table 3 presents the proportion of patients who achieved $\geq 5 \times 10^6$ CD34+ cells/kg by apheresis day.

Table 3: Study AMD3100-3101 Efficacy Results – Proportion of

Patients Who Achieved ≥ 5 x 10^6 CD34+ cells/kg by Apheresis Day in NHL Patients

Days	Proportion[a] in MOZOBIL and G-CSF (n=147[b])	Proportion[a] in Placebo and G-CSF (n=142[b])
1	27.9%	4.2%
2	49.1%	14.2%
3	57.7%	21.6%
4	65.6%	24.2%

[a]Percents determined by Kaplan Meier method
[b] n includes all patients who received at least one day of apheresis

In AMD3100-3102, 71.6% of MM patients who were mobilised with MOZOBIL and G-CSF achieved the primary endpoint of collection of ≥ 6 X 10^6 CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34.4% of patients who were mobilised with placebo and G-CSF ($p < 0.001$). Secondary CD34+ cell mobilisation outcomes were consistent with the primary endpoint (Table 4).

Table 4: Study AMD3100-3102 Efficacy Results – CD34+ Cell Mobilisation in Multiple Myeloma Patients

Efficacy Endpoint	MOZOBIL and G-CSF (n = 148)	Placebo and G-CSF (n = 154)	p-value[a]
Patients achieving ≥ 6 X 10^6 cells/kg in ≤ 2 apheresis days	106 (71.6%)	53 (34.4%)	< 0.001
Patients achieving ≥ 6 X 10^6 cells/kg in ≤ 4 apheresis days	112 (75.7%)	79 (51.3%)	< 0.001
Patients achieving ≥ 2 X 10^6 cells/kg in ≤ 4 apheresis days	141 (95.3%)	136 (88.3%)	0.031

[a]p-value calculated using Cochran-Mantel-Haenszel statistic blocked by baseline platelet count

The median number of days to reach the primary endpoint of ≥ 6 x 10^6 CD34+ cells/kg was 1 day for the MOZOBIL group and 4 days for the placebo group. Table 5 presents the proportion of patients who achieved ≥ 6 x 10^6 CD34+ cells/kg by apheresis day.

Table 5: Study AMD3100-3102 – Proportion of Patients Who Achieved ≥ 6 x 10^6 CD34+ cells/kg by Apheresis Day in MM Patients

Days	Proportion[a] in MOZOBIL and G-CSF (n=144[b])	Proportion[a] in Placebo and G-CSF (n=150[b])
1	54.2%	17.3%
2	77.9%	35.3%
3	86.8%	48.9%
4	86.8%	55.9%

[a]Percents determined by Kaplan Meier method
[b] n includes all patients who received at least one day of apheresis

For transplanted patients in the Phase 3 studies, time to neutrophil and platelet engraftment and graft durability up to 12 months post-transplantation were similar across the treatment groups. The median time to neutrophil engraftment was 10 days in AMD3100-3101 and 11 days in AMD3100-3102 ($p = 0.330$ and 0.690, respectively) and to platelet engraftment was 20 days in AMD3100-3101 and 18 days in AMD3100-3102 ($p = 0.630$ and 0.180, respectively). No difference in graft durability was observed across treatment groups in AMD3100-3101 or AMD3100-3102.

The efficacy and safety of MOZOBIL in conjunction with G-CSF in lymphoma and MM were also evaluated in two supportive Phase 2 studies (Studies AMD3100-2101 and AMD3100-2106). In these studies, patients with NHL, Hodgkin's disease, or MM received MOZOBIL 0.24 mg/kg on the evening or morning prior to apheresis. Patients received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of MOZOBIL and on each morning prior to apheresis. Mobilisation and engraftment data for these studies were similar to those data for the Phase 3 studies.

Paediatric Use
The safety and efficacy of MOZOBIL in paediatric patients have not been established in controlled clinical studies.

Geriatric Use
In the two placebo-controlled clinical studies of MOZOBIL, 24% of patients were ≥ 65 years old. No notable differences in the incidence of adverse reactions were observed in elderly and younger patients.

Carcinogenicity
Carcinogenicity studies with plerixafor have not been conducted.

Genotoxicity
Plerixafor was not genotoxic in an *in vitro* bacterial mutation assay (Ames test in *Salmonella*), an *in vitro* chromosomal aberration test using Chinese hamster ovary cells, and an *in vivo* rat bone marrow micronucleus test.

INDICATIONS

MOZOBIL is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM).

