28 March 2019
EMA/243012/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mozobil

International non-proprietary name: plerixafor

Procedure No. EMEA/H/C/001030/II/0034

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	03 Mar 2018	03 Mar 2018	☐
☐	CHMP Rapporteur Assessment Report	27 Apr 2018	26 Apr 2018	☐
☐	CHMP Co-Rapporteur Assessment Report	27 Apr 2018	n/a	☐
☐	PRAC Rapporteur Assessment Report	03 May 2018	26 Apr 2018	☐
☐	PRAC members comments		n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	08 May 2018	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	17 May 2018	17 May 2018	☐
☐	CHMP members comments	22 May 2018	22 May 2018	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 May 2018	24 May 2018	☐
☐	Request for supplementary information	31 May 2018	31 May 2018	☐
☐	Submission of responses	12 Oct 2018	12 Oct 2018	☐
☐	Re-start	15 Oct 2018	15 Oct 2018	☐
☐	CHMP Rapporteur Assessment Report	13 Nov 2018	15 Nov 2018	☐
☐	PRAC Rapporteur Assessment Report	16 Nov 2018	15 Nov 2018	☐
☐	PRAC members comments	21 Nov 2018		☐
☐	Updated PRAC Rapporteur Assessment Report	22 Nov 2018	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	29 Nov 2018	29 Nov 2018	☐
☐	CHMP members comments	3 Dec 2018	3 Dec 2018	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 Dec 2018	5 Dec 2018	☐
☐	2nd Request for supplementary information	13 Dec 2018	13 Dec 2018	☐
☐	Submission of responses	18 Jan 2019	18 Jan 2019	
☐	Re-start	30 Jan 2019	30 Jan 2019	
☐	PRAC Rapporteur Assessment Report	04 Feb 2019	05 Feb 2019	
☐	PRAC members comments	06 Feb 2019	06 Feb 2019	
☐	Updated PRAC Rapporteur Assessment Report	07 Feb 2019	08 Feb 2019	
☐	CHMP Rapporteur Assessment Report	13 Feb 2019	15 Feb 2019	
☐	PRAC endorsed relevant sections of the assessment report [3]	14 Feb 2019	14 Feb 2019	

Status of this report and steps taken for the assessment				
☐	CHMP members comments	18 Feb 2019	20 Feb 2019	
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Feb 2019	22 Feb 2019	
☐	3rd Request for supplementary information	28 Feb 2019	28 Feb 2019	
☐	Submission of responses	05 Mar 2019	05 Mar 2019	
☐	Re-start	06 Mar 2019	06 Mar 2019	
☐	CHMP Rapporteur Assessment Report	13 Mar 2019	13 Mar 2019	
☐	PRAC Rapporteur Assessment Report	13 Mar 2019	13 Mar 2019	
☐	CHMP members comments	18 Mar 2019	n/a	
☐	PRAC members comments	18 Mar 2019	n/a	
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Mar 2019	21 Mar 2019	
☐	Opinion	28 Mar 2019	28 Mar 2019	

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
CHMP Rapporteur:	Paula van Hennik
PRAC Rapporteur:	Sabine Straus

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List of abbreviations

AE:	adverse event
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
CSR:	clinical study report
CXCR4:	chemokine (C-X-C motif) receptor 4
DLT:	dose-limiting toxicity
FACS:	fluorescence-activated cell sorting
FAS:	full analysis set
GCP:	Good Clinical Practice
G-CSF:	granulocyte-colony stimulating factor
HDC:	high-dose chemotherapy
HSCs:	hematopoietic stem cells
HSCT:	hematopoietic stem cell transplantation
ICF:	informed consent form
ICH:	International Council for Harmonization
ITT:	intent-to-treat
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
NCI:	National Cancer Institute
NHL:	non-Hodgkins lymphoma
PB:	peripheral blood
PBSC:	peripheral blood stem cell
PD:	pharmacodynamic
PDCO:	paediatric committee
PIP:	Paediatric Investigational Plan, Paediatric Investiagational Plan
PK:	pharmacokinetic
SAE:	serious adverse event
SC:	subcutaneous
SDF-1:	stromal cell-derived factor-1
TEAE:	treatment-emergent adverse event

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Genzyme Europe BV submitted to the European Medicines Agency on 8 November 2017 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include paediatric patients aged 1 to 18 years for Mozobil; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP (version 10) was also submitted accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Mozobil was designated as an orphan medicinal product EU/3/04/227 on 18/08/2008. Mozobil was designated as an orphan medicinal product in the following indication: Treatment to mobilize progenitor cells prior to stem cell transplantation.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0253/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0253/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0253/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

2. Scientific discussion

2.1. Introduction

About the product

Plerixafor (Mozobil) is a small-molecule bicyclam derivative that reversibly antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α, also known as CXCL12). This interruption of the CXCR4/SDF-1α interaction results in mobilization of HSCs positive for cell surface glycoprotein CD34 (CD34+ cells) to the peripheral blood where they can be collected for HSC transplantation.

Currently, Mozobil is approved for the following indication:

Mozobil is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly (see section 4.2).

This indication was based on the evaluation of two phase 3 placebo-controlled efficacy and safety studies with plerixafor in conjunction with G–CSF in patients with non Hodgkin lymphoma (AMD3100-3101) and in patients with multiple myeloma (AMD3100- 3102). This was supported by two phase 2 efficacy and safety studies with plerixafor in conjunction with G-CSF in patients with non Hodgkin lymphoma (NHL) and multiple myeloma (MM) and 8 clinical pharmacology studies and 10 supportive studies (see EPAR Mozobil).

About the condition

Patients receiving high-dose chemotherapy (HDC) to treat malignant disorders suffer from severe and potentially fatal myeloablation. Autologous hematopoietic stem cell transplantation (HSCT) using mobilized peripheral blood hematopoietic stem cells (HSCs) collected by apheresis is a common strategy for repopulation of the bone marrow and regeneration of trilineage blood cells (red blood cells, platelets, neutrophils). To yield a sufficient number of stem cells for apheresis, HSCs are increased in the peripheral blood by treating patients with G-CSF or with non-myeloablative chemotherapy, often in combination with G-CSF. However, a significant proportion of patients may not be able to mobilize a sufficient or target number of cells for transplantation(s) with these HSC mobilization regimens.In children, single or tandem myeloablative chemotherapy with autologous stem cell support is used during the treatment of refractory lymphoma and solid tumours, such as, but not limited to medulloblastoma, neuroblastoma, Ewing's sarcoma, and germ cell tumours. Paediatric patients with these relatively chemotherapy-resistant tumours, receive high-dose chemotherapy (HDC), causing severe and potentially fatal myeloablation that requires stem cell rescue to repopulate the bone marrow and regenerate trilineage blood cells. In order to obtain stem cells from peripheral blood, the cells have to be "mobilised" from the bone marrow into the peripheral blood.

By using conventional mobilization protocols, about 20% of patients fail to collect enough cells to proceed to the autologous transplant. In order to proceed to the transplant, these patients are offered a second round of stem cell mobilization and stem cell collection using intensive chemotherapy, which requires a further inpatient admission, additional chemotherapy, and G-CSF. These additional mobilization attempts are only effective in a limited number of patients. When additional mobilization fails, patients may either be ineligible for a transplant procedure which may negatively impact their survival, or alternatively they may have to undergo allogeneic transplantation which is a more complex procedure with higher morbidity and cost. There is a need for new treatment options by which more paediatric patients needing HDC

therapy, could proceed to autologous stem cell transplantation.

This is a type II variation in order to extent the indication to *paediatric patients* (1 to less than 18 years)

The indication initially applied was:

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 children with lymphoma or solid malignant tumours and either:

- *low circulating stem cell count on the predicted day of collection after mobilisation with G-CSF (with or without chemotherapy) or*
- *who previously failed to collect sufficient haematopoietic stem cells*

The indication approved by the CHMP following this assessment was:

Mozobil in paediatric patients (1 to less than 18 years) in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells *(see section 4.2).*

To support this extension of the indication Applicant has submitted the studies as agreed in PIP (EMEA-000174-PIP-01-07-M03):

- a non-clinical juvenile animal development study completed on time (March 2010);
- a clinical study DFI12860 (also referred to as MOZ15609): Combined dose ranging and randomized, open label, comparative study of the efficacy and safety of plerixafor in addition to standard regimens for mobilization of haematopoietic stem cells into peripheral blood, and subsequent collection by apheresis, versus standard mobilization regimens alone in paediatric patients, aged 1 to less than 18 years, with solid tumours eligible for autologous transplants.

The plerixafor pharmaceutical formulation used in the paediatric study DFI12860 (MOZ15609) was the solution for injection and corresponding to the authorized pharmaceutical form.

These studies were supplemented with a review of the available literature (containing results from investigator sponsored studies, data from compassionate use programs and series of individual case reports in paediatric patients). Furthermore, support for the use of Mozobil in children may be provided by extrapolation of adult data where Mozobil is used in the HSC mobilisation regimen of subjects whose CD34+ cells mobilise poorly to standard mobilisation regimens (so-called poor mobilisers).

2.2. Quality

2.2.1. Introduction

No updates to the quality aspects of the dossier were submitted.

The below discussion is focused on the suitability (age-appropriateness) of the dosage form for the intended paediatric population.

2.2.2. Discussion on quality aspects

Mozobil is a sterile, preservative-free, clear, colourless to pale yellow, isotonic 1.2 ml solution for subcutaneous injection containing the drug substance plerixafor in a concentration of 20 mg/ml. The product is packaged in a glass vial. Each vial contains 24 mg plerixafor. pH is 6.0 – 7.5 and osmolality is 260 – 320 mOsm/kg.

A solution for injection as such can be considered a suitable dosage form for use in children.

The product contains sodium chloride, water for injections, hydrochloric acid and sodium hydroxide as excipients. No safety issues are foreseen with these excipients for use in children.

No dosing device is supplied with the drug product. Plerixafor has to be drawn up into a syringe size type which should be selected according to the weight of the patient. For low weight patients, up to 45 kg of body weight, 1 ml syringes for use in infant patients can be used. This type of syringe has major graduations for 0.1 ml and minor graduations for 0.01 ml and therefore is suitable to administer plerixafor - at a dose of 240 µg/kg - to paediatric patients of at least 9 kg body weight. For patients of more than 45 kg, 1 mL or 2 mL syringe with graduations that allow a volume to 0.1mL to be accurately measured can be used. However - based on the recommended dose for children, a single dose for e.g. a 1 year old child (of about 9.5 kg bodyweight) would be 2.28 mg; the minimum single dose volume would then be 0.114 ml.

The MAH did not perform dosing accuracy studies using the intended 1 ml syringes and the Mozobil drug product which are normally required. Instead reference is made to the criteria of ISO 7886-1 Sterile hypodermic syringes for single use which specifies general quality requirements for these type of syringes, amongst others accuracy. However, considering the composition of the drug product (active substance, sodium chloride, water for injection and excipients for pH adjustment), it is assumed that the syringe accuracy performance will not be impacted by the drug product properties and therefore the allowed range of deviation from the intended (rounded) dose volume, conform the criteria of ISO 7886-1, may be used to assess the worst case scenarios of deviation from the intended dose volume leading to potential under- and overdosing. It can be seen that the deviation from the intended (rounded) dose volume decreases with increasing dose volume. It is generally known that accuracy is lower for measuring smaller dose volumes. However, rounding of volumes normally occurs in the clinical setting for drug product doses calculated based on body weight and the fact that it concerns a drug product with no narrow therapeutic index, the maximum calculated deviations from the intended dose can be accepted. (*see also the 'Q&A on Quality-medicines; part-2, Graduation of measuring devices for liquid dosage forms' updated Nov 2018*). Therefore, the use of 1.0 ml syringes from the indicated suppliers can be accepted for measuring doses in the intended paediatric population.

2.2.3. Conclusions on quality aspects

Since the concern on the dosing accuracy was suitably addressed, there are no issues from a quality perspective for the product to be intended for the paediatric population.

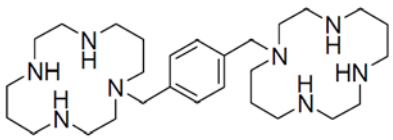
2.3. Non-clinical aspects

2.3.1. Introduction

Plerixafor (MOZOBIL, AMD3100, GZ316455) is a small molecule, bicyclam derivative (ATC code: L03AX16) that selectively and reversibly antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand stromal cell–derived factor-1α (SDF-1α). Plerixafor is approved in combination with G-CSF to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and

subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilize poorly. The structural formula of plerixafor is shown in Figure 1.

Figure 1: Structural formula of plerixafor



Three nonclinical studies have been performed in juvenile animals.

Table 1- List of Toxicity Studies in Juvenile Animals

Species (Strain)	Route of Administration	Testing Facility	Study Reference
Pig (Yorkshire)	SC	AnorMED Langley, BC, Canada	[AOM0032]
Rat (Crl:CD(SD) IGS BR VAF PLUS)	SC	Sequani Limited, Ledbury,Herefordshire, UK	[GT-249-TX-7]
Rat (Crl:CD(SD) IGS BR VAF PLUS)	SC	Sequani Limited, Ledbury,Herefordshire, UK	[GT-249-TX-9]

Abbreviations: SC: Subcutaneous

2.3.2. Pharmacology

No new non-clinical pharmacological data have been submitted in this application, which is considered acceptable.

2.3.3. Pharmacokinetics

No new non-clinical pharmacokinetic data have been submitted in this application, which is considered acceptable.

2.3.4. Toxicology

Exploratory single- and repeat-dose range-finding study in juvenile male Yorkshire pigs

In an exploratory (non-GLP) dose range-finding study, plerixafor was administered to juvenile male Yorkshire pigs (24.5-28.2 kg) at single subcutaneous (SC) doses of 1, 2, 4, 6, 8, or 12 mg/kg or repeat SC doses of 4.75 mg/kg/day for 4 days. The toxicity results were consistent with results seen in other toxicology studies. Plerixafor was well tolerated at single doses of ≤6 mg/kg and for 4 days of dosing at 4.75 mg/kg/day. After a single dose, clinical signs of lateral recumbence and “looked uncomfortable” were observed 1-2 hours post-dose at 8 mg/kg and mortality at 12 mg/kg. At doses of 4 and 2 mg/kg observed clinical signs were loose feces, and slight shaking (but this might be related to temperature difference due to separation from herd). No clinical signs were found at 1 and 6 mg/kg or after repeated administration of 4.75 mg/kg. Two distinct phases of increase of white blood cell counts (WBC) were found, peaking near 4 and 12 hrs post-dose respectively. At 24 hrs WBC were back at baseline. No clear difference in effect was found between 1, 2 and 4 mg/kg, or between 6 and 8 mg/kg. The effect (area under curve of WBC) of 6 and 8 mg/kg clearly exceeded that of the three lower doses. The plasma concentration of 28 659 ng/mL (57 µM) observed following the death at 12 mg/kg is consistent with plasma exposure concentrations with serious adverse effects in other species. Pharmacokinetics after doses of 1, 2, 4, 6 and 8 mg/kg showed an approximately dose proportional increase of $AUC_{0\text{-}24hr}$ of 10.15 – 75.40 hr.µM, a less than dose proportional increase of C_{max} of 5.02 – 23.59 µM, a t_{max} of 0.5 hr, and an

elimination half-life in the range 3.51 – 4.41 hr. In summary, plerixafor produced the expected pharmacological effect of leucocytosis. Overall, the steepness of these dose-response effects and the nature of the observed effects are consistent with those from both single and repeat-dose toxicology studies in rats and dogs. Because only one animal was tested per dose level, the interanimal variability of the toxicity response is not known.

Exploratory subcutaneous juvenile toxicity dose range-finding study in the rat

In an exploratory (non-GLP) dose range-finding toxicity study, daily SC administration of plerixafor to juvenile Sprague-Dawley rats from Postnatal Day (PND)21 to PND50 at dose levels 1.5, 5, 10, or 15 mg/kg/day was well tolerated with respect to the absence of adverse clinical signs, body weight or food consumption effects. A marked increase in white blood cell count was recorded at dose levels of ≥1.5 mg/kg/day, considered to reflect test article pharmacology. Slight effects on blood magnesium or urea were also seen at dose levels of ≥5 mg/kg/day. Higher body weight related spleen weight and a marginal increase in the age of attainment of vaginal perforation were seen at ≥5 mg/kg/day, and marginally higher liver weight at 15 mg/kg/day was also observed. The effects on organ weights were thought to reflect an adaptive response to test article administration. One male given 5 mg/kg/day (Male 23) and 1 male given 15 mg/kg/day (Male 46) were noted to have a large spleen at necropsy, and accordingly, these males had the highest absolute spleen weights recorded for the study. Enlarged spleen was also noted in toxicity studies with adult animals supporting the MAA filed for the adult patient population.

Subcutaneous juvenile toxicity study in the rat

In a GLP toxicity study (Study GT-249-TX-9), the effects of plerixafor on the juvenile development of the rat were investigated following once daily subcutaneous administration to pups from PND21 through PND50. The toxicokinetics of plerixafor in juvenile rats was also evaluated.

Thirty-six timed-mated Sprague-Dawley female rats were allowed to litter. Pups were selected so that 24 pups of each sex were allocated to each dose group (Groups 1 to 4) and each group was subdivided into Subsets I and II, consisting of 12 animals per sex. Pups were dosed once daily via subcutaneous injection with vehicle, 1.5, 7.6, or 15 mg/kg/day plerixafor from PND21 through PND50, using a constant dose volume of 5 mL/kg. Individual doses were adjusted according to the most recently recorded body weight.

Pre-weaning pup development tests were conducted for all litters prior to the commencement of dosing, and clinical observations, body weight and food consumption were recorded at regular intervals throughout the study.

Crown to rump and tarsus bone lengths were measured, and developmental and behavioural tests were conducted on Subset I pups (with the Figure Eight maze conducted on some of Subset I and II animals). Blood and urine samples for clinical laboratory investigations were also obtained towards the end of the treatment period. All Subset I pups were killed on PND51 and subjected to necropsy. Selected tissues were weighed, fixed, processed to slide and examined microscopically.

Pups allocated to Subset II were assessed for sexual development and blood samples for toxicokinetic assessment were collected on PND50. At approximately 10 weeks of age, following a treatment-free period of approximately 3 weeks, male and female pups from the same dose group were paired to assess reproductive performance. Subset II females were killed on Gestation Day (GD)13 and subjected to necropsy, where the pregnancy status, number of corpora lutea and number and distribution of implantations were recorded. Subset II males were killed and subjected to necropsy approximately 14 days after completion of the mating period. Selected tissues were retained and fixed for both sexes.

Table 2 - Mean Plasma Concentrations of Plerixafor on PND50

Species	Sex	Dose (mg/kg/day)	C_{max} (ng/mL)[a]	AUC_{0-24} (ng.h/mL) [a]
Rat	Male	1.5	1440	3980
		7.6	7440	22 800
		15	17 100	47 000
	Female	1.5	1490	4540
		7.6	6310	21 500
		15	14 000	44 800

Abbreviations: Cmax = maximal concentration; AUC = area under the concentration-time curve

a Values are rounded to 3 significant figures

Peak plasma concentration and systemic exposure to plerixafor on PND50 increased with increasing dose level in a dose proportional manner. The time of peak plasma concentration occurred 30 minutes after dosing, after which levels declined with a mean apparent half-life of 1.1 to 1.2 hours, where measurable. No marked differences in peak or systemic exposure of plerixafor between the sexes were apparent.

On Day 50 of age, concentrations of Plerixafor were measurable up to 8 hours post-dose at 1.5 mg/kg/day and up to 24 hours post-dose at 7.6 or 15 mg/kg/day, indicating continuous exposure to Plerixafor at the mid and high dose levels following repeated dosing. The data at the mid and high dose levels also indicated that steady-state had been reached by Day 50 of age.

Clinical signs of unsteady gait and/or decreased activity were noted on the first or second days of dosing for several animals given 15 mg/kg/day. These effects had fully recovered 2 hour subsequent to dose administration and there were no further clinical signs noted throughout the remainder of the study. Two males at 15 mg/kg/day were dosed twice in error on PND50, and showed clinical signs of prostration, unsteady gait, decreased activity and slow, laboured breathing; these signs were resolved by 2 hours after the second dose, and there were no additional clinical signs during the remainder of the study. Given that the clinical signs were transient in nature and present only in a limited number of animals, they were considered not to be adverse.

In the subset of rats euthanized on PND51, slightly lower group mean body weight gain over the entire treatment period was noted for males at 15 mg/kg/day and for females at all doses. There were no differences in group mean absolute body weight for a subset of animals used for the reproductive phase of the study, suggesting that any effects on body weight could recover within the short period of time between cessation of dosing on PND50 and mating approximately 3 weeks later. As the decreases in body weight gain were minor and did not produce a decline in the condition of the animals, the effects on body weight gain were considered not to be adverse. Markedly higher leukocyte counts were seen for both sexes at all dose levels of plerixafor, however, this effect was expected due to the pharmacology of the test article. Other minor haematological effects (slightly lower haemoglobin concentration and packed cell volume, and marginally lower red blood cell counts) without histopathology correlates were seen at 15 mg/kg/day plerixafor, and were not considered to be toxicologically meaningful.

Higher group mean blood urea concentrations were seen for males at 15 mg/kg/day and for females at ≥ 7.6 mg/kg/day, with some animals having individual values above the background data range. In addition, lower group mean total protein concentrations occurred in both sexes at ≥7.6 mg/kg/day, and this was considered likely to be associated with the lower calcium and magnesium concentrations also seen at these dose levels. As there were no changes in the liver or kidneys at histopathological examination and the magnitude of the changes in blood chemistry parameters was not sufficient to affect the health of the animals, these effects on blood urea and total protein were considered not to be adverse in nature.

Group mean relative (to body weight) thymus weights were slightly lower at ≥7.6 mg/kg/day in the subset of males euthanized on PND51, and group mean relative liver weights were slightly higher at 15 mg/kg/day in the subset of females euthanized on PND51. The effect on thymus weight was considered to be associated with plerixafor pharmacology and the higher liver weights were thought to be an adaptive response to plerixafor administration. No organ weight effects were noted for the reproductive subset animals, which had been allocated to a treatment-free period. Considering the organ weight findings were limited to one sex, were slight, there were no associated histopathology changes and that the effects were not present in the reproductive cohort rats, the organ weight changes were considered not to be adverse.

In conclusion, once daily subcutaneous injection of plerixafor to juvenile Sprague-Dawley rats from PND21 to PND50 at dose levels of 1.5, 7.6, or 15 mg/kg/day was generally well tolerated. Blood chemistry changes (higher blood urea concentration and lower plasma protein, calcium and magnesium concentrations) and slightly lower body weight gain were seen at ≥7.6 mg/kg/day, and transient clinical signs were noted at 15 mg/kg/day at the start of treatment; these changes were not considered adverse because of their small changes, transient nature, and/or not affecting the health of the rats. Marked leucocytosis was seen at all dose levels of plerixafor, and slightly lower thymus weights relative to body weight were recorded at ≥7.6 mg/kg/day in males; however, these effects were considered to reflect plerixafor pharmacology rather than toxicity. Higher body weight-related liver weights were also noted at 15 mg/kg/day in females, although this was considered to represent an adaptive response to plerixafor administration. Any changes in thymus or liver weight were limited only to one sex, did not correspond to histopathological changes in either affected organ, and there were no effects on organ weights in reproductive cohort animals. No adverse developmental effects were observed in these juvenile rats at any dose level tested.

Consequently, the No-Observed-Adverse-Effect Level (NOAEL) for juvenile toxicity was considered to be 15 mg/kg/day SC.

Based on body surface area, dose margins at the highest clinical paediatric dose of 11.8 mg/m2 (ie, 320 µg/kg) in children 2 to 12 years of age [MOZ15609/DFI12860], and the maximum tolerated dose (MTD) of 90 mg/m2 (ie, 15 mg/kg/day) in the juvenile rat study would be 7.6-fold based on body surface area or 47-fold based on dose. The dose margins in the GLP juvenile toxicity study in rats relative to the highest clinical paediatric dose are shown below.

