1 SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA **NAME OF FINISHED PRODUCT** Mozobil **NAME OF ACTIVE INGREDIENT** Plerixafor	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE OF STUDY:

Plerixafor and G-CSF for the Mobilisation of Peripheral Blood Stem Cells for Autologous Stem Cell Transplantation in Patients with Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD) or Multiple Myeloma (MM) – Safety Study in a General Autologous Transplant Population

INVESTIGATORS:

[redacted]

STUDY SITES:

This study was conducted at 26 centers in Europe.

PUBLICATION (REFERENCE):

Russell N, Douglas K, Ho A, Mohty M, Carlson K, Ossenkoppele G, Milone G, et al. Plerixafor (Mozobil®) and G-CSF for front-line peripheral blood stem cell mobilisation for autologous transplantation in lymphoma or multiple myeloma: preliminary results from the EU PREDICT study [Abstract]. Haematologica. 2011; In Press.

STUDIED PERIOD:	**PHASE OF DEVELOPMENT:**
Date First Patient Consented: 08 September 2008 **Date of Last Patient Out:** 18 November 2010	IIIb

OBJECTIVES:

Primary Objective:

- To confirm the safety profile of plerixafor to mobilise stem cells when used in patients with lymphoma or MM who are eligible to undergo treatment with an autologous hematopoietic stem cell transplant

Secondary Objectives:

- To assess efficacy of plerixafor and granulocyte-colony stimulating factor (G-CSF) as a mobilisation

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regimen as measured by the number of CD34+ cells collected in each apheresis session

- To assess the clinical effectiveness of plerixafor and G-CSF mobilised stem cells by examining hematopoietic cell engraftment and graft status
- To examine the influence of CD34+ cell dose infused on time to engraftment, engraftment and graft status

METHODOLOGY:

This was a multi-centre, open label single-arm study intended to investigate the safety and efficacy of plerixafor in patients with NHL, HD, or MM. Patients who have previously failed stem cell mobilization attempts or who have previously received more than one autologous or any allogeneic stem cell transplant were not eligible.

Screening for eligibility took place up to 30 days before the first dose of G-CSF. Baseline laboratory evaluations took place within 7 days prior to the first dose of G-CSF in order to determine final eligibility for enrollment. Patients received a stem cell mobilization regimen consisting of G-CSF (10 µg/kg subcutaneous [SC] administered in the morning each day) and plerixafor (240 µg/kg SC administered in the evening, beginning on the 4th day of G-CSF). The plerixafor dose was timed to allow for a 10- to 11-hour interval between each plerixafor dose and the initiation of each apheresis. Peripheral blood (PB) samples were collected for CD34+ cell analysis before and after the first dose of plerixafor. In addition, a sample was obtained from each apheresis product for determining the quantity of CD34+ cells collected each day. Patients continued to receive the evening dose of plerixafor then G-CSF the next morning followed by apheresis for up to a total of 5 apheresis procedures until a minimum of 5×10^6 CD34+ cells/kg were collected. More cells could be collected within 5 apheresis procedures at the physician's discretion. The mobilized stem cells could have been used for a tandem transplant if indicated and if a minimum number of CD34+ cells/kg was available (2×10^6 CD34+ cells/kg) for each transplant (no tandem transplants were given).

Following the last apheresis procedure, patients received pre-transplant myeloablative chemotherapy followed by transplantation of collected peripheral blood stem cells within 2 months of the last apheresis procedure. In the event that insufficient CD34+ cells for transplantation were collected, cells could be retained, pooled, and transplanted at a later date after the Investigator first obtained approval from the Sponsor. Patients were followed for 12 months after transplantation and returned to the clinic at 100 days, 6 and 12 months for safety and efficacy assessments. Patients were considered to have completed study participation after their 12-month study visit.