CONTRAINDICATIONS

General
Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

Potential for tumour cell mobilisation in patients with lymphoma and multiple myeloma
When MOZOBIL is used in conjunction with G-CSF for haematopoietic stem cell mobilisation in patients with lymphoma or multiple myeloma, tumour cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of potential re-infusion of tumour cells has not been well-studied. In clinical studies of patients with non-Hodgkin's lymphoma and multiple myeloma, mobilisation of tumour cells has not been observed with MOZOBIL.

Tumour cell mobilisation in leukaemia patients
In a compassionate use programme, MOZOBIL and G-CSF have been administered to patients with acute myelogenous leukaemia and plasma cell leukaemia. In some instances, these patients

experienced an increase in the number of circulating leukaemia cells. For the purpose of haematopoietic stem cell mobilisation, MOZOBIL may cause mobilisation of leukaemic cells and subsequent contamination of the apheresis product. Therefore, MOZOBIL is not recommended for haematopoietic stem cell mobilisation and harvest in patients with leukaemia.

Haematological effects

Leukocytosis

Administration of MOZOBIL in conjunction with G-CSF increases circulating leukocytes as well as haematopoietic stem cell populations. White blood cell counts should be monitored during MOZOBIL therapy. Clinical judgment should be exercised when administering MOZOBIL to patients with peripheral blood neutrophil counts above 50 X 10^9 cells/L.

Thrombocytopenia

Thrombocytopenia is a known complication of apheresis and has been observed in patients receiving MOZOBIL. Platelet counts should be monitored in all patients receiving MOZOBIL and undergoing apheresis.

Systemic reactions

Mild to moderate systemic reactions were observed in less than 1% of patients approximately 30 min after MOZOBIL administration. Events included one or more of the following: urticaria (n = 2), periorbital swelling (n =2), dyspnoea (n =1) or hypoxia (n =1). Symptoms generally responded to treatments (e.g., antihistamines, corticosteroids, hydration or supplemental oxygen) or resolved spontaneously. Patients should be monitored for these adverse reactions following MOZOBIL injection.

Vasovagal reactions

In MOZOBIL oncology and healthy volunteer clinical studies, less than 1% of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following subcutaneous administration of plerixafor doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of MOZOBIL administration.

Potential effect on spleen size

In nonclinical studies, higher absolute and relative spleen weights were observed following prolonged (2 to 4 weeks) daily plerixafor subcutaneous administration in rats at doses approximately 5 fold higher than the recommended human dose (based on AUC values).

The effect of MOZOBIL on spleen size in patients has not been specifically evaluated in clinical studies. The possibility that MOZOBIL in conjunction with G-CSF can cause splenic enlargement cannot be excluded. Due to the very rare occurrence of splenic rupture following G-CSF administration, individuals receiving MOZOBIL in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

Renal Impairment

MOZOBIL should be used with caution in patients with moderate and severe renal dysfunction.

Effects on Ability to Drive and Use Machines

No studies on the effects of MOZOBIL on the ability to drive and use machines have been performed. MOZOBIL may influence the ability to drive and use machines. Some patients have experienced dizziness, fatigue or vasovagal reactions; therefore caution is advised when driving or operating machinery.

Laboratory monitoring
White blood cell and platelet counts should be monitored during MOZOBIL use and apheresis.

Effects on Fertility
The potential effects of plerixafor on male and female fertility ~~and post-natal development~~ have not been evaluated in non-clinical studies. In studies conducted to measure the distribution of ^{14}C-plerixafor, there was no evidence of accumulation in testes. The staging of spermatogenesis measured in a 28-day repeat-dose toxicity study in rats revealed no abnormalities considered to be related to plerixafor at doses 36-fold higher than the recommended human dose, based on AUC values. No histopathological evidence of toxicity to male or female reproductive organs was observed in repeated dose toxicity studies.

Use in Pregnancy – Pregnancy Category D

Pregnancy Category D
SDF-1α and CXCR4 play major roles in embryo-foetal development. Animal models indicated modulation of foetal haematopoiesis, vascularisation, and cerebellar development by SDF-1α and CXCR4. Plerixafor was teratogenic in animals; it caused increased resorptions, decreased foetal weights, retarded skeletal development, and increased foetal abnormalities in rats and/or rabbits. The no-observed effect levels (NOEL) of plerixafor in rats was less than clinical exposure at the recommended human dose of 0.24 mg/kg/day based on AUC values. There are no adequate and well-controlled clinical studies in pregnant women. MOZOBIL should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Use in Lactation
The potential effects of plerixafor on post-natal development have not been evaluated in non-clinical studies. It is not known whether plerixafor is excreted in human milk. Because many drugs are excreted in human milk, and exposure of breastfed infants to plerixafor may cause serious adverse reactions, plerixafor should not be administered to a breast-feeding woman.