Table 3- Rat/human dose margins in juvenile toxicity study

Species	Study Number	Dose[a]		Rat/Human Dose Margin	
		mg/kg/day (rat) µg/kg (human)	Body Surface Area (mg/m^2)	mg/kg/day (rat) µg/kg (human)	Body Surface Area (mg/m^2)
Rat	[GT-249-TX-9]	15	90	47	7.6
Human	[MOZ15609/DFI12860][b]	320	11.8	--	--

a: No-observed-adverse-effect level and maximum tolerated dose in the rat study.

b: Pediatric study of children 2-12 years of age.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the scope described in the ERA Guideline, given that this application is for a product with Orphan Drug status in Europe, the absence of a phased approach ERA as specified in the guideline is considered justified in that the total quantity of Mozobil 20 mg/ml solution for injection used will be below the ERA Phase II Predicted Environmental Concentration in surface water ($PEC_{surfacewater}$) action limit of 0.01 µg/L. This is because epidemiology data and projected sales of the product result in a market

penetration factor (F_{pen}) which results in a $PEC_{surfacewater}$ value of <0.001 µg/L. Consequently, there would be no significant environmental risk from Mozobil 20 mg/ml solution for injection using the conservative assumptions of the Phase I ERA guidance.

Calculation of the Predicted Environmental Concentration

The data used to determine a prevalence rate in Europe of less than 1 person in 10,000 was the grounds for the orphan drug designation granted for plerixafor. At the time of orphan drug designation, treatment to mobilize progenitor cells prior to stem cell transplantation affected less than 1 in 10,000 people in the European Union (EU). This is equivalent to a total of fewer than 46,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

Based on these epidemiology data and the prevalence rate in the orphan designation, a conservative prevalence of 10 per 100,000 in the European population was used to calculate the $PEC_{surfacewater}$ using the refined formula in the CHMP ERA guideline:

$$\text{PECsurface water (mg/L)} = \frac{\text{DOSEai} \times \text{Fpen}}{\text{WASTEWinha b} \times \text{DILUTION}}$$

where :

DOSEai = Maximum daily dose of the active ingredient consumed per inhabitant per day = 20 mg/dy

$$\text{Fpen} = \%\ \text{of market penetratio n} = \frac{\text{consumptio n } (^{mg}/_{yr}) \times 100}{\text{DDD } (^{mg}/_{inh}) \times \text{inhabitant s} \times 365\ ^{dy}/_{yr}} = \frac{3.62E8 \times 100}{20mg \times 496E6 \times 365} = 0.010\% = 0.0001$$

consumptio n = maximum Orphan Drug projection for all Sanofi products containing plerixafor

DDD = Defined Daily Dose (DDD not defined so prescribed dose used) = 20 mg/dy

inhabitant s = number of inhabitant s in the European U nion per United Nations World Population Prospects : The 2012 Revision

WASTEWinha b = Amount of wastewate r generated per inhabitant per day = 200 L/dy

DILUTION = Dilution factor = 10

and

$$\text{PECsurface water (mg/L)} = \frac{20\ \text{mg/dy} \times 0.00010}{200\ \text{L/dy} \times 10} = 0.000001\ \text{mg/L} = 0.001\ \mu\text{g/L}$$

This is a conservative calculation since it does not consider metabolism or degradation of plerixafor, patient presentation, diagnosis or compliance rates and the assumption that all patients are dosed 365 days per year.

The pharmaceutical excipients in the formulation are Sodium chloride, Hydrochloric acid, Sodium hydroxide and Water for injections. All of these excipients are well known and commonly used, some in very small quantities, and comply with the Ph. Eur., in-house and other reference standards. The excipients are considered by the expert to be inactive with very low toxicity and do not present a significant environmental toxicity risk. Considerations of the environmental risk were therefore limited to the active substance plerixafor.

Although an exemption from preparation of an ERA is claimed, Genzyme performed one following the concepts of the CHMP ERA guideline for the original submission. The ERA was performed using data to identify the environmental fate and any significant environmental risks from exposure to the active substance plerixafor.

Table 4: Summary of environmental fate data for plerixafor

Study Type	Result
Water solubility (15 °C, 25 °C, 37 °C, sodium chloride (0.9 %)), PEG 400/ethanol 95 %/water 15:15:70 (v/v/v)	1-10 mg/ml
Dissociation constants (pKa) in the environmental pH range (6-10)	8.56 ± 0.02 9.31 ± 0.02
Octanol/Water Partition coefficient (Log Kow, Log Pow at pH=7)	< 0.1

In accordance with the CHMP ERA guideline, an exemption from preparation of Phase II ERA studies is claimed because there are no apparent environmental concerns about the product, and based on published epidemiology studies, the $PEC_{surfacewater}$ will be less than 0.01 µg/L. Consequently the product is unlikely to present a risk for the environment following its prescribed use in patients. As such, no precautionary and safety measures need to be imposed regarding the environmental release from use in patients or from disposal of unused products or waste materials derived from the medicinal product.

Although no Phase II ERA studies or precautionary or safety measures are needed for this medicinal product, a review of available data was made and an ERA was performed for the active substance plerixafor. These data do not indicate a significant environmental impact from its use.

To encourage proper disposal of unused medicines as a means to protect the environment and in accordance with recommendations in the CHMP 2006 Guidance, the proposed package leaflet should include the following statement: “Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.”

2.3.6. Discussion on non-clinical aspects

A dose range finding and a pivotal juvenile toxicity study, in which rats were dosed 1.5-15 mg/kg/day from PND 21 to PND 50, were submitted. Rats in the juvenile toxicity study are dosed from PND21 to PND 50 to support a paediatric indication. However, to cover human age period up to 18 years, rats should have been dosed starting earlier and ending later. Nevertheless, it is accepted that as the immune system is the pharmacological target organ and that the rat’s immune system at PND 21 is equivalent to 1 year old humans. The MAH also describes the development of the human immune system from formation of HSCs towards the development of the thymic microenvironment, which is complete between 1 and 2 years of age and at PND 21, the immune system could be compared to a human immune system of 1-2 years. As such the pharmacological effect of plerixafor has sufficiently been studied in juvenile animals. Moreover, as the safety profile of plerixafor in adult and juvenile animals is very similar, it is not expected that any new safety effects will appear in a study with younger juvenile animals, i.e. those equivalent to children between 1 and 2 years old. Therefore, it is not supported to conduct another juvenile animal study to address safety in children between below 2 years of age. However, it is recommended to keep monitoring the safety profile of plerixafor in 1-2 years aged children, which is also to be included in the safety specification (see RMP).

Plerixafor selectively and reversibly antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand stromal cell–derived factor-1α (SDF-1α). This results in mobilization of hematopoietic stem cells from the bone marrow to the peripheral blood. Thus, increased extramedullary haematopoiesis could be expected based on the pharmacological action of the product. The observed (marked) leucocytosis seen at all dose levels of plerixafor, and slightly lower thymus weights relative to body weight were

recorded at ≥7.6 mg/kg/day in males were considered to reflect plerixafor pharmacology rather than toxicity.

Plerixafor administration also result in changes in blood chemistry, such as higher blood urea concentration and lower plasma protein, calcium and magnesium concentrations. Slightly lower body weight gain was seen at doses of ≥7.6 mg/kg/day, and transient clinical signs were noted at 15 mg/kg/day at the start of treatment. These changes were not considered adverse by the applicant because of their small changes, transient nature, and/or not affecting the health of the rats. Higher body weight-related liver weights (15 mg/kg/day in females) in the pivotal and the higher spleen weights relative to body weight in the DRF study were considered adaptive responses (extracellular haematopoiesis) to plerixafor administration, by the applicant. The changes in thymus or liver weight were limited only to one sex, did not correspond to histopathological changes in either affected organ and organ weights in reproductive cohort animals were unchanged. The observed effects were regarded non adverse by the applicant resulting in a NOAEL of 15 mg/kg/day SC, which was the highest dose tested. Based on body surface area, dose margins at the highest clinical paediatric dose of 11.8 mg/m2 (ie, 320 µg/kg) in children 2 to 12 years of age [MOZ15609/DFI12860], and the maximum tolerated dose (MTD) of 90 mg/m2 (ie, 15 mg/kg/day) in the juvenile rat study would be 7.6-fold based on body surface area or 47-fold based on dose.

In addition, the pharmacological and toxicological findings in the juvenile animals are not compared to the pharmacological and toxicological findings in the adults animals (rats) as studied to support the original MAA, which was granted in 2009. This would have been informative though, to interpret the nature of the findings in the juvenile toxicity study. Furthermore, an exposure multiple between juvenile rat at the NOAEL and the paediatric dose to be used in the clinic, will be more informative then the margins between rat and human based on body surface or dose.

The potential effects of plerixafor on male fertility and postnatal development have not been evaluated in non-clinical studies.

Following discussion of the pharmacological and toxicological findings in the juvenile toxicity study in relation to those obtained in the studies with adult animals (conducted in support for the MAA, which was granted in 2009) it was found that these effects were similar, which indicates that there are no additional targets of toxicity upon plerixafor treatment in juvenile animals (see section 5.3 of the SmPC).

The MAH provided data on rat to human margins based on dose, body surface area and exposure. Margins at the highest clinical pediatric dose of 11.8 mg/m2 (ie, 320 µg/kg) in children 2 to 12 years of age and the MTD of 90 mg/m2 (ie, 15 mg/kg/day) in the juvenile rat toxicity study were 7.6-fold based on body surface area or 47-fold based on dose and ≥ 18 based on exposure. Plerixafor is thus tested in juvenile rat with a sufficient safety margin.

The studies in miniature pigs -submitted as part of the original plerixafor registration, - showed that the lethal dose for pigs is lower than the NOAEL for rats. Pig may have been a more sensitive species to test juvenile toxicity. In miniature pigs a dose of 12/mg/kg appeared lethal. According to the applicant this occurs at exposures that also appear to be lethal in other species. This underscores the need for a comparison of exposure in animals (rat and also miniature pig) with the exposure in children.

Further, the MAH was asked to justify the maximum dose in relation to the pharmacological effect on mobilisation of WBC and CD34+ cells (this issue is touched upon in the discussion on results obtained in the study with Yorkshire pigs that was included in the original application and discussed in the non clinical toxicological summary included with this application). In its response, the MAH described the mobilisation of several types of immune cell upon plerixafor administration to several species. Apparently, the pig is not such a relevant model as the number of lymphocytes is already higher in pig as compared to human. Therefore, the study in pig may be less informative with regard to dose extrapolation. In the juvenile rat

study, *'pharmacologically-mediated, markedly higher total leucocyte counts were observed in both sexes at all dose levels, and generally included all white blood cell types (with the exception of lymphocyte counts in males).*' Thus, the pharmacological effect was observed in all dose groups in the rat juvenile toxicity study. However, determination of a clinical dose required to obtain an optimal pharmacological effect, should occur based on clinical studies rather than on animals studies.

The applicant has provided a Phase I calculation using a refined F_{pen}. The data used in the Fpen and PECsurfacewater calculations in the ERA (1/10,000 persons) used substantiated data for disease prevalence for all plerixafor indications, including the current application for use in the paediatric population in Europe. The ERA is thus applicable also to this current application.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical aspects related to the extension of the indication for plerixafor to children aged 1 to 18 years are satisfactorily addressed. Section 5.3 of the SmPC was updated accordingly.

2.4. Clinical aspects

2.4.1. Introduction

One Clinical study (DFI12860) was submitted to support the extension of indication to *paediatric patients (1 to less than 18 years), to be used in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours and either:*

- *low circulating stem cell count on the predicted day of collection after mobilisation with G-CSF (with or without chemotherapy) or*
- *who previously failed to collect sufficient haematopoietic stem cells (see section 4.2).*

GCP

The clinical trial was performed in accordance with GCP as claimed by the applicant.

- Overview of clinical studies

Clinical study DFI12860 (MOZ15609) is a study of the efficacy and safety of plerixafor in addition to standard regimens for mobilization of haematopoietic stem cells into peripheral blood, and subsequent collection by apheresis, versus standard mobilization regimens alone in the paediatric setting.

This study was conducted in 2 stages: an initial dose-escalation phase (Stage 1), followed by a randomized phase (Stage 2) comparing plerixafor at the dose selected in Stage 1 plus standard mobilization to standard mobilization alone.

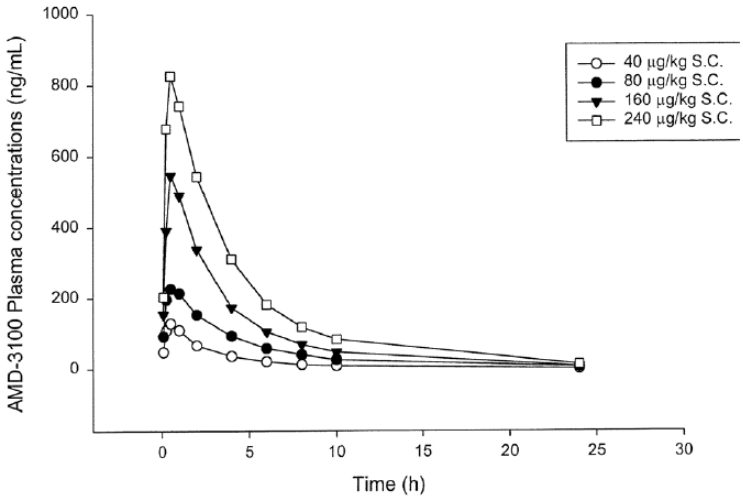
Study	Design	Scope	population	objective
DFI12860 (MOZ15609)	randomized, open label, comparative	Stage 1: dose ranging Stage 2: efficacy and safety	paediatric patients, aged 1 to <18 years, with solid tumours eligible for autologous transplants	efficacy and safety of plerixafor in addition to standard regimens for mobilization

	vs standard mobilization alone

2.4.2. Pharmacokinetics

In adults, the pharmacokinetics of plerixafor were characterized by a rapid absorption, with the Tmax occurring at approximately 0.5 to 1 hour after SC administration. Plerixafor is administered based on weight to provide a dose of 0.24 mg/kg or as fixed dose of 20 mg in patients of 83 kg or less. Based on increasing exposure with increasing body weight, the plerixafor dose should not exceed 40 mg. Patients with creatinine clearance 20-50 ml/min should have their dose of plerixafor reduced by one-third to 0.16 mg/kg (and the dose should not exceed 27 mg).

Figure 2: Average plerixafor concentration-time curves following SC administration of 4 dose levels in 18 healthy adult volunteers in the original study-1002.



Plerixafor has a low potential for involvement in P450-dependent drug-drug interactions. The major route of elimination of plerixafor is urinary and the elimination half-life (t1/2) in plasma is 3-5 hours. There is no significant effect of gender or age on the pharmacokinetics of plerixafor.

Special populations

Paediatric

In stage 1 of the paediatric clinical study DFI12860, patients received plerixafor once daily as a SC injection with the sterile solution of 20 mg/ml in doses of 160, 240 and 320 µg/kg, in accordance with the dose and age cohort see Table 5: Dose levels per cohort.

Table 5: Dose levels per cohort

Dose levels per cohort					
2 to <6 years		6 to <12 years		12 to <18 years	
400 µg/kg		400 µg/kg		400 µg/kg	
320 µg/kg	n=3	320 µg/kg	n=3	320 µg/kg	n=3
240 µg/kg	n=3	240 µg/kg	n=3	240 µg/kg	n=3
160 µg/kg	n=3	160 µg/kg	n=3	160 µg/kg	n=3

As discussed in the PIP, the doses for the dose-escalation phase of the clinical study were selected based on simulations with the adult population PK model. The CrCl was included in the model to describe clearance (weight and age as covariates). Due to the expected higher clearance in children as compared to adults, the highest dose of the 3 dose levels (160, 240 and 320 µg/kg) was predicted to result in values of Cmax and AUC that were within the range observed following administration to adults of 160 and 240 µg/kg plerixafor. Additionally, the applicant suggested that the protocol could be amended to examine higher doses (400 µg/kg) following completion of each cohort and evaluation of the safety and PK data. All dose escalation decisions during stage 1 were reviewed and approved by an independent data monitoring committee.

Pharmacokinetic parameters were determined for all 27 patients, characterised using non-compartmental methods and reported and summarised by dosing cohort using descriptive statistics. Blood samples were taken during stage 1 of the study at the following time points after the first dose of plerixafor in 12 to <18 year olds: 0.25, 0.5, 0.75, 1, 4, 8, 9 (just prior to apheresis), and 24 hours post first plerixafor dose. In younger patients (i.e., <12 years old) a reduced numbers of samples were taken because of the need to reduce sampling volumes in paediatric patients with smaller blood volumes.

Patients of the 2 to <6 age cohort (n=9) were 3.1 (2-5) years of age (mean, range) and 78% of them were females.
Patients of the 6 to <12 age cohort (n=9) were 8.8 (6-11) years of age and 22% of them were females.
Patients of the 12 to <18 years age cohort (n=9) were 15.2 (13-17) years of age and 67% of them were females.

Safety, PK and PD data from stage 1 was evaluated to determine the appropriate dose(s) and timing of plerixafor administration to be used in stage 2.

Table 6: Mean (+/-SD) (geometric mean) (CV%) pharmacokinetic parameters of plerixafor for stage 1, study DFI12860

	2 to <6 years			6 to <12 years			12 to <18 years		
PK parameters	**160µg/kg (n=3)**	**240 µg/kg (n=3)**	**320 µg/kg (n=3)**	**160 µg/kg (n=3)**	**240 µg/kg (n=3)**	**320 µg/kg (n=3)**	**160 µg/kg (n=3)**	**240 µg/kg (n=3)**	**320 µg/kg (n=3)**
C_{max}	153 ± 82.1	327 ± 244	465 ± 79.7	288 ± 61.5	625 ± 77.7	604 ± 70.9	496 ± 11.3	785 ± 275	1180 ± 205
(ng/mL)	(137) [53.6]	(223) [74.6]	(460) [17.2]	(283) [21.4]	(621) [12.4]	(601) [11.7]	(496) [2.3]	(748) [35.1]	(1170) [17.3]
T_{max} [a]	1.00	1.00	0.63	1.02	1.00	1.02	0.50	0.25	0.52
(h)	(0.87 - 1.02)	(0.62 - 1.02)	(0.50 - 0.67)	(1.00 - 1.05)	(1.00 - 1.00)	(1.02 - 1.08)	(0.25 - 0.58)	(0.25 - 0.50)	(0.25 - 0.52)
$t_{1/2z}$	1.60, 1.88[b]	2.09, 2.78[b]	1.93 ± 0.468	2.35 ± 0.674	2.59 ± 0.690	2.10 ± 0.392	4.04 ± 1.57	3.05 ± 0.503	3.20 ± 0.598
(h)	(1.73)	(2.41)	(1.89) [24.2]	(2.29) [28.7]	(2.52) [26.7]	(2.08) [18.6]	(3.83) [39.0]	(3.02) [16.5]	(3.16) [18.7]
AUC_{0-9}	655, 486[b]	1750, 1730[b]	1520 ± 126	953 ± 231	2270 ± 475	2140 ± 401	1800 ± 363	2600 ± 556	4120 ± 100
(ng•h/mL)	(564)	(1740)	(1510) [8.3]	(934) [24.2]	(2230) [20.9]	(2110) [18.7]	(1770) [20.2]	(2550) [21.4]	(4120) [2.4]

a Median (Min - Max)
b Individual values (Geometric Mean) are reported when n=2 due to poorly defined elimination phase in some patients

Figure 3: Mean (+/-SD) plasma Plerixafor concentrations

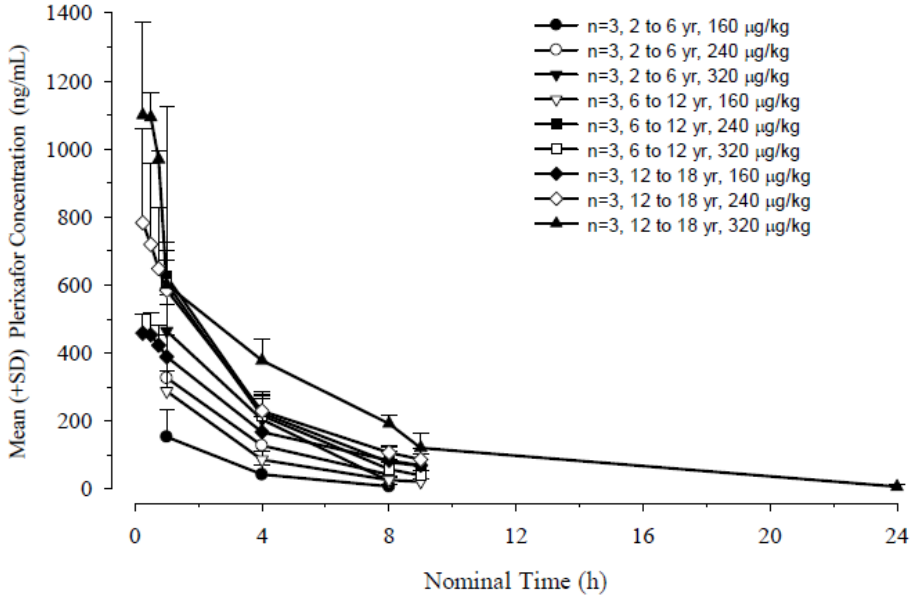


Figure 4: Mean (+/-SD) plasma Plerixafor concentrations - Semi-log Plot

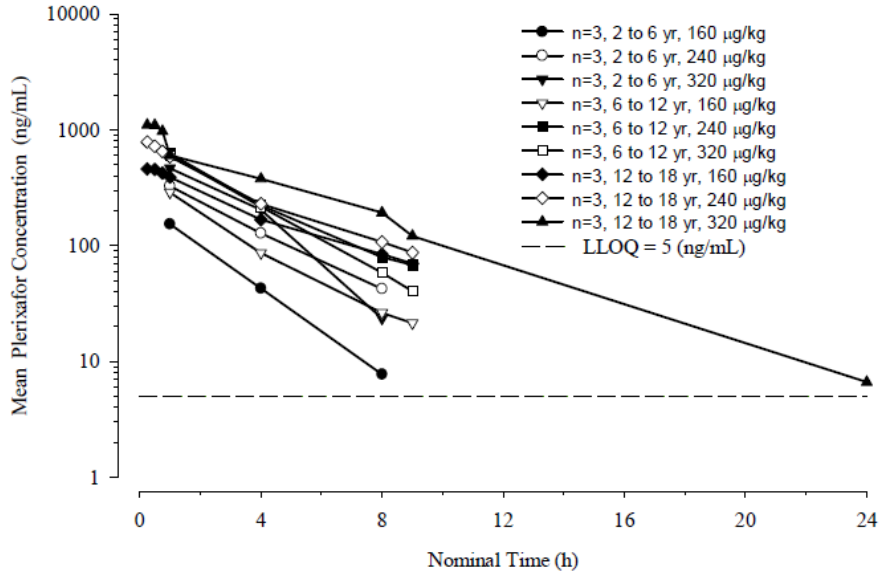


Figure 5: Individual and mean (SD) Plerixafor plasma Cmax values

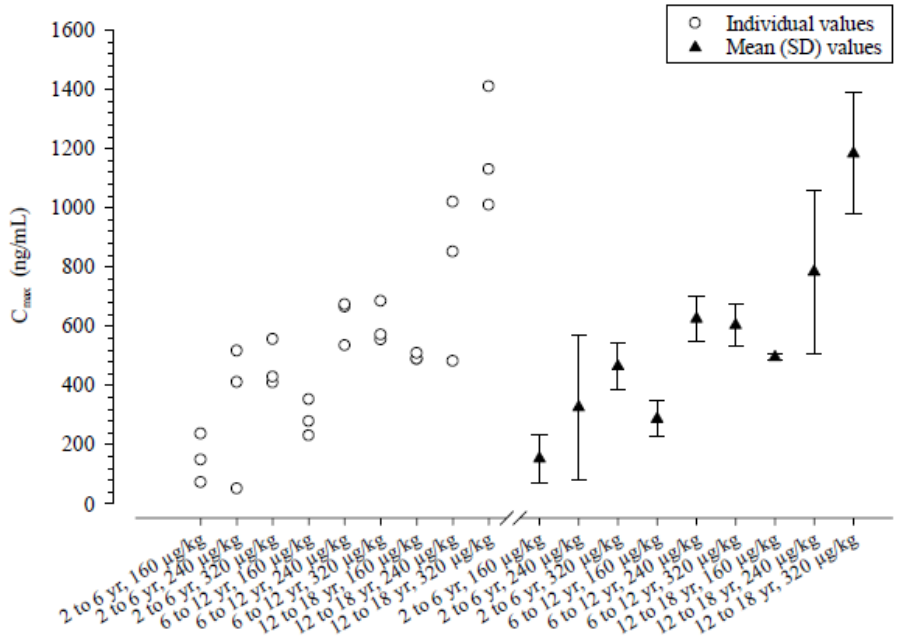
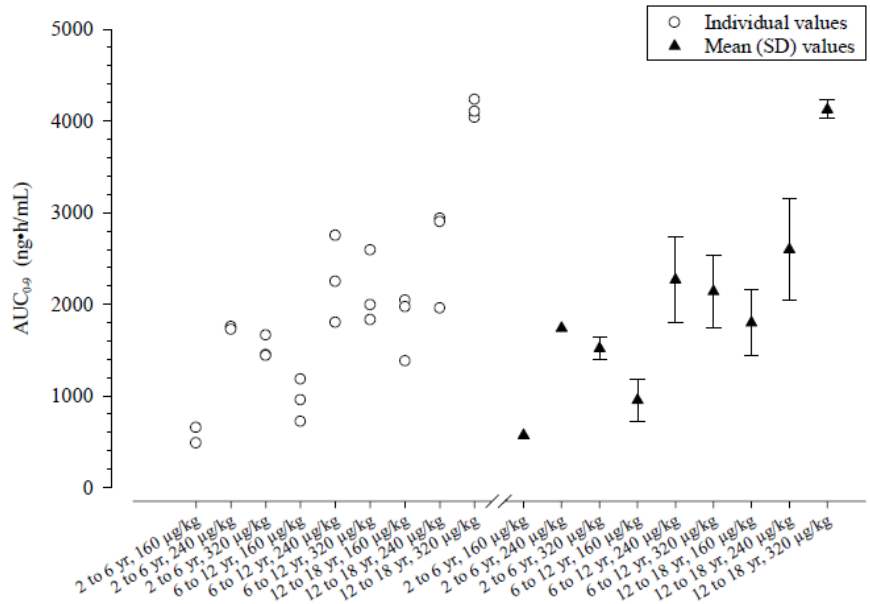


Figure 6: Individual and mean (SD) plerixafor plasma AUC0-9 values



From these data, the applicant concludes dose proportionality from 160 to 240 µg/kg in all age groups, comparable to adults. No increase in exposure (AUC0-9h) above the dose of 240 µg/kg were noted in children 2 to <6 years old or 6 to <12 years old.