NUMBER OF PATIENTS:

Screened:126

Treated with plerixafor: 118

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Planned: approximately 100

Analyzed: 118

MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

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Subjects who met all of the following inclusion criteria were eligible to participate in this study:

1. Diagnosis of MM, NHL, or HD in partial response or complete response
2. Eligible and planned for an autologous hematopoietic stem cell transplantation
3. Written informed consent
4. At least 18 years of age (inclusive)
5. Eastern Cooperative Oncology Group performance status of 0 to 1
6. White blood cell (WBC) count $\geq 2.5 \times 10^9$/L
7. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
8. Platelet count $\geq 100 \times 10^9$/L
9. Serum creatinine ≤2.2 mg/dL
10. Aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, and total bilirubin $<2.5 \times$ upper limit of normal (ULN)
11. Adequate cardiac, renal, and pulmonary function sufficient to undergo apheresis and transplantation, i.e., eligible by institutional standards for autologous stem cell transplant
12. All patients had to agree to use a highly effective method of contraception whilst on study treatment and for at least 3 months following plerixafor treatment (including both female patients of child-bearing potential and male patients with partners of child-bearing potential). Effective birth control included: a) birth control pills, depot progesterone, or an intrauterine device plus 1 barrier method, or b) 2 barrier methods. Effective barrier methods were: male and female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). For patients using a hormonal contraceptive method, information about any interaction of plerixafor with hormonal contraceptives is not known.

Exclusion Criteria:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. History of any acute or chronic leukemia (including myelodysplastic syndrome)
2. Prior allogeneic transplantation or more than one prior autologous transplantation
3. Failed previous CD34+ cell collection attempts (either due to insufficient yield in apheresis product, or ineligible for apheresis because of inadequate mobilisation of CD34+ cells into PB)
4. Less than 4 weeks since last anti-cancer therapy (including chemotherapy, biologic/immunologic, radiation) or less than 6 weeks if prior therapy with nitrosourea or mitomycin (for therapies with long-acting agents, a treatment-free interval of at least 2 half-lives should be considered) with the exception of
   - Treatment with thalidomide, dexamethasone, lenalidomide (Revlimid®), and/or bortezomib (Velcade®) which was allowed up to 7 days prior to the first dose of G-CSF.
5. Bone marrow involvement >20% assessed based on the most recent bone marrow aspirate or biopsy
6. Treated with G-CSF or other cytokine within 14 days prior to the first dose of G-CSF for mobilisation
7. Known to be human immunodeficiency virus positive
8. Active hepatitis B or hepatitis C
9. Acute infection (febrile, i.e., temperature >38°C) within 24 hours prior to dosing or antibiotic therapy within 7 days prior to the first dose of G-CSF

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10. Hypercalcemia as evidenced by >1 mg/dL above ULN
11. Previously received investigational therapy within 4 weeks of enrolling in this protocol or currently enrolled in another investigational protocol during the mobilisation phase
12. Central nervous system involvement including brain metastases or leptomeningeal disease
13. Pregnant or nursing women
14. Electrocardiogram or study result (exercise study, scan) indicative of cardiac ischemia or a history of clinically significant rhythm disturbance (arrhythmias), or other conduction abnormality in the last year that in the opinion of the Investigator warranted exclusion of the subject from the trial.
15. Co-morbid condition(s), which in the opinion of the Investigator, rendered the patient at high risk from treatment complications or impaired their ability to comply with the study treatment and protocol

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Plerixafor 240 µg/kg by once-daily SC injection.

REFERENCE TREATMENT:

Not applicable.

DURATION OF TREATMENT:

Minimum of 1 and a maximum of 5 days of treatment and apheresis.

CRITERIA FOR EVALUATION:

EFFICACY:

The number of days of apheresis required to reach the minimum ($\geq 2 \times 10^6$ CD34+ cells/kg) and optimum ($\geq 5 \times 10^6$ CD34+ cells/kg for NHL and HD or $\geq 6 \times 10^6$ CD34+ cells /kg for MM) number of CD34+ cells was evaluated, along with the number of CD34+ cells collected per day of apheresis and the fold-increase in PB CD34+ cells.

Neutrophil (PMN) and platelet (PLT) recovery were assessed according to the following criteria:

Neutrophil engraftment was 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.

Platelet engraftment was defined as the first day when the PLT count was $\geq 20 \times 10^9$/L measured by at least 3 consecutive PLT laboratory values obtained over at least 7 days without transfusion.

The date at which PLTs reached $\geq 50 \times 10^9$/L measured by at least 2 PLT values over at least 7 days without transfusion was recorded.

The date at which hemoglobin reached ≥ 10 g/L without transfusion over the preceding 7 days was also recorded.

Delayed engraftment of PLTs was defined as achieving a sustained PLT count of $\geq 20 \times 10^9$/L (stable for at least 7 days without transfusion) but not reaching $\geq 50 \times 10^9$/L as defined by at least 2 consecutive PLT laboratory values obtained over at least 7 days and occurring within 100 days post transplant (day +100).