Paediatric Use
The safety and efficacy of MOZOBIL in paediatric patients have not been established in controlled clinical studies.

Geriatric Use
In the two placebo-controlled clinical studies of MOZOBIL, 24% of patients were ≥ 65 years old. No notable differences in the incidence of adverse reactions were observed in elderly and younger patients.

Carcinogenicity
Carcinogenicity studies with plerixafor have not been conducted.

Genotoxicity
Plerixafor was not genotoxic in an *in vitro* bacterial mutation assay (Ames test in *Salmonella*), an *in vitro* chromosomal aberration test using Chinese hamster ovary cells, and an *in vivo* rat bone marrow micronucleus test.

Interactions with Other Drugs
No interaction studies have been performed.

Drug interactions have not been observed in clinical trials with MOZOBIL. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an *in vitro* study. It is therefore unlikely that there would be pharmacokinetic interactions between plerixafor and drugs that are inhibitors or substrates of p-glycoprotein.

In clinical studies of patients with Non-Hodgkin's lymphoma, the addition of rituximab to a mobilisation regimen of MOZOBIL and G-CSF did not impact patient safety or CD34+ cell yield.

Drug/Food Interactions
MOZOBIL is administered parenterally, and interactions with food and drink are considered unlikely.

Drug/Laboratory Test Incompatibilities
MOZOBIL has not been shown to interfere with any routine clinical laboratory tests.

ADVERSE EFFECTS

Clinical Trial Experience
Safety data for MOZOBIL in conjunction with G-CSF in oncology patients were obtained from two placebo-controlled Phase 3 studies and 10 uncontrolled Phase 2 studies in 543 patients. Patients were primarily treated with daily doses of 0.24 mg/kg plerixafor by SC injection. The exposure to MOZOBIL in these studies ranged from 1 to 7 consecutive days (median = 2 days).

In the two Phase 3 studies in patients with NHL and MM (AMD3100-3101 and AMD3100-3102, respectively), a total of 301 patients received daily doses of MOZOBIL 0.24 mg/kg SC and 292 patients received placebo. All patients received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of MOZOBIL or placebo and on each morning prior to apheresis.
The adverse reactions that occurred in ≥ 5% of the patients who received MOZOBIL regardless of causality and were more frequent with MOZOBIL than placebo during HSC mobilisation and apheresis are shown in Table 6.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 6: Adverse Reactions in ≥ 5% of Non-Hodgkin's Lymphoma and Multiple Myeloma Patients Receiving MOZOBIL and More Frequent than Placebo During HSC Mobilisation and Apheresis

	Percent of Patients (%)					
	MOZOBIL and G-CSF (n = 301)			Placebo and G-CSF (n = 292)		
	All Grades[a]	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhoea	37	< 1	0	17	0	0
Nausea	34	1	0	22	0	0
Vomiting	10	< 1	0	6	0	0
Flatulence	7	0	0	3	0	0
General disorders and administration site conditions						
Injection site reactions	34	0	0	10	0	0
Fatigue	27	0	0	25	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13	0	0	12	0	0
Nervous system disorders						
Headache	22	< 1	0	21	1	0
Dizziness	11	0	0	6	0	0
Psychiatric disorders						
Insomnia	7	0	0	5	0	0

[a]Grades based on criteria from the World Health Organisation (WHO)

Other adverse reactions that occurred in < 5% of patients but were reported as related to MOZOBIL during HSC mobilisation and apheresis included abdominal pain, injection site irritation, hyperhidrosis, injection site reaction, abdominal distention, dry mouth, erythema, stomach discomfort, malaise, hypoaesthesia oral, constipation, dyspepsia and injection site rash.

The adverse reactions reported in oncology-patients who received MOZOBIL in the controlled Phase 3 studies and uncontrolled studies, including a Phase 2 study of MOZOBIL as monotherapy for HSC mobilisation, are similar. No notable differences in the incidence of adverse reactions were observed for oncology patients by disease, age or sex.