The AUC0-9h after a 240 µg/kg dose of plerixafor to 6 to <12 year olds and 12 to <18 year was concluded to be similar to that achieved in adults.

It is noted that the exposure in two 2 to <6 year olds with evaluable PK data were nominally lower than the exposures reported in adults, however both subjects achieved sufficient mobilization of CD34+ HSCs to proceed to transplant.

A higher dose cohort of 400ug/kg that was permitted by the protocol, was not deemed necessary based on the PK/PD results.

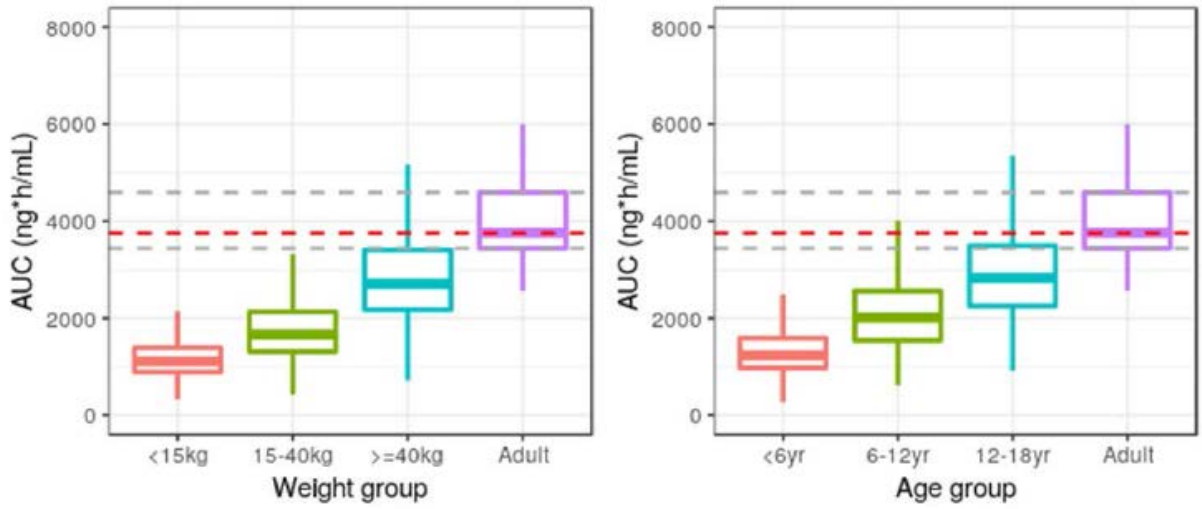
Selection of the final dose for stage 2 (240 µg/kg daily) was based on the absence of clear evidence of an age related effect, dose proportionality from 160 to 240 µg/kg in all age groups and no dose proportional exposure beyond 240 µg/kg. Thus, the dose for stage 2 was determined to be 240 µg/kg, which is the same as that approved for use in adults over 83 kg.

For stage 2, pharmacokinetics were only characterized for a subset of the treated patients. Patients were aged 1 to 18 years. Blood sampling was sparse: 2 samples, drawn 0.25 to 1 hour post dose and prior to apheresis 8- 12 hours post dose. According to the protocol, pharmacokinetic data from stage 2 was to be added to stage 1 pharmacokinetic data for determination of AUC0-9, Cmax, Tmax and t1/2.

The data used for paediatric popPK model building was reasonably rich to adequately characterize plerixafor pharmacokinetics (PK) in paediatric patients. It included data from both dense PK sampling (Stage 1) and sparse PK sampling (Stage 2) over the dose range of 160 to 320 µg/kg. The Stage 1 PK sampling ensured that the terminal and distribution phases of the PK profile in paediatric patients were well informed, especially when the adult popPK model was used as a starting point to develop the paediatric popPK model. The dataset included patients over a broad range of bodyweights over the age range of 1 to less than 18 years, essentially ensuring that the paediatric body size effect with age is appropriately characterized by using only the paediatric PK data.

Upon request for supplementary information, the applicant provided pharmacokinetic results of stage 2 as well, and developed a pediatric population pharmacokinetic model for plerixafor using the pooled PK data from stage 1 and stage 2 of study MOZ15609, based on the adult population pharmacokinetic model. Presented results of the model validation indicated good model performance. Below a plot of simulated plerixafor exposure for different age and weight categories.

Figure 7 Boxplot of simulated exposure comparison between adult and pediatric patients in different weight (left) or age (right) groups at the dose of 240 µg/kg



Abbreviation: AUC=AUC_{0-24}, area under the concentration-time curve over 24 hours.

The plots of observed area under the concentration-time curve until the last measurable concentrations (AUClast) in paediatric patients in the Stage 1 of the study MOZ15609, stratified on body weight and age are shown in the below figures.

Figure 8: Observed paediatric exposures with weight in MOZ15609

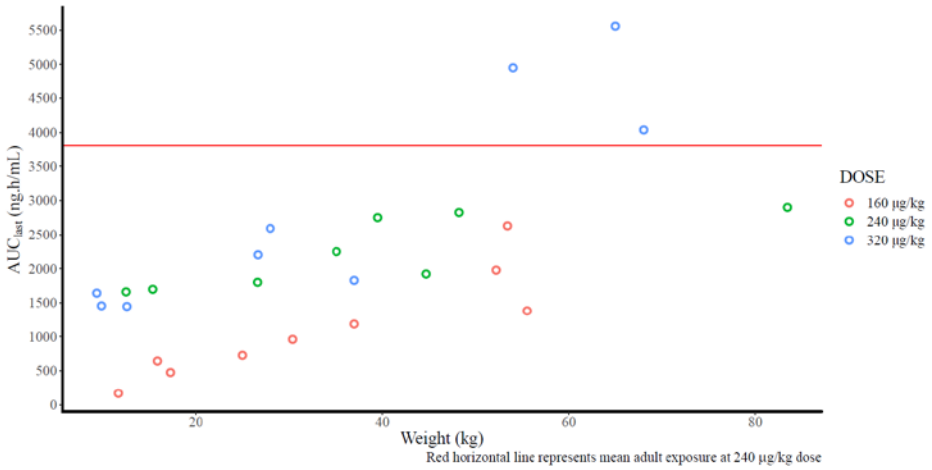
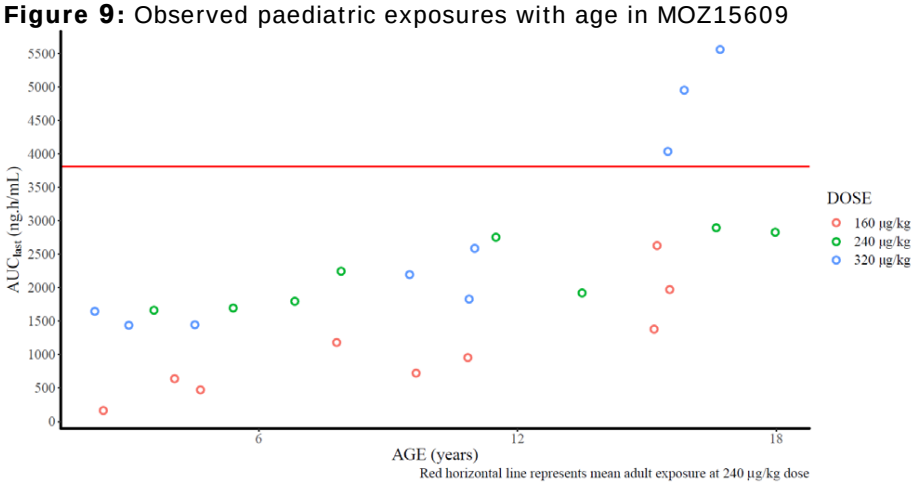


Figure 9: Observed paediatric exposures with age in MOZ15609



The observed AUClast and Cmax in paediatric patients in the Stage 1 of the study MOZ15609, stratified on body weight and age are shown in tables below.

Table 7: Observed paediatric exposures (stage 1) stratified by dose and weight compared to adult exposure at 240 mg/kg (studies AMD3100-C201, AMD3100-1101, AMD3100-1002)

Dose (µg/kg)	Weight category	N	Median weight (5th -95th percentile)	Mean (SD) [CV%]		
				AUC_{last} (ng.h/mL)[a]	C_{max} (ng/mL)	AUC_{last} arithmetic mean ratio[b,c]
160	< 15 kg	1	11.7 (-)	166.3 (-) [-]	72.8 (-) [-]	0.04
	15 to < 40 kg	5	25.0 (16.2-35.7)	795.7 (276.3) [34.7]	250.0 (74.1) [29.7]	0.21
	>40 kg	3	53.4 (52.3-55.3)	1994.2 (624.8) [31.3]	496.0 (11.3) [2.3]	0.52
240	< 15 kg	1	12.5 (-)	1662.0 (-) [-]	411.0 (-) [-]	0.44
	15 to < 40 kg	4	30.9 (17.1-38.8)	2124.9 (481.1) [22.6]	597.8 (83.2) [13.9]	0.56
	>40 kg	3	48.2 (45.1-79.9)	2548.7 (546.7) [21.4]	784.7 (275.2) [35.1]	0.67
320	< 15 kg	3	9.9 (9.5-12.3)	1511.1 (115.7) [7.7]	464.7 (79.7) [17.2]	0.40
	15 to < 40 kg	3	28.0 (26.8-36.1)	2207.0 (380.7) [17.2]	603.7 (70.9) [11.7]	0.58
	>40 kg	3	65.0 (55.1-67.7)	4849.5 (766.7) [15.8]	1183.3 (205.3) [17.3]	1.27

[a] Observed AUC_{last} was calculated by noncompartmental analysis (NCA) using WinNonLin Phoenix® version 1.4.
[b] The mean adult observed AUC_{last} is 3811.7 ng.h/mL. [c] Ratio is calculated as paediatric AUC_{last}/adult AUC_{last}.

Table 8: Observed paediatric exposures (stage 1) stratified by dose and age compared to adult exposure at 240 mg/kg (studies AMD3100-C201, AMD3100-1101, AMD3100-1002)

Dose (µg/kg)	Age category	N	Median age (5^{th} -95^{th} percentile)	Mean (SD) [CV%]		
				AUC_{last} (ng.h/mL)[a]	C_{max} (ng/mL)	AUC_{last} arithmetic mean ratio[b,c]
160	< 6 years	3	4.1 (2.6-4.6)	428.8 (242.0) [56.4]	153.3 (82.1) [53.6]	0.11
	6 to < 12 years	3	9.7 (8.0-10.7)	952.9 (230.6) [24.2]	287.7 (61.5) [21.4]	0.25
	>12 years	3	15.2 (15.2-15.5)	1994.2 (624.8) [31.3]	496.0 (11.3) [2.3]	0.52
240	< 6 years	2	4.5 (3.7-5.3)	1680.0 (25.4) [1.5]	464.0 (75.0) [16.2]	0.44
	6 to < 12 years	3	7.9 (6.9-11.1)	2267.3 (475.0) [21.0]	624.7 (77.7) [12.4]	0.59
	>12 years	3	16.6 (13.8-17.8)	2548.7 (546.7) [21.4]	784.7 (275.2) [35.1]	0.67
320	< 6 years	3	3.0 (2.3-4.4)	1511.1 (115.7) [7.7]	464.7 (79.7) [17.2]	0.40
	6 to < 12 years	3	10.9 (9.6-11.0)	2207.0 (380.7) [17.2]	603.7 (70.9) [11.7]	0.58
	>12 years	3	15.9 (15.5-16.6)	4849.5 (766.7) [15.8]	1183.3 (205.3) [17.3]	1.27

[a] Observed AUC_{last} was calculated by noncompartmental analysis (NCA) using WinNonLin Phoenix® version 1.4.
[b] The mean adult observed AUC_{last} is 3811.7 ng.h/mL. [c] Ratio is calculated as paediatric AUC_{last}/adult AUC_{last}.

2.4.3. Pharmacodynamics

Mechanism of action

Plerixafor is a small molecule bicyclam derivative that antagonises the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor 1α (SDF-1α, also known as CXCL12). The interruption of this interaction results in mobilisation of CD34+ stem cells to the peripheral blood where they can be collected for autologous transplantation.

The mechanism of action of plerixafor is the same in children as in adults; antagonism of CXCR4/SDF-1 binding.

Primary and secondary pharmacology

In Stage 1, peak CD34+ levels generally rose and peaked within the first hour after dosing, with the peak lagging behind the maximum plasma concentration of plerixafor, although individual patients showed some variation. This pattern was seen in all 3 dose groups (160, 240, and 320 µg/kg) and is consistent with the PK/PD relationship in adults treated with plerixafor.

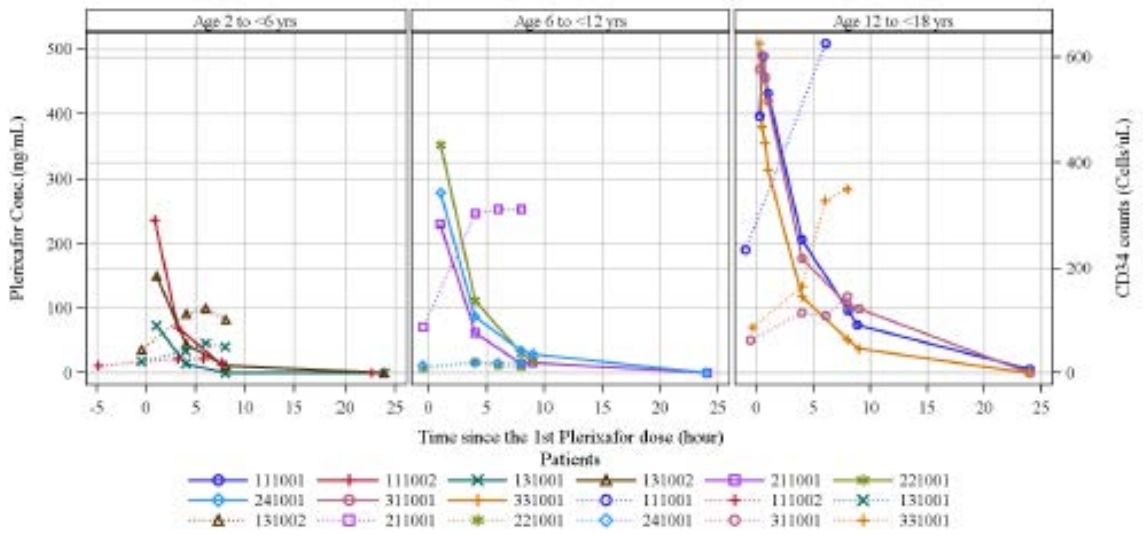


Figure 10 displays graphs of individual plerixafor concentrations for the 3 age cohorts and PB CD34+ levels at different times after first plerixafor dose administration in the 160 µg/kg group. In general, peak CD34+ levels found within the first hour after dosing lag behind the maximum plasma concentrations of

plerixafor, but individual patients show some variation. The delayed PD response (ie, increase in CD34+ cell count) with rising plasma plerixafor concentration is also observed at 240 and 320 µg/kg dose levels and is consistent with the PK/PD relationship in adults treated with plerixafor. *Note: Solid lines represent Plerixafor Concentration(ng/mL) and dotted lines represent CD34 counts(Cells/uL)*

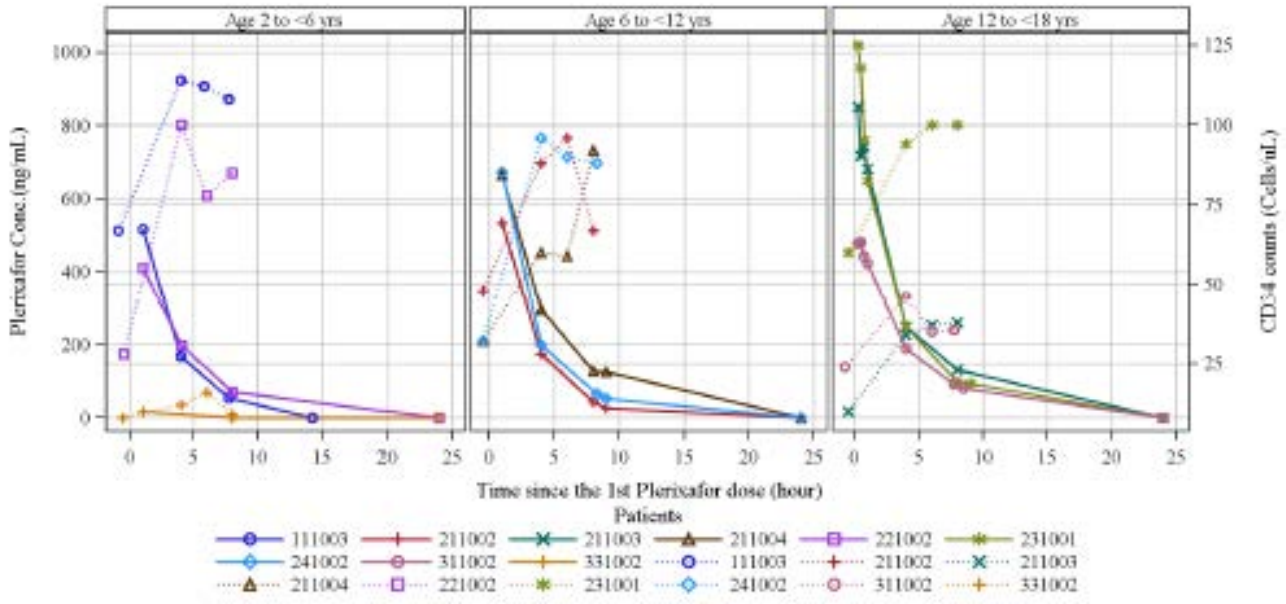


Figure 11 displays graphs of individual plerixafor concentrations for the 3 age cohorts and PB CD34+ levels at different times after first plerixafor dose administration in the 240 µg/kg group. In general, peak CD34+ levels are found within the first hour after dosing, but individual patients show some variation. *Note: Solid lines represent Plerixafor Concentration(ng/mL) and dotted lines represent CD34 counts(Cells/uL)*

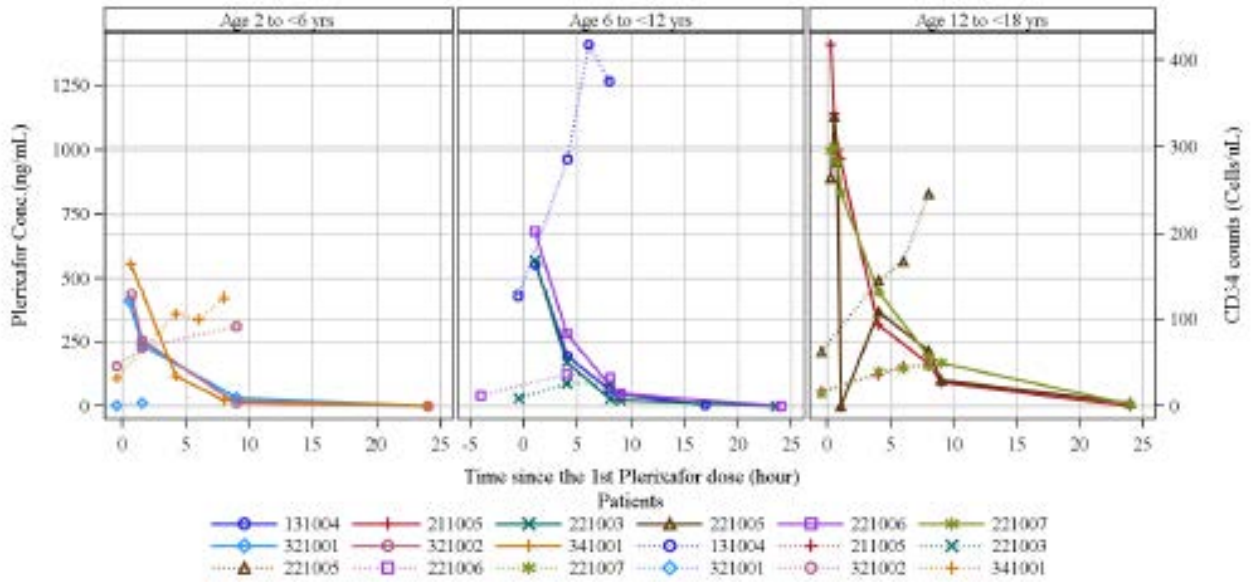


Figure 12 displays graphs of individual plerixafor concentrations for the 3 age cohorts and PB CD34+ levels at different times after first plerixafor dose administration in the 320 µg/kg group. In general, peak CD34+ levels are found within the first hour after dosing, but individual patients show some variation. *Note: Solid lines represent Plerixafor Concentration(ng/mL) and dotted lines represent CD34 counts(Cells/uL).*

In the age cohort 2 to <6 years (n=9 across the 3 dose groups) with 9 evaluable patients, 6 patients showed a doubling of CD34+ count and 8 patients reached at least 2 × 10^6 CD34+ cell/kg within the first 2 apheresis procedures.

In the age cohort 6 to <12 years (n=9 across the 3 dose groups) with 8 evaluable patients, 8 patients showed a doubling of CD34+ count and 8 patients reached at least 2 × 10^6 CD34+ cell/kg within the first 2 apheresis procedures (see Table 4).

In the age cohort 12 to <18 years (n=9 across the 3 dose groups) with 9 evaluable patients, all 9 patients showed a doubling of CD34+ count and 7 patients reached at least 2 × 10^6 CD34+ cell/kg within the first 2 apheresis procedure .(see Table 5).

Table 9 Efficacy Analysis: CD34+ (Peripheral Blood and Apheresis) age group 2 to <6

	Summary Statistics	160 mcg/kg (N=9)	240 mcg/kg (N=9)	320 mcg/kg (N=9)	Overall (N=27)
Age Group:2 to <6	N	3	3	3	9
Patients with doubling of PB CD34+ count					
Yes	n (%)	2 (67)	1 (33)	3 (100)	6 (67)
No	n (%)	1 (33)	1 (33)	0	2 (22)
Missing	n (%)	0	1 (33)	0	1 (11)
Patients reaching at least 2 x10^6 CD34+ cells/kg					
Yes	n (%)	2 (67)	3 (100)	3 (100)	8 (89)
No	n (%)	1 (33)	0	0	1 (11)
Missing	n (%)	0	0	0	0
Number of apheresis to reach 2 x10^6 CD34+ cells/kg	N	2	3	3	8
1	n (%)	1 (50)	1 (33)	2 (67)	4 (50)
2	n (%)	1 (50)	2 (67)	1 (33)	4 (50)
3	n (%)	0	0	0	0
4	n (%)	0	0	0	0
Total CD34+ yield	N	3	3	3	9
	Mean (SD)	54.18 (52.12)	26.59 (30.86)	12.82 (9.52)	31.20 (35.67)
	Median	54.63	9.62	16.54	16.54
	Min	1.84	7.93	2.01	1.84
	Max	106.07	62.21	19.93	106.07

Note: Central laboratory data has been used. However, when central lab value is missing, local value is used.
Names of input datasets: CRT.COMVAR, CRT.LB_ LOCAL_MD1, CRT.LB_LOCAL_MD_3, EXTERNAL.LB_ CD34_C and EXTERNAL.PB_APH_CD34_T
Output: T-PB-APH-CD34.rtf
Program name: Global-Biostats\Plerixafor\Transplant\MOZ15609\Stage1\Programs\Output\T-PB-APH-CD34.sas
Creation date of output 14.2.2.2.1: 27JAN2013 9:56

Table 10 Efficacy Analysis: CD34+ (Peripheral Blood and Apheresis) Age group 6 to <12

	Summary Statistics	160 mcg/kg (N=9)	240 mcg/kg (N=9)	320 mcg/kg (N=9)	Overall (N=27)
Age Group:6 to <12	N	3	3	3	9
Patients with doubling of PB CD34+ count					
Yes	n (%)	2 (67)	3 (100)	3 (100)	8 (89)
No	n (%)	1 (33)	0	0	1 (11)
Missing	n (%)	0	0	0	0
Patients reaching at least 2 x10^6 CD34+ cells/kg					
Yes	n (%)	2 (67)	3 (100)	3 (100)	8 (89)
No	n (%)	0	0	0	0
Missing	n (%)	1 (33)	0	0	1 (11)
Number of apheresis to reach 2 x10^6 CD34+ cells/kg	N	2	3	3	8
1	n (%)	1 (50)	3 (100)	1 (33)	5 (63)
2	n (%)	1 (50)	0	2 (67)	3 (38)
3	n (%)	0	0	0	0
4	n (%)	0	0	0	0
Total CD34+ yield	N	2	3	3	8
	Mean (SD)	5.84 (2.26)	9.04 (4.60)	54.33 (79.82)	25.22 (49.09)
	Median	5.84	8.85	12.72	8.15
	Min	4.23	4.53	3.92	3.92
	Max	7.44	13.72	146.36	146.36

Note: Central laboratory data has been used. However, when central lab value is missing, local value is used.
Names of input datasets: CRT.COMVAR, CRT.LB_ LOCAL_MD1, CRT.LB_LOCAL_MD_3, EXTERNAL.LB_ CD34_C and EXTERNAL.PB_APH_CD34_T
Output: T-PB-APH-CD34.rtf
Program name: Global-Biostats\Plerixafor\Transplant\MOZ15609\Stage1\Programs\Output\T-PB-APH-CD34.sas
Creation date of output 14.2.2.2.1: 27JAN2013 9:56

Table 11 Efficacy Analysis: CD34+ (Peripheral Blood and Apheresis) Age 12 to <18

	Summary Statistics	160 mcg/kg (N=9)	240 mcg/kg (N=9)	320 mcg/kg (N=9)	Overall (N=27)
Age Group:12 to <18	N	3	3	3	9
Patients with doubling of PB CD34+ count					
Yes	n (%)	3 (100)	3 (100)	3 (100)	9 (100)
No	n (%)	0	0	0	0
Missing	n (%)	0	0	0	0
Patients reaching at least 2 x10^6 CD34+ cells/kg					
Yes	n (%)	2 (67)	3 (100)	2 (67)	7 (78)
No	n (%)	1 (33)	0	1 (33)	2 (22)
Missing	n (%)	0	0	0	0
Number of apheresis to reach 2 x10^6 CD34+ cells/kg	N	2	3	2	7
1	n (%)	2 (100)	3 (100)	1 (50)	6 (86)
2	n (%)	0	0	1 (50)	1 (14)
3	n (%)	0	0	0	0
4	n (%)	0	0	0	0
Total CD34+ yield	N	3	3	3	9
	Mean (SD)	9.51 (9.30)	8.40 (6.84)	19.94 (20.81)	12.62 (13.11)
	Median	8.94	4.95	15.14	8.94
	Min	0.52	3.97	1.95	0.52
	Max	19.08	16.28	42.73	42.73

Note: Central laboratory data has been used. However, when central lab value is missing, local value is used.
Names of input datasets: CRT.COMVAR, CRT.LB_ LOCAL_MD1, CRT.LB_LOCAL_MD_3, EXTERNAL.LB_ CD34_C and EXTERNAL.PB_APH_CD34_T
Output: T-PB-APH-CD34.rtf
Program name: Global-Biostats\Plerixafor\Transplant\MOZ15609\Stage1\Programs\Output\T-PB-APH-CD34.sas
Creation date of output 14.2.2.2.1: 27JAN2013 9:56

Stage 2 data

The Applicant has further analysed the effect of age on mobilisation using data collected in stage 2 of the study; these data indicate that despite lower exposure to plerixafor patients of the low age categories do not seem, in general, to behave differently than these of the oldest age category.

2.4.4. PK/PD

In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg based and fixed (20 mg) doses, a trial was conducted in adult patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor. The trial was conducted in patients weighing 70 kg or less (median: 63.7 kg , min: 34.2 kg, max: 70 kg). The fixed 20 mg dose showed 1.43-fold higher exposure ($AUC_{0\text{-}10h}$) than the 0.24 mg/kg dose. The fixed 20 mg dose also showed numerically higher response rate (estimated difference between treatment arms was 5.2% [60.0% vs 54.8%] based on the local lab data and 11.7% [63.3% vs 51.6%] based on the central lab data) in attaining the target of ≥ 5 × 10^6 CD34+ cells/kg than the mg/kg-based dose. The median time to reach ≥ 5 × 10^6 CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Body weight of 83 kg was selected as the cut-off point to transition patients from fixed to weight based dosing (83 kg x 0.24 mg = 19.92 mg/kg).

Table 7 Systemic Exposure ($AUC_{0\text{-}10h}$) comparisons of fixed and weight based regimens

Regimen	Geometric Mean AUC
Fixed 20 mg (n=30)	3991.2
0.24 mg/kg (n=31)	2792.7
Ratio (90% CI)	1.43 (1.32,1.54)

2.4.5. Discussion on clinical pharmacology

In both adults and children HSCT rescue is being used for patients suffering from a malignancy requiring HDC. However, the underlying malignancies require HDC varies between the adult and paediatric population. In adults the two commonest diseases treated by HDC followed by HSCT are multiple myeloma and lymphoma. In children the commonest reason for HDT and HSCT is treatment of a solid tumour. As a consequence, the chemotherapy regimen is likely to be different between adults and children, both the chemotherapy administered before HSC collection as the HDC regimes for which HCS rescue is needed. These differences may affect the subjects response to mobilisation regimen as well as the marrow recovery and ability for HCS engraftment. However none of these differences would be expected to affect the mode of action of Mozobil, i.e. CXCR4/ SDF-1α interactions and therefore the ability of Mozobil to mobilise stem cells. Thus the mechanism of action of Mozobil is presumed to be the same in children as in adults.

Limited data on CXCR4 expression in children or adolescents is available. Results of Shalekoff (Shalekoff et al. 2004, Clin Diagn Lab Immun), showed that expression of CXCR4 on peripheral blood leukocytes in very young children is well below adult levels, but from the age of 15 months onwards, it approached adult levels. Based on the available data, it is noted that currently, only in the very young children, there is uncertainty regarding the comparability in CXCR4 expression levels with that of the rest of the population.

The immune system is for some specifications different in adults and children, for example in the numbers of percentage of different white blood cells. These immune differences are most pronounced in paediatric patients under the age of 2. In neonates greater numbers of circulating CD34+ stem cells are seen. Therefore, in principle a lower exposure to Mozobil might be sufficient in the lower age group for reaching the target amount of CD34+ cells needed for HSCT ($2x10^6$/kg). Whether this is the case, needs to be determined by a dose finding study stratified by age.

In conclusion, although there are differences in disease treated and HDC regimens used between paediatric and adult populations, the need for HSCT rescue following HDC and thus need for stem cell mobilisation to collect sufficient numbers of HSC is the same between adult and paediatric population. As the mechanism of action of Mozobil and the expression of CXCR4 and SDF-1 is similar in children as in adults a similar response in children as in adults is to be expected. However, the doses needed to obtain this response might be different.

The pharmacokinetics of plerixafor were evaluated in 48 paediatric patients (1 to less than 18 years) with solid tumours at subcutaneous doses of 0.16, 0.24 and 0.32 mg/kg with standard mobilisation (G-CSF plus or minus chemotherapy). Based on population pharmacokinetic modeling and similar to adults, µg/kg-based dosage results in increase in plerixafor exposure with increasing body weight in paediatric patients. At the same weight-based dosing regimen of 240 µg/kg, the plerixafor mean exposure (AUC_{0-24h}) is lower in paediatric patients aged 2 to < 6 years (1410 ng.h/mL), 6 to <12 years (2318 ng.h/mL), and 12 to <18 years (2981 ng.h/mL) than in adults (4337 ng.h/mL). However, mobilization of PB CD34+ count was observed in stage 2 of the trial.

In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg based and fixed (20 mg) doses, a trial was conducted in adult patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor weighing 70 kg or less. The fixed 20 mg dose showed 1.43-fold higher exposure (AUC_{0-10h}) than the 0.24 mg/kg dose and numerically higher response rate in attaining the target cells/kg than the mg/kg-based dose with the same median time to target cells/kg (3 days) for both treatment groups, and similar safety profile between the groups. An age related effect on the pharmacokinetics of plerixafor is noted consisting of an increase in clearance and decrease of

exposure for the younger patients. This observation and the population pharmacokinetic analyses indicate that plerixafor exposure decreases with decreased age/body weight.

The full study modelling was performed according to the guideline on Reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06) and included Visual Predictive Checks (VPC) stratified on age, VPCs stratified on weight- and prediction-corrected VPCs, ETA's versus weight and age. The plots allow for a good comparison of data. It clearly confirms the previous conclusions of a weight effect, and possible age effect, on the pharmacokinetics of plerixafor. Although there is an (expected) high correlation of age and weight in the study population, the conclusion can be drawn that exposure following weight-based dosing increased with weight as well as age.

Findings from the observed data, and from the simulated data, confirm the expectation that exposure at the dose of 320 µg/kg in paediatric patients is more in line with the exposure in adults at 240 µg/kg than the paediatric dose of 240 µg/kg.

These results have been reflected in the SmPC section 5.2.

2.4.6. Conclusions on clinical pharmacology

Plerixafor exposure decreases with decreased age/body weight, but this lower exposure does not seem to affect the response to plerixafor containing mobilisation. The markedly lower exposure in the paediatric population is reflected in the SmPC. Exposure in different age groups for the 320 µg/kg dose is provided to allow the treating physician to decide on potentially increasing the dose if deemed necessary.

2.5. Clinical efficacy

The clinical paediatric study DFI12860 (MOZ15609) consisted of an initial dose escalation study (Stage 1) followed by a randomized, comparative study extension (Stage 2) at the dose identified as most appropriate in the dose escalation part of the study. Stage 2 compared plerixafor administered in combination with standard mobilization, to standard mobilization alone.

Overall, this development program included 72 paediatric patients aged 1 to <18 years with 57 patients treated with plerixafor plus standard mobilization (27 in Stage 1 and 30 Stage 2) and 15 treated with standard mobilization alone (Stage 2).

The evaluation of efficacy is focussed on the data collected within study DFI12860, in particular stage 2 of this study.

2.5.1. Dose response study: DFI12860 Stage 1

The primary objective was to determine the age appropriate dose and to characterize the safety, pharmacokinetics, and pharmacodynamics of plerixafor when given in addition to standard mobilization regimens in paediatric patients (aged 2 to <18 years) with Ewing's sarcoma/soft tissue sarcoma, neuroblastoma, brain tumours, and other malignancies, who were planned to undergo high dose chemotherapy, followed by autologous HSCT. Patients with any form of leukaemia were excluded because of the concerns about potential tumour cell mobilization and subsequent contamination of apheresis product. Similar inclusion and exclusion criteria were applied as in Stage 2 of the study (see below), except that Stage 1 included patients age 2 to <18 years and Stage 2 included patients age 1 to <18 years.

The primary objective of Stage 1 of this study was to determine the appropriate dose, and to characterize the safety, pharmacokinetics and pharmacodynamics of plerixafor across age and size in paediatric cancer patients when given in addition to standard mobilization of HSCs into peripheral blood.

Dose per age cohort was determined using a standard three plus three dose parallel escalation strategy where three patients would be enrolled in a cohort by age group and dose. Three plerixafor dose levels were evaluated: 160 µg/kg, 240 µg/kg, and 320 µg/kg (see Table 6).

The decision whether to expand a particular age-dose cohort to 6 patients or to treat the next cohort of 3 patients at the next dose-level (240 µg/kg and 320 µg/kg, respectively) was based on the occurrence of dose-limiting toxicity (DLT). DLTs were defined as non-hematological AEs of toxicity Grade 3 or higher according to National Cancer Institute (NCI) criteria that was considered by the Investigator to be definitely related or at least possibly related to plerixafor.

Table 8. Age group versus dose

Dose levels per cohort					
2 to <6 years		6 to <12 years		12 to <18 years	
400 µg/kg		400 µg/kg		400 µg/kg	
320 µg/kg	n=3	320 µg/kg	n=3	320 µg/kg	n=3
240 µg/kg	n=3	240 µg/kg	n=3	240 µg/kg	n=3
160 µg/kg	n=3	160 µg/kg	n=3	160 µg/kg	n=3

Patients were to begin treatment with standard mobilization (GCSF ± chemotherapy), and peripheral blood CD34+ counts were to be monitored daily until a "trigger point" minimum of 7 PB CD34+ cells/µL was reached. Once the required threshold for PB CD34+was met, patients were to receive their first dose of plerixafor the same day in the evening, and were to begin apheresis the next day (approximately one hour after administration of G-CSF, 8 to 12 hours after administration of plerixafor). If necessary, treatment with plerixafor and G-CSF was to be continued according to the same schedule until a yield of at least $2x10^6$ CD34+ cells/kg was reached, or for a maximum of 5 aphereses (see Figure 12).

For all patients, venous blood samples for peripheral blood CD34+ fluorescence-activated cell sorting (FACS) analysis were taken on the morning of the day preceding the first apheresis day and in the morning prior to administration of the once daily G-CSF dose on the apheresis day itself. For all patients, on each subsequent day of apheresis (up to a maximum of 5 aphereses) samples for FACS analysis were collected immediately prior to the dose of G-CSF on the morning of apheresis.

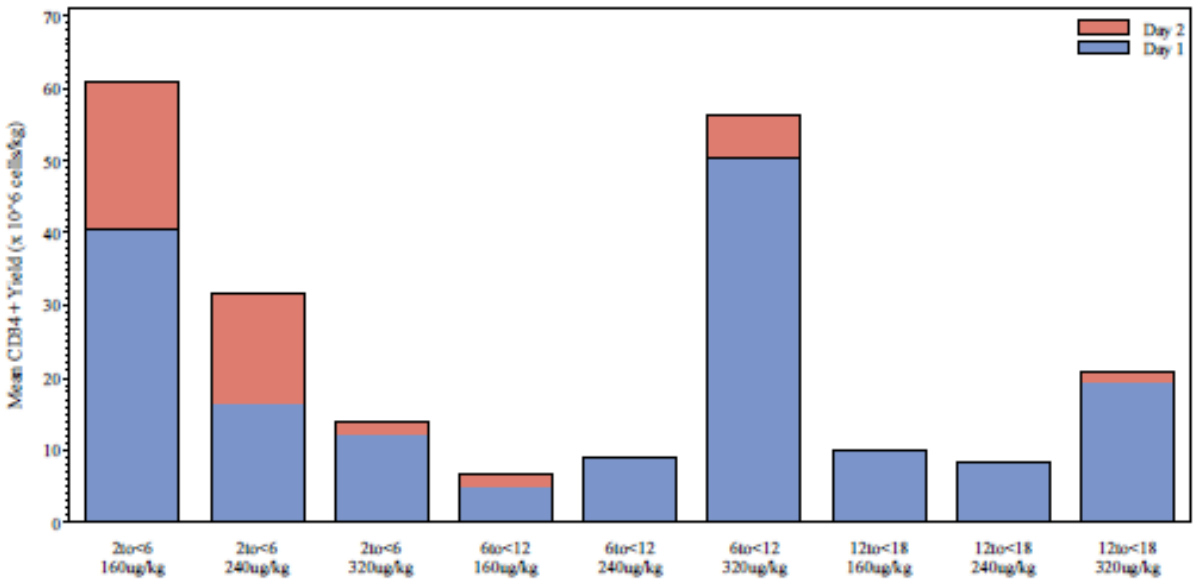


Figure 9 CD34+ yield per day in the safety set, analyzed by age cohort and dose group.

23 of 27 patients demonstrated mobilization sufficient for transplantation.

Based on the per cohort dose escalation PK and PD data, the dose proposed for use in Stage 2 will be 240 µg/kg which is the same as that approved for use in adults.

The dose escalation part of the PIP study DFI12860 (MOZ15609) (Stage 1) was completed in 2013. After discussion between the Sponsor and the EMA Paediatric Committee (PDCO), the plerixafor treatment regimen selected for Stage 2 was the same as that used in adults, 240 µg/kg the evening prior to apheresis approximately 8 to 12 hours later. The resulting protocol proposal for Stage 2 was agreed with EMA/Pediatric Committee (PDCO) further to a PIP RfM (EMA Decision dated 29 October 2013).

2.5.2. Main study: DFI12860 Stage 2

Title of Study: A Phase 1/2 Combined Dose Ranging and Randomized, Open-label, Comparative Study of the Efficacy and Safety of Plerixafor in Addition to Standard Regimens for Mobilization of Hematopoietic Stem Cells into Peripheral Blood, and Subsequent Collection by Apheresis, Versus Standard Mobilization Regimens Alone in Pediatric Patients, Aged 1 to <18 Years, with Solid Tumors Eligible for Autologous Transplants (DFI12860/MOZ15609 or MOZAIC).

Methods

A study diagram of Stage 2 is provided in Figure 11

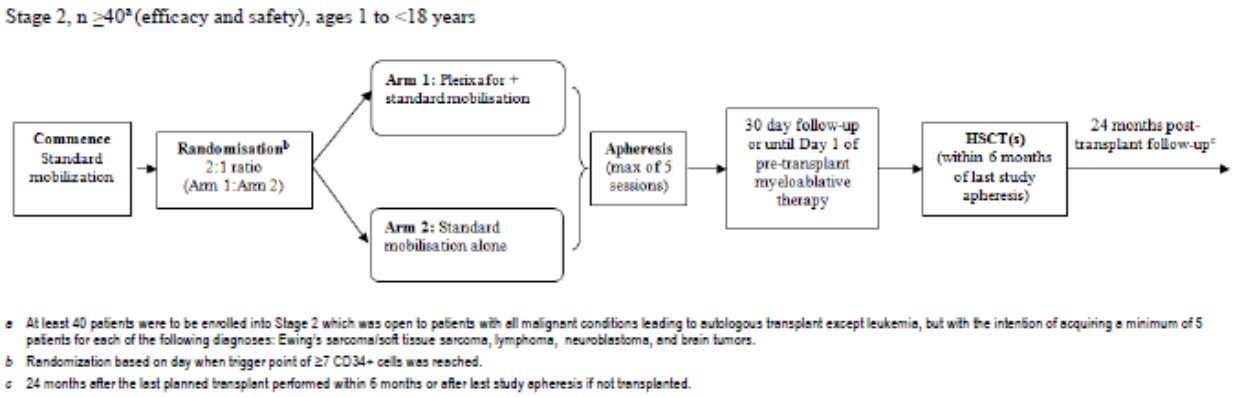


Figure 10 Schematic diagram of Stage 2 study design

Study participants

This study was conducted at 25 active study centres in Israel and 11 European countries: Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, and United Kingdom.

Adequate harvesting techniques were not yet available for children <2year of age during Stage 1; therefore, paediatric patients in this age range were not included.

In order to maximize study sample representativeness, the following tumour groups were included for analysis: Ewing's sarcoma/soft tissue sarcoma, lymphoma, neuroblastoma, and other malignancies including brain tumours. Leukaemia was excluded as the clinical significance and risks of potential tumour cell mobilization and re-infusion had not yet been determined.

Inclusion criteria were:

- Stage 2: Age 1 to <18 years (Note: for children aged between 1 and 2 years, owing to the technical limitations for apheresis in this population, sites should have contacted the Sponsor to ensure optimization of risk to benefit of the procedure).
- Ewing's sarcoma, soft tissue sarcoma, lymphoma, neuroblastoma, or other malignancy including brain tumours (excluding any form of leukaemia) requiring treatment with high dose chemotherapy and autologous transplant as rescue therapy.
- Eligible for autologous transplantation.
- Recovered from all acute significant toxic effects of prior chemotherapy.
- Adequate performance status.
    - for patients ≥16 years of age, defined as Karnofsky score >60
    - for patients <16 years of age, defined as Lansky score >60

  Adequate Laboratory functions
- Absolute neutrophil count >0.75 x 10^9/L
- Platelet count >50 x 10^9/L
- Calculated creatinine clearance (using the Schwartz method), >60 mL/min/1.73 m^2
- Liver functions <3 x upper limit of normal
    - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT),
    - Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), and
    - Total bilirubin
- The patient and/or their parent/legal guardian was willing and able to provide signed informed consent.
- Patients who were sexually active must be willing to abstain from sexual intercourse or agree to use an approved form of contraception while receiving plerixafor and/or standard mobilization treatment and for at least 3 months following any plerixafor treatment.

Exclusion criteria were:

- Any form of leukaemia.
- A co-morbid condition, such as ventricular arrhythmias, which, in the view of the Investigator, rendered the patient at high-risk from treatment complications.
- Previous stem cell transplantation.
- Patients with persistent high percentage marrow involvement prior to mobilization were prohibited (Specific guidelines for different indications are provided in 16-1-1-amendment1 with details of bone marrow examination requirements at Screening).
- Ongoing toxicities (excluding alopecia) Grade ≥2 resulting from prior chemotherapy.
- Acute infection.
- Fever (temperature >38.5°C) - if fever was between 37°C and 38.5°C, infection must be excluded as a cause.
- Known HIV seropositivity, AIDS, hepatitis C or active hepatitis B infections.
- Positive pregnancy test in post pubertal girls.
- History of clinically significant cardiac abnormality or arrhythmia.
- Use of an investigational drug which was not approved in any indication either in adults or paediatrics within 2 weeks prior to the first dose of G-CSF was to be administered as part of the patient's planned standard mobilization regimen, and/or during the study up until engraftment of the transplant. If patients were on investigational drugs as part of their anticancer regimen, this should have been discussed with the Sponsor before screening. Drugs approved for other indications that were being used in a manner considered standard of care for this transplant procedure are allowed.
- The patient (and/or their parent/legal guardian), in the opinion of the Investigator, was unable to adhere to the requirements of the study.