Myocardial Infarction

In clinical studies, seven of 679 oncology patients experienced myocardial infarctions after HSC mobilisation with MOZOBIL and G-CSF. All events occurred at least 14 days after last MOZOBIL administration. Additionally, two female oncology patients in the compassionate use program experienced myocardial infarctions following HSC mobilisation with MOZOBIL and G-CSF. One of these events occurred 4 days after last MOZOBIL administration. Lack of temporal relationship in 8 of 9 patients coupled with risk profile of patients with myocardial infarction does not suggest MOZOBIL confers an independent risk for myocardial infarction in patients who also receive G-CSF

Systemic Reactions

MOZOBIL has been associated with potential systemic reactions related to SC injection. (See PRECAUTIONS)

Gastrointestinal Disorders
In MOZOBIL clinical studies of oncology patients, there have been rare reports of severe gastrointestinal events, including diarrhoea, nausea, vomiting and abdominal pain.

Paresthesias
Paresthesias are commonly observed in oncology patients undergoing autologous transplantation following multiple disease interventions. In the placebo-controlled Phase 3 studies, the incidence of paraesthesias was 20.6% and 21.2% in the MOZOBIL and placebo groups, respectively.

DOSAGE AND ADMINISTRATION

MOZOBIL therapy should be initiated and supervised by a physician experienced in oncology and/or haematology. MOZOBIL therapy should be administered by a nurse, physician, or other health care professional.

Begin treatment with MOZOBIL after the patient has received G-CSF once daily for 4 days. The recommended dose of MOZOBIL is 0.24 mg/kg body weight by subcutaneous injection. MOZOBIL should be administered 6 to 11 hours prior to initiation of apheresis. In clinical trials, subcutaneous administration to the abdomen was recommended; however, some patients received SC injections in the extremities. G-CSF should be continued each morning prior to apheresis.

MOZOBIL has been commonly used for 2 to 4 consecutive days. It has been used for up to 7 consecutive days in a clinical setting.

The patient's actual body weight will be used to calculate the volume of MOZOBIL to be administered. Each vial delivers 1.2 mL of 20 mg/mL solution, and the volume to be administered to patients will be calculated from the following equation:

0.012 X patient's actual body weight (in kg) = dose to be administered (in mL)

In clinical studies, MOZOBIL dose has been calculated based on actual body weight in patients up to 175% of ideal body weight. MOZOBIL dose and treatment of patients weighing more than 175% of ideal body weight have not been investigated.

The weight used to calculate the volume of MOZOBIL should be obtained within 1 week of the first dose of MOZOBIL

Recommended Concomitant Medications
In pivotal clinical studies supporting the use of MOZOBIL, all patients received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of MOZOBIL and on each morning prior to apheresis. (See CLINICAL TRIALS)

Dose Modification Guidelines
Patients with moderate and severe renal insufficiency (CrCl 20 - 50 mL/min based on Cockroft-Gault formula) should have their dose of MOZOBIL reduced by one-third to 0.16 mg/kg. Similar systemic exposure is expected if the dose is reduced by one-third in patients with moderate and severe renal impairment compared with subjects with normal renal function. Clinical data with this dose adjustment in patients with renal impairment are limited.

There is insufficient information to make dosage recommendations in patients on haemodialysis or those with creatinine clearance < 20 mL/min.

OVERDOSAGE

In clinical trials of MOZOBIL in oncology patients, patients received up to 0.32 mg/kg SC for HSC mobilisation. Some patients have received MOZOBIL at a dose of ≥ 0.48 mg/kg SC for HSC mobilisation. Adverse events reported in these patients were similar to those reported in patients who received the recommended dose of 0.24 mg/kg SC.

Contact the Australian Poisons Information Centre (telephone 13 11 26) or the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

MOZOBIL is supplied as a sterile, preservative-free, clear, colourless to pale yellow, pH neutral, isotonic solution in a single-use 2.0 mL clear glass (Type I) vial, sealed with a rubber stopper and aluminium seal with a plastic flip-off cap. Each vial contains 24 mg plerixafor in 1.2 mL solution.

Store MOZOBIL at 25^{o}C (77^{o}F); excursions permitted to 15^{o}-30^{o}C (59^{o}-86^{o}F).

DO NOT USE MOZOBIL after the expiration date indicated on the vial. Each vial of MOZOBIL is intended for single use only. Any unused drug remaining after injection must be discarded.

MOZOBIL is supplied as a ready-to-use formulation. The contents of the vial must be transferred to a suitable syringe for SC administration. Vials should be inspected visually for particulate matter and discolouration prior to administration and should not be used if there is particulate matter or if the solution is discoloured.

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POISON SCHEDULE OF THE MEDICINE

S4, Prescription Only Medicine

DATE OF APPROVAL

TGA approval date: 18 May 2010

MOZOBIL® is a registered trademark of Genzyme Corporation, USA.
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