Treatments

Subjects started on a standard mobilization (G-CSF ± chemotherapy as per site standard practice). The dose of once daily G-CSF was to be 10 µg/kg (which could be increased up to a maximum of 15 µg/kg in poor mobilizers). When the trigger point minimum of 7 CD34+ cells/µL in peripheral blood (measured locally) was achieved, patients were randomized 2:1 to either receive either plerixafor at a dose of 240 µg/kg daily starting on the same day in the evening plus standard mobilization or standard mobilization alone.

Plerixafor was to be administered as a SC injection at a separate anatomical site from the patient's standard mobilization treatment. In exceptional circumstances (eg, significant thrombocytopenia), plerixafor may have been administered via the intravenous (IV) route, but only with prior authorization from the Sponsor. The patients were to begin apheresis the next day (approximately one hour after administration of G-CSF, 8 to 12 hours after administration of plerixafor). If necessary, treatment with plerixafor and G-CSF was to be continued according to the same schedule until a yield of at least $2x10^6$ CD34+ cells/kg was reached, or for a maximum of 5 aphereses (see Figure 12).

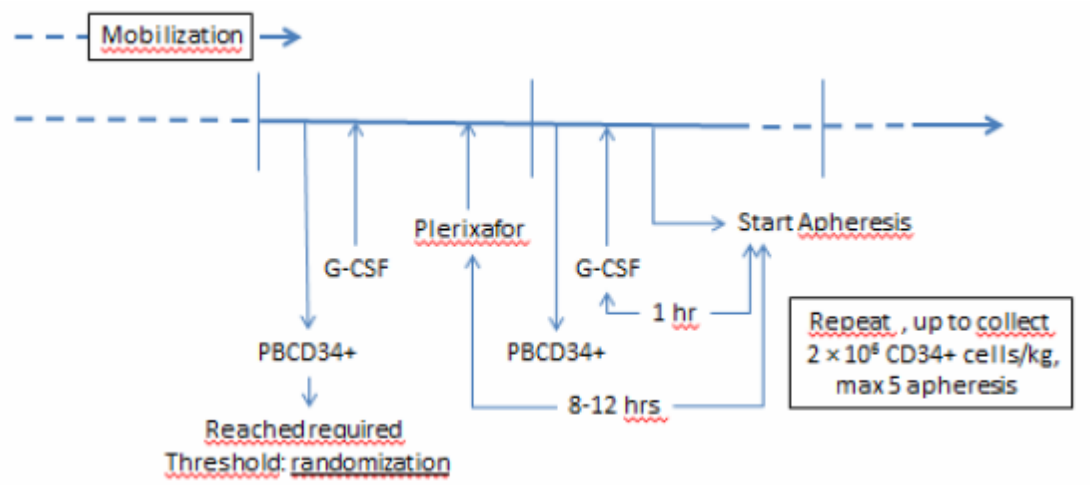


Figure 11 Schematic time schedule for administration of G-CSF, plerixafor, and apheresis, and respective time for measurement of CD34+ cells in peripheral blood

Apheresis was to occur if the PB CD34+ count, on the scheduled day of apheresis was ≥20 cells/ μL. Stem cell collection was to take place using standard procedures and, wherever possible, employing a 3 blood volume (±25%) apheresis.

Prior and concomitant therapy

Concomitant medications were not required to be recorded on the eCRF with the exception of medications that were administered to treat AEs and/or SAEs recorded during the study. Hematologic growth factors and blood products were to be recorded on the appropriate eCRF pages.

A study diagram of Stage 2 is provided in Figure 13.

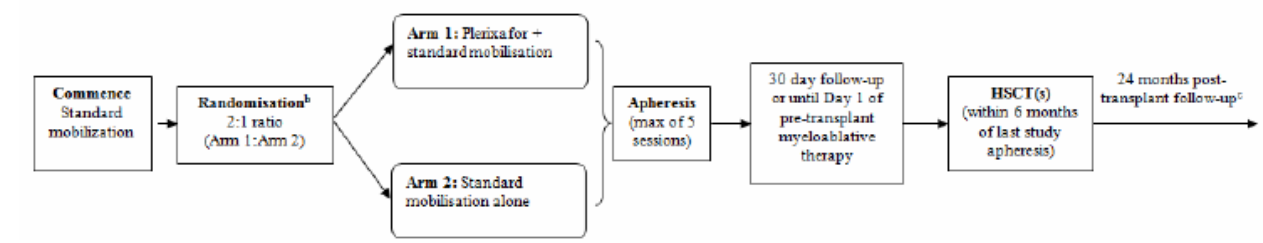


Figure 12 Schematic diagram of stage 2 study design

Objectives

The primary endpoint in Stage 2 was the difference between the 2 treatment arms in the proportion of patients achieving at least a doubling of peripheral blood CD34+ count from the morning of the day preceding the apheresis day to the morning of the apheresis day.

The secondary objectives of Stage 2 of this study were to confirm the efficacy and safety of plerixafor in paediatric cancer patients, and to compare the efficacy between the 2 treatment arms by examining the degree and rate of change of PB CD34+ counts, number of CD34+ cells collected by apheresis, percentage of patients proceeding to transplant, and percentage of transplanted patients with durable engraftment at 3, 6, 12 and 24 months post-transplantation.

Outcomes / endpoints

The primary efficacy endpoint was successful mobilization, defined as at least a doubling of the PB CD34+ count observed from the morning of the day preceding the first planned apheresis day to the morning prior to apheresis.

The secondary efficacy variables in Stage 2 were comparisons between the 2 treatment arms in:

- Number of days of apheresis required to reach $\geq 2 \times 10^6$ CD34+ cells/kg
- CD34+ yield for each apheresis
- Total CD34+ yield
- Percentage of patients proceeding to transplant
- Percentage of patients successfully engrafting
- Percentage of patients with durable engraftment at 3, 6, 12 and 24 months post-transplant.

Variables for exploratory endpoints in Stage 2 included:

- CD34+ count transplanted (infused)
- Percentage of patients with 2-fold increase in peripheral blood CD34+ AND reaching the study site-specific threshold level required to initiate apheresis
- Increase in peripheral blood CD34+ counts
- Total blood volume processed
- Time to neutrophil engraftment (in days)
- Time to platelet engraftment (in days).

No statistical testing was planned for the secondary efficacy endpoints. For every continuous secondary endpoint, a descriptive summary including mean, median, SD, minimum, and maximum, is provided.

The safety of patients was assessed via monitoring of AEs, laboratory safety parameters, disease recurrence or progression, graft status (delayed engraftment or failure), tumour cell mobilization, secondary malignancies, survival status, hospitalization, incidence of fever and infections, and other safety parameters including physical examination and vital signs.

The duration of follow-up for safety evaluation was dependent on mobilization treatment and transplant status. All patients who underwent transplant(s) within 6 months after last study apheresis were to be evaluated for up to 24 months after the last transplant; otherwise patients were to be evaluated for up to 24 months after last dose of study mobilization treatment (see also Figure 13).

CD34+ cell counts

Peripheral blood samples were to be analysed for CD34+ cell content by both local and central laboratories. Local laboratories provided data for clinical decisions during treatment. Central laboratory data were used in the primary analyses of efficacy. Data from the local laboratory were used for supportive analysis. The PB CD34+ counts measured each day and the absolute increase in PB CD34+ counts on the apheresis day from the day prior were summarized descriptively for each arm and by apheresis day.

The product volume and the absolute number of CD34+ cells per unit volume were calculated. The total yield of CD34+ cells/kg was recorded prior to cryopreservation, and also after thawing, prior to infusion. The cumulative total CD34+ cells/kg yield was calculated by summing the CD34+ yield from each apheresis.

Engraftment

Data to determine engraftment included ANC and platelet count. The dates of engraftment were defined as below:

- Date of Neutrophil Engraftment: defined as the first day when the ANC was $\geq 0.5 \times 10^9$/L for 3 consecutive laboratory values on 3 different days, or $\geq 1.0 \times 10^9$/L for 1 day.
- Date of Platelet Engraftment: defined as the first day when the platelet count was $\geq 20 \times 10^9$/L measured by at least 3 consecutive platelet laboratory values obtained over at least 7 days that show that level was achieved and maintained. The patient should not have had any platelet transfusions in the 7 days prior to the date selected for achieving $\geq 20 \times 10^9$/L, and the date should have been the first of 3 consecutive laboratory values tested on different days.

Sample size

The sample size was determined by the ability to recruit patients to the study, based on known numbers of autologous transplants carried out in paediatric cancer patients, diagnoses to be included in this study, and limiting participation to larger sites that have capability to achieve sufficient patient numbers within a reasonable amount of time. No formal statistics-based sample size calculations were performed.

The full analysis set (FAS) comprised all patients randomized in Stage 2 according to the intent-to-treat principle.

The per-protocol set (PP) was a subset of the full analysis set excluding patients who have major protocol deviations that significantly affect the assessment of efficacy.

Also an Exploratory full analysis set was defined including patients treated with plerixafor in Stage 2 and 9 patients treated at the 240 µg/kg dose level in Stage 1.

Randomisation

Patients were allocated to treatment using an automated interactive response system. At least 40 patients in total were to be randomized.

Blinding (masking)

This was an open-label study, so no blinding was needed. No formal statistics-based sample size calculations were performed.

Statistical methods

The sample size was determined by the ability to recruit patients to the study, based on known numbers of autologous transplants carried out in paediatric cancer patients, diagnoses to be included in this study, and limiting participation to larger sites that have capability to achieve sufficient patient numbers within a reasonable amount of time. No formal statistics-based sample size calculations were performed.

The randomized population was to include any patient enrolled in Stage 2 of the study who had been allocated to a randomized treatment regardless of whether the treatment kit was used.

Results

Participant disposition for stage 2

Forty- five (45) patients were randomized in Stage 2, 30 to receive plerixafor plus standard mobilization and 15 to receive standard mobilization alone.

The majority of patients (35/45, 77.8%) completed the study period. Ten (10) patients discontinued the study prematurely (i.e. prior to completing the 24 month follow-up visit).

Table 9 Patient disposition

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)	All (N=45)
Enrolled population in stage 2	15	30	45
Randomized but not treated	0	0	0
By tumor type			
Sarcoma	4 (26.7%)	8 (26.7%)	12 (26.7%)
Lymphoma	1 (6.7%)	2 (6.7%)	3 (6.7%)
Neuroblastoma	7 (46.7%)	14 (46.7%)	21 (46.7%)
Other	3 (20.0%)	6 (20.0%)	9 (20.0%)
By age group			
1 to <6 years	10 (66.7%)	16 (53.3%)	26 (57.8%)

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)	All (N=45)
6 to <12 years	3 (20.0%)	9 (30.0%)	12 (26.7%)
12 to <18 years	2 (13.3%)	5 (16.7%)	7 (15.6%)
Did not complete study period	5 (33.3%)	5 (16.7%)	10 (22.2%)
Reason for study discontinuation			
Adverse Event	0	0	0
Progressive Disease	1 (6.7%)	0	1 (2.2%)
Physician Decision	0	0	0
Lack Of Efficacy	0	0	0
Death	3 (20.0%)	3 (10.0%)	6 (13.3%)
Other	0	1 (3.3%)	1 (2.2%)
Lost to follow up[a]	0	0	0
Subject's request	1 (6.7%)	1 (3.3%)	2 (4.4%)
Status at last study contact			
Alive	10 (66.7%)	25 (83.3%)	35 (77.8%)
Dead	4 (26.7%)	3 (10.0%)	7 (15.6%)
Unknown	1 (6.7%)	2 (6.7%)	3 (6.7%)
Lost to follow up[a]	0	0	0

a A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit.

Note: Percentages are calculated using the number of patients randomized as denominator.

The status of patients 362002, 922001 and 132005 are unknown at last study contact, because they terminated the study before being transplanted.

PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/dis_dispo_stg2_r_t.sas OUT=REPORT/OUTPUT/dis_dispo_stg2_r_t_x.rtf (07AUG2017 - 15:03)

Recruitment

In Stage 2 45 subjects were enrolled. Patients were enrolled in 12 countries (Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, and United Kingdom and Israel) in a total of 25 study centres.

Conduct of the study

There was 1 critical deviation impacting efficacy analysis. This deviation involved Patient 222008 in the standard mobilization arm, for whom both central and local laboratory PB CD34+ data from baseline were missing. It was therefore impossible to include this patient in the primary efficacy endpoint analysis.

Other major deviations included:

- 2 patients who were randomized before reaching the protocol defined trigger point of 7 CD34+ cells/μL, both in the standard mobilization arm.
- 2 patients were reported to have persistent high percentage marrow involvement prior to mobilization, one in each arm. Both patients were included in the analysis.

Baseline data

Table 10 Summary of demographic and baseline characteristics by age group in Stage 2 - Full Analysis Set

	Age 1 to <6 years			Age 6 to <12 years			Age 12 to <18 years		
	Standard Mobilization Alone	Plerixafor + Standard Mobilization	All	Standard Mobilization Alone	Plerixafor + Standard Mobilization	All	Standard Mobilization Alone	Plerixafor + Standard Mobilization	All
N	10	16	26	3	9	12	2	5	7
Gender									
Male	4 (26.7%)	9 (30.0%)	13 (28.9%)	2 (13.3%)	6 (20.0%)	8 (17.8%)	1 (6.7%)	4 (13.3%)	5 (11.1%)
Female	6 (40.0%)	7 (23.3%)	13 (28.9%)	1 (6.7%)	3 (10.0%)	4 (8.9%)	1 (6.7%)	1 (3.3%)	2 (4.4%)
Race									
Caucasian/White	9 (60.0%)	16 (53.3%)	25 (55.6%)	3 (20.0%)	8 (26.7%)	11 (24.4%)	2 (13.3%)	5 (16.7%)	7 (15.6%)
Not Reported	1 (6.7%)	0	1 (2.2%)	0	1 (3.3%)	1 (2.2%)	0	0	0
Ethnicity									
Hispanic or Latino	1 (6.7%)	1 (3.3%)	2 (4.4%)	0	1 (3.3%)	1 (2.2%)	0	2 (6.7%)	2 (4.4%)
Not Hispanic or Latino	8 (53.3%)	15 (50.0%)	23 (51.1%)	3 (20.0%)	7 (23.3%)	10 (22.2%)	2 (13.3%)	3 (10.0%)	5 (11.1%)
Not Reported	1 (6.7%)	0	1 (2.2%)	0	1 (3.3%)	1 (2.2%)	0	0	0
Tumor Type									
Lymphoma	1 (6.7%)	0	1 (2.2%)	0	0	0	0	2 (6.7%)	2 (4.4%)
Neuroblastoma	6 (40.0%)	12 (40.0%)	18 (40.0%)	1 (6.7%)	2 (6.7%)	3 (6.7%)	0	0	0
Sarcoma	0	0	0	2 (13.3%)	6 (20.0%)	8 (17.8%)	2 (13.3%)	2 (6.7%)	4 (8.9%)
Other	3 (20.0%)	4 (13.3%)	7 (15.6%)	0	1 (3.3%)	1 (2.2%)	0	1 (3.3%)	1 (2.2%)

Note: All percent values are based on the total number of patients in each treatment group.
Source: Study DFI12860 final CSR Table 9, Table 10, and Table 11

Table 11 Number (%) of patients with baseline PB CD 34+ count (cells/μL) less than 10, 15, or 20 (as measured on the day prior to the day of apheresis)

Laboratory measurement	Standard Mobilization Alone N=15	Plerixafor + Standard Mobilization N= 30
Local laboratory measurement		
<10	2 (13.3%)	9 (30.0%)
<15	3 (20.0%)	13 (43.3%)
<20	4 (26.7%)	21 (70.0%)
Central laboratory measurement		
<10	3 (20.0%)	4 (13.3%)
<15	4 (26.7%)	14 (46.7%)
<20	4 (26.7%)	17 (56.7%)

Note: Patients may be counted in more than 1 category.
Source: Study DFI12860 final CSR Appendix dfi12860-16-2-6 [Table 16.2.6.37].

Using the definition of poor mobilizers as those patients with <20 cells/μL PB CD34+ cells on the day prior to the first apheresis, 21 of 30 patients (70.0%) in the plerixafor plus standard mobilization arm were poor mobilizers versus 5 of 15 patients (33.3%) in the standard mobilization alone arm.

Using the definition of poor mobilizers as those patients with <15 cells/μL PB CD34+ cells on the day prior to the first apheresis, 13 of 30 patients (43.3%) in the plerixafor plus standard mobilization arm were poor mobilizers versus 3 of 15 patients (20.0%) in the standard mobilization alone arm.

Also the median PB CD34+ count at baseline for patients in the plerixafor plus standard mobilization group were substantially lower than the median of PB CD34+ count for patients in the standard mobilization alone group (15 × 10^6 cells/L versus 35 × 10^6 cells/L).

Exposure

Patients in the plerixafor plus standard mobilization arm received a median of 1.00 dose administration of plerixafor (range: 1.0 – 3.0). Median total plerixafor dose level administered (per kg body weight) was 240.0 μg/kg (range: 234.0 - 720.0 μg/kg). During Stage 2, 27 of 30 patients from the plerixafor arm received a single dose of plerixafor. Of the 3 remaining patients, 2 patients (Wilm's tumor, neuroblastoma) received 2 doses of plerixafor and one patient (Ewing's sarcoma) received 3 doses of plerixafor.

In Stage 2, median total G-CSF exposure (per kg body weight) was slightly lower in the plerixafor plus standard mobilization arm than in the standard mobilization alone arm (89.59 µg/kg versus 97.60 µg/kg)

The percentage of patients who received chemotherapy as part of the standard mobilization regimen was lower in the plerixafor plus standard mobilization arm (23.3%) than in the standard mobilization alone arm (33.3%).

Numbers analysed

Forty- five (45) patients were randomized in Stage 2, 30 to receive plerixafor plus standard mobilization and 15 to receive standard mobilization alone.

Table 12 Population analysis sets

	Number of Patients					
	Standard Mobilization Alone		Plerixafor + Standard Mobilization		All	
Randomized population in stage 2	15	(100%)	30	(100%)	45	(100%)
Efficacy populations						
Full analysis set	15	(100%)	30	(100%)	45	(100%)
Exploratory full analysis set	15	(100%)	39	(130%)	54	(120%)
Per-protocol set	13	(86.7%)	30	(100%)	43	(95.6%)
Safety Set*	15		57		72	
Stage 1	0		27		27	
Stage 2	15		30		45	

PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/dis_populations_a_t.sas
OUT=REPORT/OUTPUT/dis_populations_a_t_x.rtf (28JUN2017 - 18:30)

* The safety population patients are tabulated according to treatment actually received (as treated). For the other populations, patients are tabulated according to their randomized treatment.

"Safety set" refers to the combination of "Safety Set for Stage 2" and "Overall Safety Set".

Note: Exploratory full analysis set Includes 30 patients treated with plerixafor in Stage 2 and 9 patients treated at the 240 µg/kg dose level in Stage 1.

Note: Two patients were excluded from the Standard Mobilization Alone Per-Protocol Set (see Section 9.2)

Outcomes and estimation

Efficacy analysis was performed on the Full Analysis Set (FAS) population.

The primary efficacy endpoint was successful mobilization: The proportion of patients with successful mobilization was significantly greater in the plerixafor plus standard mobilization arm (80%, 24 of 30 patients) compared to the standard mobilization only arm (28.6%, 4 of 14 patients) (p=0.0019) (see Table 11). Supportive analysis using local laboratory data showed successful mobilization in 27of 30 patients (90%) in the plerixafor plus standard mobilization arm compared to 4 of 14 patients (28.6%)in the standard mobilization alone arm (p <0.0001)

The rate of successful mobilization was similar across age and disease categories in the plerixafor plus standard mobilisation arm.

Table 13 Summary of primary endpoint (FAS)

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Primary analysis [a]		
Successful mobilization [b] [n/N_1(%), 95% CI]	4/14 (28.6%)	24/30 (80.0%)
	[8.4%, 58.1%]	[61.4%, 92.3%]
Difference of proportion of successful mobilization [c]	NA	51.4
95% CI		[18.5%, 84.3%]
P-value [d]		0.0019
Supportive analysis [a]		
Successful mobilization [b] [n/N_1(%), 95% CI]	4/14 (28.6%)	27/30 (90.0%)
	[8.4%, 58.1%]	[73.5%, 97.9%]
Difference of proportion of successful mobilization [c]	NA	61.4
95% CI		[30.2%, 92.7%]
P-value [d]		<0.0001

a Data for the primary analysis is from central lab, supportive from local lab. In case of missing data from the central laboratory, the corresponding local laboratory result will be used for primary analysis; in case of missing data from the local laboratory, the corresponding central laboratory result will be used for the supportive analysis.

b Successful mobilization is achieved when at least a doubling of the PB CD34+ count is observed from the morning of the day preceding the first planned apheresis day to the morning prior to apheresis. The 95% CIs are calculated with exact method.

c The difference of proportion of successful mobilization is relative to standard mobilization alone treatment arm. The CI of the difference is based on the Wald asymptotic CI with continuity correction method.

d The p-value is based on the Fisher's exact test comparing the proportion of successful mobilization between the 2 treatment arms.

n=Number of patients who successfully mobilized

N_1= Number of patients excluding patients having both local and central laboratory missing records

Note: N_1 is less than N if both local and central lab records are missing, otherwise N_1 and N are the same

PGM=PRODOPS/GZ316455/MOZ15609/CSR 2017/REPORT/PGM/eff mob 1.sas OUT=REPORT/OUTPUT/eff mob f 1 x.rtf (28JUN2017 - 18:35)

In the pivotal registration study of mozobil for adults, the percentage of patients with successful mobilization was no efficacy endpoint.

Secondary efficacy endpoints

- Number of days of apheresis required to reach ≥2 x 10^6 CD34+ cells/kg

The number of patients reaching the threshold of collecting ≥2 × 10^6 CD34+ cells/kg at first apheresis was 26 of 29 (89.7%) evaluated patients in the plerixafor plus standard mobilization arm and 13 of 14 (92.9%) evaluated patients in the standard mobilization arm (see Table 12). The median number of apheresis days required to collect ≥ 2 x 10^6 CD34+ cells/kg was identical (1 day) in both treatment arms.

One patient in the standard mobilization alone group and 3 patients in the plerixafor plus standard mobilization group failed to reach 2 x 10^6 CD34+ cells/kg by central laboratory assessment. For 3 of these patients local laboratory values were >2 × 10^6/kg.

Table 14 Summary of number of days of apheresis required to collect ⩾2 x 106 CD34+ cells/kg (FAS)

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Primary analysis [a]		
Cumulative patients reaching ≥2 x 10^6 CD34+ cells/kg [b]		
Day 1	13 (92.9%)	26 (89.7%)
Day 2	13 (92.9%)	26 (89.7%)
Day 3	13 (92.9%)	26 (89.7%)
Day 4	13 (92.9%)	26 (89.7%)
Day 5	13 (92.9%)	26 (89.7%)
Median Time to Reach Target (Days) [b]	1.0	1.0
95% CI	NC, NC	NC, NC
Patients not reaching target by apheresis Day 5 [b]	1 (7.1%)	3 (10.3%)
Supportive analysis 1		
Cumulative patients reaching ≥2 x 10^6 CD34+ cells/kg [b]		
Day 1	15 (100%)	25 (83.3%)
Day 2	15 (100%)	27 (94.4%)
Day 3	15 (100%)	27 (94.4%)
Day 4	15 (100%)	27 (94.4%)
Day 5	15 (100%)	27 (94.4%)
Median Time to Reach Target (Days) [b]	1.0	1.0
95% CI	NC, NC	NC, NC
Patients not reaching target by apheresis Day 5 [b]	0	3 (10.0%)

a Data for the primary analysis is from central lab, supportive from local laboratory.

b Percentage and the median time to reach target (and its 95% CI with a log-log transformation) are estimated by Kaplan-Meier method.

PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/eff_days_cd_t.sas OUT=REPORT/OUTPUT/eff_days_cd_ef_t_x.rtf (28JUN2017 - 18:35)

- CD34+ yield for each apheresis

Table 15: Summary of CD34+ yields by apheresis for stage 2 study DFI12860

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Day 1 - Day of First Planned Apheresis		
CD 34+ Collection (10^6 cells/kg) – Primary[1]		
Number	14	29
Mean (SD)	17.57 (20.79)	19.44 (36.70)
Median	10.15	9.13
Min : Max	0.3 : 66.0	0.0 : 200.4
CD 34+ Collection (10^6 cells/kg) – Supportive[1]		
Number	15	30
Mean (SD)	17.73 (20.43)	12.34 (12.72)
Median	11.14	7.27
Min : Max	2.3 : 74.4	0.0 : 43.0
Day 2 Apheresis		
CD 34+ Collection (10^6 cells/kg) – Primary[1]		
Number	2	3
Mean (SD)	2.80 (3.30)	0.69 (1.07)
Median	2.80	0.10
Min : Max	0.5 : 5.1	0.0 : 1.9
CD 34+ Collection (10^6 cells/kg) – Supportive[1]		
Number	4	3
Mean (SD)	2.90 (0.48)	0.94 (0.72)
Median	2.71	1.27
Min : Max	2.6 : 3.6	0.1 : 1.4
Day 3 Apheresis		
CD 34+ Collection (10^6 cells/kg) – Primary[1]		
Number	0	1
Mean (SD)		0.06 (NC)
Median		0.06
Min : Max		0.1 : 0.1

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
CD 34+ Collection (10^6 cells/kg) – Supportive[1]		
Number	1	1
Mean (SD)	1.62 (NC)	0.00 (NC)
Median	1.62	0.00
Min : Max	1.6 : 1.6	0.0 : 0.0

[1] Data for primary analysis is from central laboratory and for supportive is from local laboratory.
Date of extract from clinical database: 07JUN2017.
PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/eff_cd_aph_t.sas OUT=REPORT/OUTPUT/eff_cd_aph_f_t_x.rtf (12JUL2017 - 19:30)

- Total CD34+ yield

In case of missing result from central laboratory, the local laboratory result was used.

The median total CD34+ cell yield was 10.15 × 10^6 cells/kg in the standard mobilization alone arm versus 9.13 × 10^6 cells/kg in the plerixafor arm.

The applicant states that this numerical difference in favour of the standard mobilization arm in terms of total cell yields was unexpected given the difference in mobilization (see primary endpoint). Therefore the Applicant has performed a post hoc exploratory analysis by analysing the increase of PB CD34+ count between the baseline and the next day prior to apheresis (see below).

- Percentage of patients proceeding to transplant

The percentage of patients proceeding to transplant was numerically higher in the plerixafor plus standard mobilization arm (76.7%) than in the standard mobilization alone arm (66.7%).

- Percentage of patients successfully engrafting

All patients in each treatment arm who were transplanted (10 in the standard mobilization arm, 23 in the plerixafor plus standard mobilization arm) successfully engrafted.

- Percentage of patients with durable engraftment at 3, 6, 12 and 24 months post-transplant.

Summary of durable engraftment at the 3, 6, 12 and 24 month assessments showed no consistent differences between treatment arms.

Table 16 Summary of durable engraftment (FAS of stage 2)

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Number of patients who received transplants	10	23
Percentage of durable engraftment after transplant (95% CI)[a]		
Month 3	10 (100%) [69.2% , 100.0%]	21 (91.3%) [72.0% , 98.9%]
Month 6	9 (90.0%) [55.5% , 99.7%]	20 (87.0%) [66.4% , 97.2%]
Month 12	8 (80.0%) [44.4% , 97.5%]	20 (87.0%) [66.4% , 97.2%]
Month 24	8 (80.0%) [44.4% , 97.5%]	19 (82.6%) [61.2% , 95.0%]

a CI is estimated using exact method. Percentages are based on N_t.

PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/eff_eng_t.sas OUT=REPORT/OUTPUT/eff_eng_f_t_x.rtf (12JUL2017 - 19:32)

All patients who were transplanted were successfully engrafted, for the majority of patients the engraftment was durable (more than 24 months). No difference was seen between the treatment arms.

Exploratory endpoints:

- CD34+ count transplanted (infused)

The median number of CD34+ cells infused was higher in the plerixafor plus standard mobilization arm (77.20 x 10^6 cells) than in the standard mobilization alone arm (68.18 x 10^6 cells).

- Percentage of patients with 2-fold increase in peripheral blood CD34+ AND reaching the study site-specific threshold level required to initiate apheresis

More patients in the plerixafor plus standard mobilization arm (27 of 30 patients [90%], 95% CI: 73.5% to 97.9%) achieved at least a 2-fold increase in PB CD34+ count AND reached the site-specific threshold required to initiate apheresis than in the standard mobilization alone arm (4 of 13 patients [30.8%], 95% CI: 9.1% to 65.4%).

- Increase in peripheral blood CD34+ counts

Table 17: PB CD34+ counts on the morning of the day prior to apheresis, on the morning of the day of apheresis and the relative increase in CD34+ counts.

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
(Day) Prior to First Planned Apheresis		
PB CD34 counts measured – Primary[1]		
Number	14	28
Mean (SD)	84.000 (94.473)	31.429 (56.069)
Median	35.000	15.000
Min : Max	5.00 : 300.00	1.00 : 306.00
Day 1 - Day of First Planned Apheresis		
PB CD34 counts measured – Primary[1]		
Number	14	29
Mean (SD)	139.786 (162.957)	149.448 (200.975)
Median	64.000	77.000
Min : Max	11.00 : 510.00	0.00 : 959.00
% Increase in PB CD 34+ Counts from the day prior – Primary[1]		
Number	14	27
Mean (SD)	133.353 (264.004)	496.160 (587.888)
Median	39.029	220.833
Min : Max	-19.10 : 1010.00	-100.00 : 2042.86

[1] Data for primary analysis is from central laboratory.
PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/eff_pct_inc_cd_t.sas OUT=REPORT/OUTPUT/eff_pct_inc_cd_f_t_x.rtf (04AUG2017 - 19:44)
Source: Study DFI12860 Interim CSR, Table 21

The median baseline PB CD34+ count for patients in the plerixafor plus standard mobilization arm (15.000 x 10^6 cells/L and 15.338 x 10^6 cells/L by central and local laboratory assessment, respectively) was lower than in the standard mobilization alone arm (35.000 x 10^6 cells/L and 29.000 x 10^6 cells/L by central and local laboratory assessment, respectively).

On the day of apheresis PB CD34+ counts were higher in the plerixafor plus standard mobilization arm (77.000 x 10^6 cells/L and 75.310 x 10^6 cells/L by central and local laboratory assessment, respectively) than in the standard mobilization alone arm (64.000 x 10^6 cells/L and 60.955 x 10^6 cells/L by central and local laboratory assessment, respectively)

Results of a post hoc analysis of the increase in PB CD34+ counts showed a median increase in PB CD34+ cells of 220.8% in the plerixafor plus standard mobilization arm versus a median increase of 39.0% in the standard mobilization alone arm when calculated using central laboratory values.

- Total blood volume processed

Median total volume processed was slightly lower in the plerixafor plus standard mobilization arm (3.00 L) than in the standard mobilization alone arm (3.27 L).

- Time to neutrophil engraftment (in days)

Median time to neutrophil engraftment was numerically shorter in the plerixafor plus standard mobilization arm (12 days, 95% CI: 11 to 13) versus the standard mobilization alone arm (14 days, 95% CI: 11 to 15)

- Time to platelet engraftment (in days).

Median time to platelet engraftment was numerically longer in the plerixafor plus standard mobilization arm (28 days, 95% CI: 18 to 37) versus the standard mobilization alone arm (23 days, 95% CI: 11 to 31)

Ancillary analyses

For Stage 2, the number and percentage of patients with at least a doubling of the PB CD34+ count observed from the morning of the day preceding the first apheresis day to the morning prior to apheresis were estimated by subgroups for age (1 to <6 years, 6 to <12 years, and 12 to <18 years), tumour type (Ewing's sarcoma/soft tissue sarcoma, lymphoma, neuroblastoma, and other paediatric tumours including brain tumours), and marrow involvement at baseline (yes/no) (see Table 14).

For each subgroup, the proportion of patients with at least a doubling of the PB CD34+ was numerically greater in the plerixafor plus standard mobilization arm compared to the standard mobilization alone arm based on central laboratory data, except for the subgroup of patients positive for marrow involvement in which 100% of patients (1 of 1 patient) in each arm had successful mobilization.

Table 18 **Analysis of successful mobilisation per age category opr tumour type**

Successful mobilization [n/N1(%), 95% CI][a]	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Primary analysis[b]		
Successful mobilization[a] by age group		
1 to <6 years	4/10 (40.0%) [12.2%, 73.8%]	13/16 (81.3%) [54.4%, 96.0%]
6 to <12 years	0/2 [0.0%, 84.2%]	7/9 (77.8%) [40.0%, 97.2%]
12 to <18 years	0/2 [0.0%, 84.2%]	4/5 (80.0%) [28.4%, 99.5%]
Successful mobilization[a] by tumor type		
Sarcoma	0/3 [0.0%, 70.8%]	6/8 (75.0%) [34.9%, 96.8%]
Lymphoma	0/1 [0.0%, 97.5%]	2/2 (100%) [15.8%, 100.0%]
Neuroblastoma	2/7 (28.6%) [3.7%, 71.0%]	11/14 (78.6%) [49.2%, 95.3%]
Other	2/3 (66.7%) [9.4%, 99.2%]	5/6 (83.3%) [35.9%, 99.6%]
Successful mobilization[a] by extent of marrow involvement at diagnosis and harvesting		
Negative	2/8 (25.0%) [3.2%, 65.1%]	19/25 (76.0%) [54.9%, 90.6%]
Positive	1/1 (100%) [2.5%, 100.0%]	1/1 (100%) [2.5%, 100.0%]
Supportive analysis[b]		
Successful mobilization[a] by age group		
1 to <6 years	3/10 (30.0%) [6.7%, 65.2%]	14/16 (87.5%) [61.7%, 98.4%]
6 to <12 years	1/2 (50.0%) [1.3%, 98.7%]	9/9 (100%) [66.4%, 100.0%]
12 to <18 years	0/2 [0.0%, 84.2%]	4/5 (80.0%) [28.4%, 99.5%]
Successful mobilization[0] by tumor type		
Sarcoma	0/3 [0.0%, 70.8%]	7/8 (87.5%) [47.3%, 99.7%]
Lymphoma	0/1 [0.0%, 97.5%]	2/2 (100%) [15.8%, 100.0%]
Neuroblastoma	2/7 (28.6%) [3.7%, 71.0%]	12/14 (85.7%) [57.2%, 98.2%]
Other	2/3 (66.7%)	6/6 (100%)
Successful mobilization[a] by extent of marrow involvement at diagnosis and harvesting		
Negative	3/8 (37.5%) [8.5%, 75.5%]	23/25 (92.0%) [74.0%, 99.0%]
Positive	0/1 [0.0%, 97.5%]	0/1 [0.0%, 97.5%]

a The 95% CIs are calculated with exact method. Records with missing values for factors or response were excluded from statistical analyses.
b Data for the primary analysis are from central laboratory, supportive analysis from local laboratory. In case of missing data from the central
laboratory, the corresponding local laboratory result was used for primary analysis; in case of missing data from the local laboratory, the
corresponding central laboratory result was used for the supportive analysis.
N = Number of patients who successfully mobilized in the Subgroup
N1 = Number of patients in the Subgroup excluding missing responses

Summary of main study

Table 15 summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19 Summary of Efficacy for trial

Title DFI12860/MOZ15609 or MOZAIC			
Study identifier	DFI12860		
Design	**Phase ½ combined dose ranging and randomized, open-label, comparative study of the efficacy and safety of plerixafor in addition to standard regimens for mobilization of hematopoietic stem cells into peripheral blood, and subsequent collection by apheresis, versus standard mobilization regimens alone in paediatric patients, aged 2 to <18 years, with solid tumour eligible for autologous transplants**		
	Study steps;		Standard mobilization; randomisation (2:1 plerixafor vs standard), treatment, apheresis (max of 5 sessions; 30 day follow up before day one of HDC; HSCT (within 6 months of last study apheresis); 24 months post-transplant follow up
objective	Establishing the difference between standard and plerixafor treatment in the proportion of patients achieving at least a doubling of PB CD34+ count from the morning of the day preceding the apheresis day to the morning of the apheresis day.		
Treatments groups	plerixafor plus standard mobilization including G-CSF		<SC plerixafor 240 µg/kg daily 8-12 hours prior to planned apheresis + G-CSF 10 µg/kg 1 hour prior to planned apheresis
	Standard mobilization including G-CSF		G-CSF 10 µg/kg 1 hour prior to planned apheresis
Endpoints and definitions	Primary endpoint	Successful mobilization	defined as at least a doubling of the PB CD34+ count observed from the morning of the day preceding the first planned apheresis day to the morning prior to apheresis
	Secondary endpoints	Number of days of apheresis required to reach >2 x 10^6 CD34+ cells/kg	
		Total CD34+ yield	
		Percentage of patients proceeding to transplant	
		Percentage of patients successfully engrafting	

		Percentage of patients with durable engraftment at 3, 6, 12 and 24 months post-transplant	
Study completion date	09 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS		
Descriptive statistics and estimate variability	Treatment group	standard mobilization alone	Plerixafor+standard mobilization
	Number of subject	15	30
	successful mobilization	28.6% (8.4%-58.1%)	80.0% (61.4%-92.3%)
	difference	51.4% (18.5%-84.3%)	p=0.0019 >
Effect estimate per comparison	Secondary endpoint Number of day of apheresis required to reach >2 x 10^6 34+ cells/kg	standard mobilization alone	Plerixafor+standard mobilization
		1 day	1 day
	Secondary endpoint; number of patients reaching the threshold	92.9%	89.7%
	Secondary endpoint Total CD34+ yield; median	10.15x 10^6 cells/ kg	9.13x 10^6 cells/ kg
	Secondary endpoint Percentage of patients proceeding to transplant	66.7%	76.7%
	Secondary endpoint Percentage of patients successfully engrafting	100%	100%

	Secondary endpoint Percentage of patients with durable engraftment at 3, 6, 12 and 24 months post-transplant	3 months 100% 6 months 90.0% 12 months 80.0% 24 months 80.0%	91.3% 87.0% 87.0% 82.6%

Supportive study(ies)

The Applicant provided a literature review relating to the use of plerixafor as mobilizing agent in children who are candidates for high-dose chemotherapy followed by autologous peripheral blood stem cell (PBSC) support. Only references with information on at least 3 patients were retained for this review.

From 2011 to 2016, 16 publications reporting on 3 or more patients were identified. No randomized controlled trial was found in the published literature. Only few prospective uncontrolled experiences have been performed and most of the available data are retrospective analyses of case reports or are compassionate use programs that were initiated after plerixafor was first approved in the adult population. The publications encompass a total of 163 patients treated with at least 1 dose of plerixafor. The dose was 240 µg/kg with a few exceptions. In all publications but one, plerixafor was part of a mobilization protocol that included G-CSF ± chemo-mobilization. In the vast majority of the cases, plerixafor was administered to patients with a history of failed prior conventional PBSC mobilization with G-CSF ± chemotherapy, or a history of stem cell apheresis insufficient to proceed to transplant, or on rescue basis in the course of an inadequate mobilization attempt (insufficient PB CD34+ to proceed to apheresis). Successful harvest was achieved in 66.7% to 100% of the patients in all studies evaluating plerixafor combined with G-CSF ± chemo-mobilization as mobilisation protocol.

The MAH has provided data from 2 publications of retrospective analysis of the 2 pivotal studies in adults by subgroups according to categories of baseline Day 4 CD34+ counts (study AMD 3101-3101 in NHL and study AMD3101-3102 in MM).

The data regarding the fold increases between Day 4 pre-apheresis PB CD34+ count and at the day of apheresis is of particular interest. In both studies it is noted that while the fold-increase in PB CD34+ counts were of similar magnitude across the five Day 4 pre-apheresis PB CD34+ count subgroups in the control arm, these were higher in all subgroups in the plerixafor-treated arm, and in particular in the subgroup with the lowest Day 4 pre-apheresis PB CD34+ counts. A similar pattern is noted for cell yields. This suggest a larger efficacy of plerixafor in poor mobilizer adult patients. This is supported by the observation of fewer days of apheresis and a lower incidence of a second round of mobilization in the adult patients initially randomized to plerixafor.

While paediatric data are more limited, and there is a skewing of patients with low Day 4 PB CD34 count in the plerixafor arm, a similar pattern in the fold-increase is suggested in study DFI12860. Also in this study the fold–increase in CD34 count seems rather independent of the Day 4 PB CD34 count in the control arm, while in the plerixafor arm there seems to be a tendency of numerically higher increase in subjects with lower Day 4 PB CD34 count. This similar PD effect between adults and paediatric patients suggest that also in children a greater efficacy of plerixafor can be expected in subjects with low PB CD34+ values on the day prior to apheresis.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical paediatric study DFI12860 (MOZ15609) consisted of an initial dose escalation study (Stage 1) followed by a randomized, comparative study extension (Stage 2) at the dose identified as most appropriate in the dose escalation part of the study. Stage 2 compared plerixafor administered in combination with standard mobilization, to standard mobilization alone.

The study has been conducted in accordance with a PDCO agreed paediatric investigation plan. Overall, this development program included 72 paediatric patients aged 1 to <18 years with 57 patients treated with plerixafor plus standard mobilization (27 in Stage 1 and 30 Stage 2) and 15 treated with standard mobilization alone (Stage 2).

The primary objective of stage 1 of the study was to determine the appropriate dose for stage 2. At Stage 2 of the study, patients were randomized at a 2:1 ratio to receive plerixafor at the selected dose of 240µg/kg plus standard mobilization or standard mobilization alone. The primary objective of the second stage of the study was to establish the difference between the 2 treatment arms in the proportion of patients achieving at least a doubling of peripheral blood CD34+ count for the morning of the day preceding the apheresis day to the morning of the apheresis day.

Secondary endpoints included number of subjects reaching the threshold of $\geq 2x10^6$ CD34+ cells/kg, number of days of apheresis required to reach $\geq 2 \times 10^6$ CD34+ cells/kg, CD34+ yield for each apheresis, total CD34+ yield, percentage of patients proceeding to transplant, percentage of patients successfully engrafting and percentage of patients with durable engraftment at 3, 6, 12 and 24 months post-transplant. The time to neutrophil and platelet engraftment are exploratory endpoints.

No formal statistical hypothesis based sample size calculations were performed and except for the primary endpoint no statistical hypothesis testing was preformed, results are only descriptive.

The primary endpoint reflects the anticipated pharmacodynamic effect of the plerixafor added to standard mobilisation, as it provides data on whether or not CD34+ cells can be mobilized by plerixafor. However, with this endpoint the clinical benefit of plerixafor treatment can not directly be determined, as it does not show that plerixafor treatment allows more patients to proceed to transplant. The percentage of patients who reach the threshold of $\geq 2 \times 10^6$ CD34+ cells/kg, that proceed to transplant and who have successful engraftment are important secondary parameters as these reflect the intent of CD34+ mobilization, the collection of sufficient numbers of CD34+ cells to allow for successful stem cell transplantation.

The inclusion and exclusion criteria are generally representative of the paediatric patient population who are in need of myeloablative high dose chemotherapy and thus of stem cell rescue. This population is different from the sought paediatric indication where subjects should also comply with one of two requirements intended to restrict the target population to those paediatric subjects who (are expected to) mobilise poorly. Importantly the proposed indication represents a population of poor mobilisers for which the addition of plerixafor to the standard mobilisation regime could address an unmet medical need. The PIP was agreed before the marketing authorisation was granted, without requiring a restriction in the study to the paediatric population of poor mobilisers. However, the sensitivity to determine a difference between control and active treatment in clinically relevant endpoints (e.g. achieving sufficient CD34+ cells for transplant) may be reduced due to the inclusion of normal (non-poor) mobilising subjects in the studied population.

In the study, 4 subjects were aged between 1 and 2 years, 3 subjects received standard mobilisation alone, and 1 received plerixafor + standard mobilisation. This indicates that there is a need for autologous SCT in this age category.

Efficacy data and additional analyses

A statistically significant difference is seen between the stage 2 study arms in the primary endpoint point: proportion of patients with successful mobilization. Doubling of the PB CD34+ count from the morning before the apheresis day to the morning of the apheresis day was reported for 80% of the patients in the plerixafor plus standard mobilisation arm and in 28.6% of the patients in the standard mobilisation arm ($p<0.0019$).

Regarding the clinically relevant endpoints, no clear difference was noted between the study arms. The number of patients reaching the threshold of collecting $\geq 2 \times 10^6$ CD34+ cell/kg was comparable between the treatment groups (89.7% vs 92.9% for plerixafor plus standard mobilisation and standard mobilisation respectively). For both treatment groups the median number of apheresis days needed to collect the threshold number of cells was 1 day. While the percentage of patients who proceeded to transplant was higher for the plerixafor plus standard mobilisation arm than for the control arm (76.7% vs 66.7%, respectively), no difference was noted in the reasons for not proceeding to HSCT. Insufficient stem cell harvest was reported for only 1 subject, in the plerixafor arm.

For both treatment arms, all patients who were transplanted successfully engrafted, and the percentages of patients with engraftment after 3, 6, 12 and 24 months, were comparable. Only minor differences occurred in time to neutrophil engraftment (12 vs 14 day, plerixafor plus standard mobilisation vs standard mobilisation) and time to platelet engraftment (28 vs 23 days, plerixafor plus standard mobilisation vs standard mobilisation).

The total amount of CD34+ cells yield was slightly lower for the plerixafor plus standard mobilisation arm than for the control arm (9.13×10^6 cells/kg vs 10.15×10^6 cells/kg, respectively), which may, in part, be explained by the slightly lower blood volume which was processed in the plerixafor plus standard mobilisation than for the control arm (3.0 L vs 3.75L, respectively. Also the small differences in the percentage of patients who received chemotherapy as part of the standard mobilization regimen (23.3% vs 33.3% plerixafor vs control), and the median total GCSF dose (89.59 µg/kg vs 97.60 µg/kg, plerixafor vs control) between the study arms may have contributed to this imbalance.

Importantly, the median amount of CD34+ cells at baseline was significantly lower (15×10^6 cells/ ml vs 35×10^6 cells/ml) in the plerixafor plus standard mobilisation arm. Thus the absolute increase in PB CD34+ count (also needed to reach the relatively similar CD34+ yield) was higher in the plerixafor plus standard mobilisation arm. Also the relative increase in PB CD34+ counts was higher in the plerixafor plus standard mobilisation arm (+220% vs +39%).

The results of the efficacy endpoints demonstrate the pharmacodynamic effect of plerixafor added to a standard mobilisation regime in the paediatric population: an additional increase (absolute and relative) in the amount of circulating CD34+ cells at the day of apheresis when compared to a standard mobilisation regime (G-CSF +/- chemotherapy) alone, taking the day before apheresis as baseline. This pharmacodynamic effect is the first step needed for proof of clinical benefit. Unfortunately, of the secondary endpoints reflecting a clinical goal of treatment and thus benefit only the percentage of patients proceeding to transplant, shows a positive trend. This lack of benefit in clinically relevant parameters might be due to the limited number of paediatric patients included in the study and the fact that the studied population was relatively insensitive for demonstrating a clinical difference as inclusion was not restricted to patients who were poor mobilizers and therefore in need of plerixafor addition above standard mobilisation therapy.

Overall, the data from the paediatric study alone is insufficient to support an extension of indication due to the lack of benefit on clinically relevant parameters in the studied population. To compensate for this, an extrapolation approach was taken building on the established clinical benefit in poor mobilising adults by comparing the effects seen in adults to those in the paediatric population. Both in adults and in children a similar pattern is noted in the fold increase in PB CD34+ count between Day 4 /pre-apheresis day and at the day of apheresis suggesting a greater treatment effect of plerixafor in potentially poor mobilizing population (based on low CD34+ PB count day4/pre-apheresis) both in adults and in children. A similar effect is noted for cell yields. This suggest a larger effect of plerixafor in poor mobilizers.

Further, it is noted that of the subjects in the paediatric study with PB CD34+ count below <20/µL, 1 of 4 control subjects had > 4-fold increase in CD34+ counts on the day of apheresis, while in the plerixafor arm, 9 of 17 subjects had > 4-fold increase in CD34+ counts on the day of apheresis. This also suggests benefit of plerixafor treatment in (potential) low mobilising subjects.

The similarity in the relationship between the PD response (fold increase) and pre-apheresis PB CD34+ count between adults and paediatric patients, and the established efficacy in the adult population together with the difference in frequency of potentially poor mobilising subjects with strong increase (>4 fold) in CD34+ counts between control and plerixafor-treated subjects in the paediatric study provide sufficient support for adding plerixafor to the standard mobilization in children who are (expected to) mobilise poorly.

The need for a lower age cut off has been discussed with the Applicant during the procedure. Data on the effect of plerixafor in children below the age of 2 is limited to 1 subject. In this patient, a > 6 fold increase in PB CD34+ cells from Day 4 to Day 5 PB CD34+ counts was noted (6.2 by central assessment and 7.1 by local assessment). This high increase suggests that plerixafor was active in this infant (13 months, 8.9 kg). Thus the available (but very limited) data do not suggest that the potential lower exposure in children aged < 2 years is clinically relevant. Given this observation the age restriction to 1 year and older as no data are available in subjects below the age of 1 year was endorsed. While an extrapolation approach could be envisaged allowing to remove a lower age limit from the indication, the 1 year cut off is accepted in view of lack of data.

The Applicant has discussed the complexities of defining a poor mobiliser among adults and infants. As mobilisation failure is multifactorial, no single parameter with a clear cut off can be identified that can accurately discriminate between subjects who are expected to fail mobilization and those who are not. It is also acknowledged that there may be institutional/national differences in algorithms to guide optimization of mobilization. As such it is agreed that specifying a specific threshold triggering pre-emptive use of plerixafor is not the best option.

The final agreed indication is considered to better capture the intent of pre-emptive plerixafor treatment than the initially proposed text, namely to target those subjects who are at likely to/at high risk for mobilisation failure, that is insufficient mobilisation to allow for collection of sufficient number of CD34+ stem cells to allow for autologous stem cell transplantation.

2.5.4. Conclusions on the clinical efficacy

Overall, it is considered that with the currently provided analyses, focussing on the potentially low mobilising subjects (based on pre-apheresis PB CD34+ counts), a clinically relevant effect of plerixafor treatment in children (1 to less than 18 years) who are expected to mobilise poorly is sufficiently supported.

2.6. Clinical safety

Introduction

In adults Mozobil treatment has been associated with injection and infusion site reactions, including allergic and anaphylactic reactions, gastrointestinal disorders (diarrhoea, nausea, vomiting, abdominal pain, stomach discomfort, dyspepsia, abdominal distention, constipation, flatulence, hypoaesthesia oral, dry mouth), fatigue, malaise, insomnia, hyperhidrosis, erythema, arthralgia, and musculoskeletal pain. Furthermore, specific warnings in the SmPC include potential for tumour cell mobilization in leukaemia patients, increased circulating leukocytes and decreased platelet counts, and splenic enlargement.

The clinical study (DFI12860) is provided for this application, consisting of 2 stages: Stage 1 a dose-escalation study and stage 2 an open-label, comparative study. For further description of the study, see clinical efficacy section.

For safety assessment 3 safety populations can be defined:

- Safety set for Stage 1 (defined as all patients who received at least one dose of plerixafor in Stage 1)
- The safety set for Stage 2 (defined as all randomized patients who received at least one study dose (either plerixafor or standard mobilization) in Stage 2).
- The overall safety set; combining plerixafor patients treated in Stage 1 and Stage 2.

All AEs, regardless of causality, were collected from the time the patient signed the Informed Consent Form until 30 days after the last dose of the patient's mobilization regimen or until the first dose of their next anticancer therapy or myeloablative therapy for transplant, whichever occurred first. From the first dose of marrow ablative chemotherapy until the last follow-up visit, only serious adverse events (SAEs) considered by the Investigator to be related to study treatment were recorded.

The primary focus of AE reporting was on TEAEs. Pretreatment and post-apheresis AEs were described separately.

The duration of follow-up for safety evaluation was dependent on mobilization treatment and transplant status. All patients who underwent transplant(s) within 6 months after last study apheresis were to be evaluated for up to 24 months after the last transplant; otherwise patients were to be evaluated for up to 24 months after last dose of study mobilization treatment (see Figure 11). During the 24-month post-transplant period (i.e., 24 months after the last planned transplant performed in the 6 month period after last study apheresis), disease recurrence or progression, graft failure, and Grade 3 or higher infections were recorded as SAEs.

Disease recurrence or progression were to be recorded as SAEs. Data recorded on graft status was to include delayed platelet engraftment and graft failure; if applicable, primary and secondary graft failure was to be reported as an SAE.

Other events that were to be recorded included tumour cell mobilization (to be evaluated by assessment of samples for the presence of tumour cells in peripheral blood), second malignancies (as opposed to relapse or recurrence) and hospitalisation (both initial hospitalization for mobilization and apheresis, as well as other periods of hospitalization throughout the duration of the study).

Patient exposure and baseline characteristics

Among the 27 patients in Stage 1, and the 45 randomized patients in Stage 2 all received at least one dose of study treatment and were therefore included in respective the safety populations.

There was an imbalance in the standard mobilisation treatment between the study arms: the percentage of patients who received chemotherapy as part of the standard mobilization regimen (23.3% vs 33.3%) and the median total GCSF dose (89.59 µg/kg vs 97.60 µg/kg) were slightly lower in the plerixafor plus standard mobilisation arm when compared to standard mobilisation alone.

More information on received doses and baseline characteristics, is provided in the efficacy section.

Adverse events

Frequency

During Stage 1, TEAEs were reported in 59% of patients, with TEAEs assessed by the investigator as related to study treatment reported in only 1 patient. TEAEs of Grade 3-4 were recorded for 8 patients (30%). The only Grade 3/4 TEAEs reported in 2 or more patients were febrile neutropenia (2 patients with Grade 3 and 1 patient with Grade 4 TEAEs) and pancytopenia (1 patient with Grade 3 and 1 patient with Grade 4 TEAEs)

During stage 2, TEAEs were reported in 77% of patients in the plerixafor plus standard mobilization arm and 67% patients in the standard mobilization only arm. Treatment–emergent AEs assessed by the investigator as related *to study procedure* were reported more frequently in the plerixafor plus standard mobilization arm than in the standard mobilization alone arm (43.3% versus 40.0%, respectively). Treatment–emergent AEs assessed by the investigator as related *to study treatment* were reported in 4 (13.3%) patients in the plerixafor plus standard mobilization arm and none in the standard mobilization alone arm. The events reported were mild (Grade 1 in severity) included injection site reactions (2 patients, 6.7%), and hypokalaemia and blood bicarbonate increased (1 patient each, 3.3%). These were considered consistent with the known safety profile of plerixafor.

Table 20 Overview of treatment-emergent adverse events (TEAE) (Safety Set for Stage 2)

	Standard Mobilization Alone (N=15)		Plerixafor + Standard Mobilization (N=30)	
Patients with any TEAE	10	(66.7%)	23	(76.7%)
Patients with any TEAE related to study procedure	4	(26.7%)	12	(40.0%)
Patients with any TEAE related to study treatment	0		4	(13.3%)
Patients with any grade 3-4 TEAE	6	(40.0%)	13	(43.3%)
Patients with any grade 3-4 TEAE related to study procedure	4	(26.7%)	9	(30.0%)
Patients with any grade 3-4 TEAE related to study treatment	0		0	
Patients with any treatment-emergent SAE	4	(26.7%)	9	(30.0%)
Patients with any treatment-emergent SAE related to study procedure	1	(6.7%)	3	(10.0%)
Patients with any treatment-emergent SAE related to study treatment	0		0	
Patients with TEAE leading to death	0		0	
Patients with TEAE related to study procedure leading to death	0		0	
Patients with TEAE related to study treatment leading to death	0		0	
Patients with any TEAE leading to permanent treatment discontinuation	0		0	
Patients with TEAE related to study procedure leading to permanent treatment discontinuation	0		0	
Patients with TEAE related to study treatment leading to permanent treatment discontinuation	0		0	

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event

n(%) = number and percentage of patients with at least one TEAE

Note: Grade 5 are not collected in the database but are derived from AE outcome, grade 3-4 only including non-fatal TEAE

PGM=PRODOPS/GZ316455/MOZ15609/CSR_2017/REPORT/PGM/ae_overview_onco_s_t.sas OUT=REPORT/OUTPUT/ae_overview_onco_stg2_s_t_x.rtf (28JUN2017 - 18:38)

AE profile

During stage 1, the most common TEAEs reported by > 15% of patients were: vomiting (5 patients), anaemia (4 patients), febrile neutropenia (4 patients) and pyrexia (4 patients). 1 patient had 2 TEAEs (abdominal pain and vomiting) assessed by the investigator as related to study treatment.

The only Grade 3-4 TEAEs reported in 2 or more patients were febrile neutropenia (2 patients with Grade 3 and 1 patient with Grade 4 TEAEs) and pancytopenia (1 patient with Grade 3 and 1 patient with Grade 4 TEAEs).

During stage 2, the most common TEAEs reported by ≥10% of patients in the plerixafor plus standard mobilization arm were anaemia, platelet count decreased, rhinitis, febrile neutropenia, hypoalbuminaemia, diarrhoea, vomiting, and pyrexia. The most common Grade 3 or higher TEAEs reported by ≥10% of patients were anaemia, platelet count decreased, and febrile neutropenia in the plerixafor plus standard mobilization arm.

In the standard mobilization alone arm, the most common TEAEs reported by >10% of patients were hypokalaemia, alanine aminotransferase increased, febrile neutropenia, vomiting, platelet count

decreased, fatigue, nausea, and anaemia. The most common Grade 3 or higher TEAEs reported by ≥10% of patients were anaemia, febrile neutropenia, hypokalaemia, and platelet count decreased in the standard mobilization alone arm.

No major difference in occurrence of any type of AEs was observed between the study arms (see Table 17).

Treatment-related TEAE included injection site reactions (2 patients, 6.7%), and hypokalaemia and blood bicarbonate increased (1 patient each, 3.3%). All TEAEs considered related to study treatment were mild.

Table 21 Number (%) of patients with TEAE(s) reported in ≥2 patients in either treatment arm by SOC and PT, safety set for stage 2

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Any class	10 (66.7%)	23 (76.7%)
INFECTIONS AND INFESTATIONS	5 (33.3%)	6 (20.0%)
Rhinitis	1 (6.7%)	3 (10.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (33.3%)	13 (43.3%)
Anaemia	3 (20.0%)	9 (30.0%)
Pancytopenia	0	2 (6.7%)
Febrile neutropenia	2 (13.3%)	3 (10.0%)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
METABOLISM AND NUTRITION DISORDERS	2 (13.3%)	5 (16.7%)
Hypocalcaemia	1 (6.7%)	2 (6.7%)
Hypokalaemia	2 (13.3%)	1 (3.3%)
Hypoalbuminaemia	1 (6.7%)	3 (10.0%)
NERVOUS SYSTEM DISORDERS	0	3 (10.0%)
Headache	0	2 (6.7%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (20.0%)	2 (6.7%)
Cough	1 (6.7%)	2 (6.7%)
GASTROINTESTINAL DISORDERS	5 (33.3%)	6 (20.0%)
Abdominal pain	0	3 (10.0%)
Diarrhoea	1 (6.7%)	3 (10.0%)
Nausea	3 (20.0%)	2 (6.7%)
Vomiting	2 (13.3%)	3 (10.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (33.3%)	6 (20.0%)
Injection site reaction	0	2 (6.7%)
Pyrexia	1 (6.7%)	3 (10.0%)
Fatigue	3 (20.0%)	0
INVESTIGATIONS	4 (26.7%)	6 (20.0%)
Platelet count decreased	2 (13.3%)	6 (20.0%)
Alanine aminotransferase increased	2 (13.3%)	2 (6.7%)
Aspartate aminotransferase increased	1 (6.7%)	2 (6.7%)

Source: DFI12860 Final CSR (Table 27 and appendix-16-2-7-ae-data[16.2.7.3]).

During the post-apheresis period, AEs were reported in 18 (60.0%) patients in the plerixafor plus standard mobilization arm and 9 (60.0%) patients in the standard mobilization alone arm. The most frequently reported post-apheresis AEs (by PT) in both the plerixafor plus standard mobilization arm and the standard mobilization alone arm were disease progression (2 patients, 6.7% and 4 patients, 26.7%, respectively), febrile neutropenia (6 patients, 20.0% and 2 patients, 13.3%, respectively) and neuroblastoma recurrent (4 patients, 13.3% and 2 patients, 13.3%, respectively).

Serious adverse event / deaths / other significant events

Deaths

No deaths occurred within 30 days of the last study treatment in either stage of the study.

During the post-treatment follow-up period, 5 patients died in stage 1 of the study, 3 due to disease progression. In stage 2, 6 patients died (3 in each treatment arm), all deaths were due to disease progression.

Survival rates post-transplant were reported for stage 2 (see Table 18).

Table 22 Survival rate at 3, 6, 12, and 24 months post-transplant for patients who received transplant - Safety Set for Stage 2

	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Number of patients who received transplants (N_1)	10	23
Number of deaths while on study [n (%)]	3 (30.0%)	3 (13.0%)
Number of patients censored [n (%)]	7 (70.0%)	20 (87.0%)
Kaplan-Meier estimated overall survival rate, (95% CI) [a]		
Month 3 (90 days)	1.000	0.957 (0.729 to 0.994)
Month 6 (180 days)	0.900 (0.473 to 0.985)	0.957 (0.729 to 0.994)
Month 12 (365 days)	0.900 (0.473 to 0.985)	0.957 (0.729 to 0.994)
Month 24 (730 days)	0.675 (0.291 to 0.882)	0.870 (0.648 to 0.956)

a CIs are estimated by Kaplan-Meier method, using a log-log transformation

Percentages are based on N1

Source: DFI12860 Final CSR (Table 16.2.7.35)

Serious TEAEs

In stage 1, serious TEAEs were reported in 9 (33%) patients, none assessed by the Investigator as related to study treatment (see Table 19).

In stage 2, serious TEAEs were reported in 9 (30.0%) patients in the plerixafor plus standard mobilization arm and in 4 (26.7%) patients in the standard mobilization alone arm, none were assessed by the Investigator as related to study treatment (see Table 20). Treatment-emergent SAEs reported for patients in the plerixafor treatment plus standard mobilization arm included febrile neutropenia, (3 patients [10%]) pancytopenia and pyrexia (2 patients [6.7%] each), and hydrocephalus and bone marrow failure (1 patient [3.3%] each).

Serious AEs reported post-apheresis in the plerixafor plus standard mobilization arm were reported in 7 patient (device-related infection [2], appendicitis, clostridial sepsis, pneumonia, upper respiratory tract infection, and urinary tract infection). Neoplastic recurrence and disease progression occurred in 2 + 4 subjects in the standard mobilization alone arm, and 7 + 2 subjects in the plerixafor plus standard mobilization arm. No primary or secondary graft failures were reported in the standard mobilization arm alone. In the plerixafor plus standard mobilization arm primary graft failure was reported in 1 (4.3%) patient and 1 secondary graft failure was also reported in this arm (was considered secondary due to missing data on platelet engraftment).

Table 23 Number (%) of patients with treatment-emergent SAEs by primary SOC and PT by patient age - Safety Set for Stage 1

System Organ Class Preferred Term	2 - < 6 yrs (N=9) Patients n (%)	6 - < 12 yrs (N=9) Patients n (%)	12 - < 18 yrs (N=9) Patients n (%)	Total (N=27) Patients n (%)
Patients with Events	1 (11)	4 (44)	4 (44)	9 (33)
Blood and lymphatic system disorders	0 (0)	4 (44)	2 (22)	6 (22)
Febrile neutropenia	0 (0)	2 (22)	1 (11)	3 (11)
Neutropenia	0 (0)	0 (0)	1 (11)	1 (4)
Pancytopenia	0 (0)	2 (22)	0 (0)	2 (7)
Gastrointestinal disorders	0 (0)	0 (0)	2 (22)	2 (7)
Diarrhoea	0 (0)	0 (0)	1 (11)	1 (4)
Gastrointestinal inflammation	0 (0)	0 (0)	1 (11)	1 (4)
Stomatitis	0 (0)	0 (0)	1 (11)	1 (4)
General disorders and administration site conditions	0 (0)	2 (22)	0 (0)	2 (7)
Pyrexia	0 (0)	2 (22)	0 (0)	2 (7)
Injury, poisoning and procedural complications	1 (11)	0 (0)	0 (0)	1 (4)
Blood stem cell harvest failure	1 (11)	0 (0)	0 (0)	1 (4)
Investigations	0 (0)	0 (0)	1 (11)	1 (4)
Neutrophil count decreased	0 (0)	0 (0)	1 (11)	1 (4)
Metabolism and nutrition disorders	0 (0)	1 (11)	1 (11)	2 (7)
Dehydration	0 (0)	0 (0)	1 (11)	1 (4)
Hyponatraemia	0 (0)	1 (11)	0 (0)	1 (4)
Surgical and medical procedures	1 (11)	0 (0)	0 (0)	1 (4)
Bone marrow harvest	1 (11)	0 (0)	0 (0)	1 (4)

Note: If a patient had more than one event for a particular SOC, he/she is counted only once for that SOC.
Note: If a patient had more than one event for a particular PT, he/she is counted only once for that PT.
Note: Summary includes treatment emergent SAE that occurred within 30 days of the last treatment administration, or the start of the anticancer therapy, whichever earlier.
Source: DFI12860 Interim CSR Table 10

Table 24 Number (%) of patients with treatment-emergent SAEs by primary SOC and PT by severity grade - Safety Set for Stage 2

	Standard Mobilization Alone (N=15)						Plerixafor + Standard Mobilization (N=30)					
Primary System Organ Class Preferred Term n(%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Infections and infestations												
Abdominal infection	0	0	1 (6.7%)	0	0	1 (6.7%)	0	0	0	0	0	0
Enterobacter bacteremia	0	0	1 (6.7%)	0	0	1 (6.7%)	0	0	0	0	0	0
Blood and lymphatic system disorders												
Febrile neutropenia	0	0	2 (13.3%)	0	0	2 (13.3%)	0	0	3 (10.0%)	0	0	3 (10.0%)
Pancytopenia	0	0	0	0	0	0	0	0	0	2 (6.7%)	0	2 (6.7%)
Bone marrow failure	0	0	0	0	0	0	0	1 (3.3%)	0	0	0	1 (3.3%)
Leukopenia	1 (6.7%)	0	0	0	0	1 (6.7%)	0	0	0	0	0	0
Nervous system disorders												
Hydrocephalus	0	0	0	0	0	0	0	0	0	1 (3.3%)	0	1 (3.3%)
Respiratory, thoracic and mediastinal disorders												
Pulmonary embolism	0	0	0	1 (6.7%)	0	1 (6.7%)	0	0	0	0	0	0
General disorders and administration site conditions												
Pyrexia	0	0	0	0	0	0	2 (6.7%)	0	0	0	0	2 (6.7%)

N = number of patients; TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 20.0
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all TEAE summaries. In case of several occurrences for the same PT (respectively SOC), the maximal intensity is used.
Source: DFI12860 Final CSR (Table 31)

Additional AE parameters

- No AEs related to vital signs or physical examination observations were reported that were assessed by the Investigator as related to study treatment.
- No secondary malignancies were reported in Stage 2 of the study.

- Relapse rate: The post-transplant relapse rate (95% CI) for patients who received transplant within 6 months of last study apheresis was similar in the plerixafor plus standard mobilization arm and the standard mobilization alone.
- Unplanned hospitalizations due to AEs were reported in 10 (76.9%) patients of the standard mobilization arm only and in 17 (63.0%) patients of the plerixafor plus standard mobilization arm. Other unplanned hospitalizations (at any time during the study) were reported in 6 (46.2%) patients of the standard mobilization arm only and in 15 (55.6%) patients of the plerixafor plus standard mobilization arm.
- Tumour cell mobilisation: Blood samples (2 mL per sample) were to be collected on the day preceding the first apheresis day and prior to G-CSF administration on the first apheresis day itself, as well as in apheresis product prior to cryopreservation in patients with neuroblastoma, Ewing's sarcoma and alveolar rhabdomyosarcoma. Real-time quantitative reverse transcriptase polymerase chain reaction technology using tumor type-specific mRNA was used for tumour cell detection.

Table 25 relapse rate for patients who received transplant within 6 months of last apheresis

	plerixafor plus standard mobilization	the standard mobilization alone
Month 3	0.087 [0.022 to 0.305]	0.100 [0.015 to 0.527]
Month 6	0.087 [0.022 to 0.305	0.100 [0.015 to 0.527
Month 12	0.130 [0.044 to 0.352	0.100 [0.015 to 0.527]
Month 24	0.304 [0.158 to 0.534	0.550 [0.266 to 0.873],

In Stage 1, there were 61 evaluable samples (35 in BP, 26 in apheresis), all were found to be negative for tumour cell RNA. In Stage 2, target messenger RNA (mRNA) was detected at low levels in 1 of 61 PB and 5 of 37 apheresis samples successfully analysed. Positive samples were collected from 3 patients in the standard mobilization only arm, and 1 patient in the plerixafor plus standard mobilization arm.

Table 26 Summary of results for tumour cell mobilisation assay

	Blood			Apheresis product		
	Positive	Negative	Not evaluable	Positive	Negative	Not evaluable
Phase 1	0%	90%	10%	0%	96%	4%
Phase 2	1%	91%	8%	13%	82%	5%

Adverse events of special interest (AESI)

The database was queried for events potentially meeting criteria for the following AESI

- Pregnancy occurring in a female patient included in the clinical trial
- Vasovagal reaction: Orthostatic hypotension, syncope, bradycardia
- Systemic allergic reactions including anaphylactic reaction and anaphylactic shock
- Overdose of IMP/NIMP
- Symptomatic leukocytosis.

Three TEAEs resulted from this search: 1 patient had an event of Grade 3 urticaria and Grade 1 allergic transfusion reaction associated with platelet transfusion. One patient experienced Grade 3 stomatitis. All 3 events were assessed by the Investigators as not related to study treatment

Laboratory findings

Serum chemistry (sodium, potassium, calcium, chloride, blood urea nitrogen, bicarbonate, creatinine, ALT/SGPT, AST/SGOT, total bilirubin, alkaline phosphatase, total protein, albumin, glucose, phosphate, and magnesium) and haematology (Complete blood count (CBC) with differential was to be evaluated in peripheral blood samples, and was to include platelets, haematocrit, haemoglobin, red blood cells, and WBCs with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) were to be assessed by the site's local laboratory at the study visits.

In stage 1 no clinically meaningful variations were noted between baseline and the day following apheresis for liver function tests, plasma creatinine, and electrolytes.

In each of the 3 age categories neutrophils increased and platelets decreased while RBC indices did not change appreciably between baseline and the day following apheresis.

In stage 2, abnormalities in liver and renal function indices reported were similar between treatment arms, electrolyte abnormalities were uncommon. The effect on haematology in stage 3 is shown in Table 23.

Table 27 Summary of haematological laboratory abnormalities at baseline and during on-treatment period - Safety Set for Stage 2

	Standard Mobilization Alone (N=15)		Plerixafor + Standard Mobilization (N=30)	
Laboratory abnormality n/N_1 (%)	**All Grades**	**Grades 3,4**	**All Grades**	**Grades 3,4**
Baseline[a]				
Leukopenia	4/15 (26.7%)	3/15 (20.0%)	4/30 (13.3%)	3/30 (10.0%)
Neutropenia	4/12 (33.3%)	4/12 (33.3%)	3/20 (15.0%)	3/20 (15.0%)
Anemia	13/15 (86.7%)	2/15 (13.3%)	20/29 (69.0%)	4/29 (13.8%)
Thrombocytopenia	8/15 (53.3%)	1/15 (6.7%)	16/30 (53.3%)	5/30 (16.7%)
Lymphopenia	10/12 (83.3%)	3/12 (25.0%)	14/23 (60.9%)	7/23 (30.4%)
During on-treatment period[b]				
Leukopenia	2/14 (14.3%)	1/14 (7.1%)	2/29 (6.9%)	1/29 (3.4%)
Neutropenia	3/10 (30.0%)	1/10 (10.0%)	7/20 (35.0%)	3/20 (15.0%)
Anemia	13/14 (92.9%)	1/14 (7.1%)	24/29 (82.8%)	4/29 (13.8%)
Thrombocytopenia	13/14 (92.9%)	5/14 (35.7%)	25/29 (86.2%)	8/29 (27.6%)
Lymphopenia	10/11 (90.9%)	1/11 (9.1%)	12/20 (60.0%)	4/20 (20.0%)

a Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N_1) at baseline.

b Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during on-treatment period.

Source: DFI12860 Final CSR dfi12860-16-2-8-clin-lab-data (Table 16.2.8.5 and Table 16.2.8.7)

Safety in special populations

Given the small number of patients in the safety set, analysis of safety variables by subgroups was not conducted for this application.

Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions or other interactions was not discussed in this application.

Discontinuation due to adverse events

No patients in Stage 1 had any TEAEs leading to leading to permanent treatment discontinuation or leading to death.

No patients had dose interruptions or discontinuations of study treatment during Stage 2.

No patients in Stage 2 in either arm had any TEAEs leading to death or permanent treatment discontinuation.

Post marketing experience

The cumulative analysis to summarize the AEs collected from solicited and unsolicited reporting and reported in Sanofi global pharmacovigilance database, Application for Worldwide Adverse Event Reporting and Evaluation (AWARE) are presented below. The data were retrieved cumulatively until 06 June 2017 (the time of the data cut off) for all cases occurring in patients under age 18 (paediatric use).

A total of 270 AEs were collected cumulatively in the safety database as of the cut-off date (06 June 2017), with the majority (219 AEs) reported as serious. Due to one duplicate case with 1 SAE reported, the total number of AEs and SAEs were 269 and 218 respectively. The events are summarised (by SOC) in Table 24.

One study reported a cluster of 4 cases of serious visual hallucinations and nightmares in children 25-58 months of age (Son et al, 2013). After the cumulative analysis of all cases retrieved from the safety database, the MAH concluded that the cumulative weighted evidence support a causal association between plerixafor and the onset of abnormal dreams and nightmares. The product information was updated accordingly.

Table 28 Overall adverse events summarized by system organ class (SOC) collected post-marketing

MedDRA SOC (descending frequency)	Serious	Non serious	Total	
	N	N	N	Reporting Rate
General disorders and administration site conditions	61	8	69	0,2556
Blood and lymphatic system disorders	53	2	55	0,2037
Infections and infestations	29	2	31	0,1148
Respiratory, thoracic and mediastinal disorders	23	6	29	0,1074
Injury, poisoning and procedural complications	11	11	22	0,0815
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22		22	0,0815
Nervous system disorders	20	2	22	0,0815
Gastrointestinal disorders	14	7	21	0,0778
Vascular disorders	19	2	21	0,0778
Cardiac disorders	14	4	18	0,0667
Psychiatric disorders	7	11	18	0,0667
Metabolism and nutrition disorders	12	2	14	0,0519
Endocrine disorders	9		9	0,0333
Musculoskeletal and connective tissue disorders	8	1	9	0,0333
Renal and urinary disorders	7	1	8	0,0296
Hepatobiliary disorders	6		6	0,0222
Immune system disorders	5	1	6	0,0222
Skin and subcutaneous tissue disorders	2	1	3	0,0111
Investigations	2		2	0,0074
Surgical and medical procedures	2		2	0,0074
Reproductive system and breast disorders	1		1	0,0037
All SOCs	219	51	270	1,0000

Note: There was one instance of duplicate reporting for Nervous System Disorders, Serious.
Note: Reporting rate (RR) the number of a specific AE reported in a particular subset divided by the total count of all the AEs reported in the same subset
Source: Sanofi global pharmacovigilance database, AWARE (Application for Worldwide Adverse Event Reporting and Evaluation), 06 June 2017 data cutoff

In summary, the overall profiles of the AEs reported in the safety database were consistent with the reference safety information of plerixafor. No any new or different safety issue identified.

Also a review of literature relating to the use of plerixafor as mobilizing agent in children who are candidates for high-dose chemotherapy followed by autologous peripheral blood stem cell (PBSC) support was conducted. For description of literature database, see efficacy section.

From 2011 to 2016, 16 publications reporting on 3 or more patients were identified (for further description see efficacy section). No appreciable side effects associated with administration of plerixafor were reported in most of these 16 publications. Most of the reported toxicities have been already documented as possibly associated with plerixafor in adults. One publication (Son et al, 2013) reported nightmares, nyctophobia, and visual hallucinations in 4 out of the 6 patients treated with G-CSF and plerixafor. These events resolved within one week, although, visual hallucinations persisted about one month in one patient. These 4 patients received 3 to 10 doses of plerixafor. As possible explanation for these psychological adverse events, the authors hypothesized on a possible difference in CXCR4 expression in the brain tissues and/or a difference in the degree of neuronal dysregulation by plerixafor between adults and young children. Sevilla at al. (2012), also reported 1 patient out of 8 who experienced anxiety and nightmares following administration of plerixafor. The report by Son et al (2013) has been previously discussed as included in post marketing pharmacovigilance activities and has led to an update of the product information.

2.6.1. Discussion on clinical safety

The safety of plerixafor added to a standard mobilisation regime in the paediatric population has been studied in clinical study DFI12860, consisting of 2 stages: Stage 1 a dose-escalation study and stage 2 an open-label, comparative study. The collection and reporting of the AEs during this study is sufficient to allow for a general impression of the effect of adding plerixafor to a standard mobilisation regime in children and for a high-level comparison of the safety profile between adults and children.

Among the 27 patients in Stage 1, and the 45 randomized patients in Stage 2 all received at least one dose of study treatment and were therefore included in respective the safety populations. Due to the restricted sample size in children potential small differences in frequencies or uncommon new AEs could not be captured. However this can be accepted as more extensive safety data has been obtained in adults, and the mechanism of action of plerixafor is expected to be similar between children and adults.

TEAEs were reported in 59% of patients in stage 1 subjects with TEAEs of Grade 3-4 recorded for 8 patients (30%). In stage 2 TEAEs were reported in 77% of patients in the plerixafor plus standard mobilization arm and 67% patients in the standard mobilization only arm. Grade 3-4 recorded TEAEs were recorded in 40 respectively 43% of subjects. Treatment–emergent AEs assessed by the investigator as related to study treatment were reported in 1 subject during stage 1, and during stage 2 in 4 (13.3%) patients in the plerixafor plus standard mobilization arm and none in the standard mobilization alone arm.

The observed adverse events in paediatric population are consistent with the known safety profile of plerixafor in adults.

In stage 2, the frequencies of TEAEs and TEAEs related to study treatment were higher in the plerixafor plus standard mobilisation arm when compared to the standard mobilisation arm alone. However this is not unexpected for an add-on therapy and differences were modest.

Overall, during both stages of the study, no unexpected AEs, SEAs, AE of special interest were noted in the plerixafor + standard mobilisation arm, and the observed events are consistent with the known safety profile of plerixafor in adults. Data on survival, relapse rate, hospitalisations and tumour cell mobilisation also do not point toward any unexpected safety concerns, and no obvious differences were noted between the two treatment arms in stage 2 of the study. The observed effect on haematology parameters (i.e. increase neutrophils, decrease platelets) are in line with the intended effects of CD34+ mobilization, with again no major differences between the study arms.

Review of the post marketing experience and of literature on the use of plerixafor in the paediatric patient population also did not reveal new safety signals which have not been discussed previously with the Applicant during post marketing pharmacovigilance activities.

2.6.2. Conclusions on clinical safety

Overall it can be concluded that the safety profile of plerixafor added to standard mobilisation is consistent to what has been reported previously, and that no new safety concerns have been identified. Notably, due to the restricted sample size in this study the sensitivity to detect potential small differences in frequencies or uncommon new AEs is limited.
Long-term safety (patients >1 year) should be followed up in the PSURs as a safety concern to be further monitored and characterized over time.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Significance of paediatric studies

The CHMP is of the opinion that DFI12860, which is contained in the agreed Paediatric Investigation Plan EMEA-000174-PIP01-07, which is completed, and has been completed after 26 January 2007, is considered as significant.

3. Risk management plan

The MAH submitted an updated RMP version 10.0 with this application. The proposed updates includes the results of the paediatric study DFI12860/MOZ15609 and migration to new EU-RMP template. In response to the PRAC Rapporteurs 3 rounds of requests for supplementary information, the MAH submitted an updated RMP (version 10.3) with the following content:

Summary of the Safety Concerns

Important identified risk	Splenomegaly and splenic rupture
Important potential risks	Interstitial lung disease Myocardial infarction Tumor cell mobilization Drug level NOS increased Anxiety, hallucination (including hallucination, visual hallucination, and auditory hallucination) Effect on embryo-fetal development (including teratogenicity and fetal growth restriction)
Missing information	safety profile in paediatrics under 2 years of age

Summary of pharmacovigilance activities and risk minimization activities by safety concern:

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Splenomegaly and splenic rupture	**Routine risk minimization measures:** Labelled in Section 4.4 and 4.8 of the SmPC **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risks		
Interstitial lung disease	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Myocardial Infarction	**Routine risk minimization measures:** Labelled in Section 4.8 of the SmPC **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Tumor cell mobilization	**Routine risk minimization measures:** Labelled in section 4.4 of the SmPC **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Drug level NOS increased	**Routine risk minimization measures:** Section 4.2 of the SmPC Posology and method of administration **Additional risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: None	**activities:** None
Anxiety, hallucination (including hallucination visual hallucination, auditory hallucination),	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Effect on embryo-fetal development (including **teratogenicity and fetal growth restriction)**	**Routine risk minimization measures:** Labelled in Sections 4.6 and 5.3 of the SmPC. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
Safety profile in pediatric under 2 years of age	**Routine risk minimization measures:** Labelled in pharmacological properties) of the SmPC **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pediatric investigation Plan: MOX15609

NOS: Not Otherwise Specified; SmPC: Summary of Product Characteristics.

3.1. Overall conclusion on the RMP

☒ The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

4. Changes to the Product Information

As a consequence of this variation, section 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the present application for a new paediatric indication of Mozobil does not bring any significant change to Patient Information Leaflet tested for Mozobil 20 mg/ml solution for injection. Therefore, no additional Readability testing was performed.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Patients receiving high-dose chemotherapy (HDC) to treat malignant disorders suffer from severe and potentially fatal myeloablation. Autologous haematopoietic stem cell transplantation (HSCT) using mobilized peripheral blood hematopoietic stem cells (HSCs) collected by apheresis is a common strategy for repopulation of the bone marrow and regeneration of trilineage blood cells (red blood cells, platelets, neutrophils). To yield a sufficient number of stem cells for apheresis, HSCs are increased in the peripheral blood by treating patients with G-CSF and/or with non-myeloablative chemotherapy. However, a significant proportion of patients may not be able to mobilize a sufficient or target number of cells for transplantation(s) with these HSC mobilization regimens, the so-called poor mobilisers.

5.1.2. Available therapies and unmet medical need

Currently, Mozobil is approved as for treatment for adult patients who are poor mobilisers in conjunction with G-CSF. Plerixafor (Mozobil) is a small-molecule bicyclam derivative that reversibly antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α, also known as CXCL12). This interruption of the CXCR4/SDF-1α interaction results in mobilization of HSCs positive for cell surface glycoprotein CD34 (CD34+ cells) to the peripheral blood where they can be collected for HSC transplantation.

There are no clear alternatives to plerixafor, since higher G-CSF and another chemotherapy cannot quickly be used when CD34+ turnout is low.

In this application, Mozobil in paediatric patients (1 to less than 18 years) 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 children with a lymphoma or a solid malignant tumour, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

This indication is considered to better capture the intent of pre-emptive plerixafor treatment that the initially proposed text, namely to target those subjects who are at likely to/at high risk for mobilisation failure, that is insufficient mobilisation to allow for collection of sufficient number of CD34+ stem cells to allow for autologous stem cell transplantation. Indeed, these are the subjects with the highest unmet medical need, as poor mobilisation may result in a failure to collect a sufficient number of CD34+ stem cells needed for HSCT. These poor mobilising patients may be offered a second round of stem cell mobilization and stem cell collection requiring additional mobilisation therapy and inpatient admission. In case patients are then still poorly mobilising, patients are at high risk of failure to obtain sufficient number of stem cells. These patients may as a consequence become ineligible for an autologous transplant procedure and thus cannot receive the high dose chemotherapy (HDC) because the absence of stem cell rescue. This may negatively impact their survival, or alternatively they may have to undergo allogeneic transplantation which is a more complex procedure with higher morbidity. While Mozobil has been registered for poor mobilising adults, there is still a need for an additional mobilisation treatment option for paediatric patients in need of HDC, in particular those who are (at high risk to be) poor mobilisers. This to increase mobilisation of stem cell and thereby ensure collection of sufficient number of

stem cells which would allow these patients to proceed to potentially life-saving HDC therapy because of the availability of subsequent stem cell rescue.

5.1.3. Main clinical studies

The study supporting this extension of the indication encompassed a dose-escalation phase (Stage 1) and a randomisation phase (Stage 2) comparing plerixafor at the dose selected in Stage 1 plus standard mobilization to standard mobilization alone. This study design was discussed and agreed to by the PDCO.

As the mechanism of action of plerixafor and the expression of CXCR4 and SDF-1 is similar between children and adults, a similar response in children as in adults is to be expected. However, direct extrapolation of adult efficacy data based on pharmacokinetics only was not possible as there may be differences in PK/PD between adults and children. This issue was addressed in Stage 1 of the study. Furthermore, as the underlying malignancies requiring HDC is different between the adult and paediatric population, the chemotherapy regimen is also likely to be different between adults and children. This concerns both the chemotherapy administered before HSC collection and the HDC regimes for which HCS rescue is needed. In principle, these differences might affect the response of the subject to mobilisation regimen as well as the marrow recovery and ability for HSC engraftment. This issue was addressed in Stage 2 of the study.

The inclusion and exclusion criteria are generally representative of the paediatric patient population who are in need of myeloablative HDC and thus stem cell rescue. However, there was no requirement for the subjects in the study to be (expected to be) a poor mobiliser. As a consequence, the studied population may have been insensitive for differences in the more clinically relevant endpoints (stem cell yield sufficient for transplantation, transplantation rate, etc.). The study design is in accordance with the agreed PIP (EMEA-000174-PIP01-07) with appropriate endpoints to collect the pharmacodynamic effect (primary endpoint) and potential clinically relevant effects (secondary endpoints) of adding plerixafor to standard mobilisation regime. The conduct of the study was of sufficient standard.

5.2. Favourable effects

The primary endpoint of Stage 2 was met: the proportion of patients with successful mobilization, defined as doubling of the PB CD34+ count from the morning before the apheresis day to the morning of the apheresis day, was significantly greater in the plerixafor plus standard mobilization arm (80%, 24 of 30 patients) compared to the standard mobilization only arm (28.6%, 4 of 14 patients) (p=0.0019). The results of the primary (pharmacodynamic) endpoint were supported by the other secondary/exploratory pharmacodynamic parameters.

Results for the clinically relevant endpoints in the plerixafor plus standard mobilisation group in stage 2 were good: 26 of 29 (89.7%) of evaluated patients reached the threshold of collecting $\geq 2 \times 10^6$ CD34+ cells/kg at first apheresis in the plerixafor plus standard mobilization. The rate of successful mobilization was similar across age and disease categories in the plerixafor plus standard mobilisation arm.

The percentage of patients who proceeded to transplant was 76.7% in the plerixafor plus standard mobilization, which was higher than that seen in the control arm where 66.7% of patients proceeded to transplant. All patients who were transplanted (23 in the plerixafor plus standard mobilization arm and 10 in the standard mobilization arm) successfully engrafted. Only minor differences in time to neutrophil engraftment (12 vs 14 day, for respectively plerixafor plus standard mobilisation vs standard mobilisation only) and time to platelet engraftment (28 vs 23 days, for respectively plerixafor plus standard mobilisation vs standard mobilisation only) were noted with overlapping 95% confidence intervals. Thus plerixafor exposure did not seem to negatively impact transplant efficiency.

A similar pattern in PD parameters was noted between adults and the paediatric population, this particularly concerns the effect of plerixafor on fold-increase in PB CD34+ count between Day 4 /pre-apheresis day and at the day of apheresis and the stem cell yield. The response to treatment of these parameters suggest a greater treatment effect of plerixafor in potentially poor mobilizing population.

Of the subjects in the paediatric study with PB CD34+ count below <20/µL (a risk factor for poor mobilisation), 1 of 4 control subjects had > 4 fold increase in CD34+ counts on the day of apheresis, while in the plerixafor arm, 9 of 17 subjects had > 4 fold increase in CD34+ counts on the day of apheresis. This also suggests efficacy of plerixafor treatment in (potential) low mobilising subjects in the paediatric population.

One subject < 2 years of age was randomised to the plerixafor + standard mobilisation arm, a high increase CD34+ cells from Day 4 to Day 5 PB CD34+ counts was noted in this subject (> 6 fold), suggesting that plerixafor was active in this small infant (13 months, 8.9 kg).

5.3. Uncertainties and limitations about favourable effects

There were no uncertainties about the favourable effects.

5.4. Unfavourable effects

In adults plerixafor treatment has been associated with injection and infusion site reactions, including allergic and anaphylactic reactions, gastrointestinal disorders (diarrhoea, nausea, vomiting, abdominal pain, stomach discomfort, dyspepsia, abdominal distention, constipation, flatulence, hypoaesthesia oral, dry mouth), fatigue, malaise, insomnia, hyperhidrosis, erythema, arthralgia, and musculoskeletal pain. Furthermore, specific warnings in the product information include potential for tumour cell mobilization in leukaemia patients, increased circulating leukocytes and decreased platelet counts, and splenic enlargement.

TEAEs were reported in 59% of paediatric patients in stage 1 subjects with TEAEs of Grade 3-4 recorded for 8 patients (30%). In stage 2 TEAEs were reported in 77% of paediatric patients in the plerixafor plus standard mobilization arm and 67% patients in the standard mobilization only arm. Grade 3-4 recorded TEAEs were recorded in 40% versus 43% of subjects.

Treatment–emergent AEs assessed by the investigator as related to study treatment were reported in 1 subject during stage 1, and during stage 2 in 4 (13.3%) patients in the plerixafor plus standard mobilization arm and none in the standard mobilization alone arm.

The observed adverse events in paediatric population were consistent with the known safety profile of plerixafor in adults.

5.5. Uncertainties and limitations about unfavourable effects

Due to the limited sample size in children potential small differences in frequencies or uncommon new AEs will not be captured.

5.6. Effects Table

Table 1. Effects Table for Mozobil for paediatric patients (1 to less than 18 years), to be used in combination with G-CSF to enhance mobilisation of haematopoietic stem cells (data cut-off: May 2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
successful mobilization	defined as at least a doubling of the PB CD34+ count observed from the morning of the day preceding the first planned apheresis day to the morning prior to apheresis	proportion of patients (n)	80% (24 of 30)	28.6% (4 of 14)	Statistically significant difference (p=0.0019) consistent across age and disease categories.
	number of patients reaching the desired threshold of $\geqslant 2 \times 10^6$ CD34+ cells/kg	proportion of patients (n)	90% (26 of 30)	93% (13 of 15)	No difference between the treatment arm. This is most likely due to the fact that patients were not selected for poor mobilisation status.
	number of days of apheresis required to collect $\geqslant 2 \times 10^6$ CD34+ cells/kg	Median day	1	1	No difference between the treatment arm. This is most likely due to the fact that patients were not selected for poor mobilisation status.
	total CD34+ cell yield	cells/kg	9.13×10^6	10.15×10^6	Local lab values were slightly different suggesting a certain level of variability in CD34+ counts.
	patients proceeding to transplant	proportion of patients (n)	76.7%	66.7%	
	Maximum increase in PB CD34+ counts (highest values in PB on the days of apheresis)	Relative to baseline levels	220%	39%	Post hoc exploratory analysis.
Unfavourable Effects					
TEAE		% (n)	77% (23)	67% (10)	
TEAE grade $\geqslant$ 3		% (n)	43% (13)	40% (6)	
TEAE related to treatment		% (n)	13% (4)	0	
SAE (including deaths)		% (n)	30% (9)	27% (4)	
Deaths due to AE		%	0	0	
Most common TEAE (SOC)	Any class Infections Blood and lymphatic Metabolism Nervous system Respiratory tract Gastrointestinal General disorders	% (n)	77% (23) 20% (6) 43% (13) 17% (5) 10% (3) 7% (2) 20% (6) 20% (6)	67% (10) 33% (5) 33% (5) 13% (2) 0 13% (2) 33% (5) 33% (5)	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	investigations		20% (6)	27% (4)	

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Overall, the data from the paediatric study taken together with an extrapolation approach building on the established clinical benefit in poor mobilising adults by comparing the effects seen in adults to those in the paediatric population are sufficient to support a paediatric indication. The similarity in the relationship between the PD response (fold increase) and pre-apheresis PB CD34+ count between adults and paediatric patients, and the established efficacy in the adult population is supportive of this extrapolation approach. The higher frequency of potentially poor mobilising subjects with a strong increase (>4 fold) in CD34+ counts in plerixafor-treated subjects in the paediatric study further supports the claim of efficacy. Together, this sufficiently supports the benefit of the addition of plerixafor to the standard mobilization for children who (are expected to) mobilise poorly.

Regarding the unfavourable effects, it is important to note that the observed safety profile in the paediatric population is consistent with that in adults, and that no new safety signals have been observed. Moreover, plerixafor exposure did not seem to negatively impact transplant efficiency.

Data on the effect of plerixafor in the age group <2 years is limited to 1 subject. A high increase in PB CD34+ cells following treatment was noted suggesting that plerixafor was active in this small infant (13 months, 8.9 kg). Thus the available (but very limited) data do not suggest that the potential lower exposure in children aged < 2 years is clinically relevant. Given this observation, the final indication is defined in children above 1 years old.

5.7.2. Balance of benefits and risks

Overall, it is considered that the provided PD and clinical data, focussing on the potentially low mobilising subjects (based on pre-apheresis PB CD34+ counts) and on similarities between adults and children in combination with the known mechanism of action of plerixafor, are sufficient to support the claim of a clinical relevant effect of plerixafor treatment in children who (are expected to) mobilise poorly. This effect of plerixafor is expected to reduce the risk of insufficient stem cell harvest and thereby of the need to undergo an additional round of stem cell mobilisation and apheresis or bone marrow harvest in order to collect sufficient stem cell numbers to proceed to potentially life-saving HSCT. Further, though limited data are available, based on the current results no major safety concerns have been identified and the overall safety profile is deemed acceptable also for the paediatric population. Therefore, it is considered that the benefit-risk balance of adding plerixafor to standard mobilisation for patients who (are expected to) mobilise poorly is positive. Overall, the currently presented data from this study and the extrapolation from the adult indication support the requested extension of indication.

5.8. Conclusions

The overall B/R of Mozobil in paediatric patients (1 to less than 18 years) in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with a lymphoma or a solid malignant tumour, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired haematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

is positive.

6. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include paediatric patients aged 1 to 18 years for Mozobil; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP (version 10.2) was agreed.

is recommended for approval.

This variation leads to amendments to the SmPC, Package Leaflet and to the Risk Managemnet Plan.

7. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Mozobil-H-C-1030-II-0034'