Graft failure in the absence of evidence of other causes such as progressive cancer, renal failure, chronic bleeding, severe infection, drug induced cytopenias, development of new hematological problems was defined as follows:

Primary PMN graft failure was defined as the failure to achieve a sustained ANC of $\geq 0.5 \times 10^9$/L (defined by 3 consecutive laboratory values on 3 different days) within 30 days post transplant (day +30).

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Primary PLT graft failure was defined as the failure to achieve a sustained PLT count $\geq 20 \times 10^9$/L (defined by at least 3 consecutive PLT laboratory values obtained over at least 7 days without transfusion) within 100 days post transplant (day +100).

Secondary PLT graft failure was defined as after achieving primary PLT recovery of $\geq 20 \times 10^9$/L there was a subsequent decrease in PLT counts below 10×10^9/L for 7 days (defined by at least 2 consecutive PLT laboratory values obtained over at least 7 days) or requirement for sustained PLT transfusion support.

Secondary PMN graft failure was defined as: After a sustained recovery of ANC $\geq 0.5 \times 10^9$/L there was a subsequent decrease in ANC such that the ANC fell to $<0.5 \times 10^9$/L for at least 7 days regardless of growth factor support.

Based on investigator determination, patients were assessed for disease recurrence or progression and/or death during the first 12 months following transplant.

SAFETY:

Patient safety was assessed based on extent of exposure and the monitoring of adverse events (AEs). The investigator graded AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0). Adverse events were recorded as follows: During the screening period (from signing consent form to first dose of G-CSF), only AEs related to study procedures were recorded.

All grade 3 and 4 AEs and all serious AEs (SAEs) that occurred from the first dose of G-CSF up to 30 days after the last dose of plerixafor or until the first dose of myeloablative chemotherapy, whichever occurred first, were documented.

Any AE regardless of grade that occurred during the immediate post-injection time period (30 minutes to 1 hour after plerixafor injection) was recorded.

Any AE, regardless of grade, that resulted in permanent discontinuation of plerixafor during the mobilization period was recorded.

Any SAE that occurred after the 30-day follow-up period that came to the attention of the site staff that may have been causally related to study drug was reported to the Sponsor regardless of time elapsed.

Any grade 3 or 4, study drug-related AE or any SAE was followed until resolution, return to baseline, or until mutually agreed upon by both the Investigator and the Sponsor safety physician to discontinue.

Disease progression, graft failure, and/or death were reported as SAEs for up to 12 months post-transplant.

Clinical significance for laboratory values was defined as any variation in a laboratory parameter that resulted in an intervention or otherwise an alteration in medical care. Laboratory values of clinical significance included but were not limited to: those meeting the criteria as a SAE, those causing study drug dose modifications and/or delays, or those that were the reason for a patient to discontinue study participation.

STATISTICAL METHODS:

This was an open-label, multi-centre study with no randomization.

POWER AND SAMPLE SIZE:

No formal sample size calculation was performed for this study.

ANALYSIS SETS:

The Safety Set and Full Analysis Set (FAS) were identical and consisted of all patients who were treated with at least one dose of plerixafor.

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EFFICACY:

All efficacy data summaries were performed on the FAS. The following efficacy parameters are tabulated:

Patients reaching minimum target CD34+ cells/kg within 4 days of apheresis - The number (%) of patients reaching a minimum target CD34+ cells/kg within 4 days of apheresis. Minimum target is defined as a cumulative yield $\geq 2 \times 10^6$ CD34+ cells/kg.

Days to reach minimum target CD34+ cells/kg - Days to reach minimum target, i.e., median number of aphereses needed to harvest $\geq 2 \times 10^6$ CD34+ cells/kg, are summarized.

Patients reaching optimum target CD34+ cells/kg within 4 days of apheresis - The number (%) of patients reaching an optimum target CD34+ cells/kg within 4 days of apheresis. Optimum target is defined as a cumulative yield $\geq 5 \times 10^6$ CD34+ cells/kg for NHL and HD or $\geq 6 \times 10^6$ CD34+ cells /kg for MM.

Days to reach optimum target CD34+ cells/kg - Days to reach optimum target is summarized.

Number of CD34+ cells/kg by day of apheresis - Summary statistics of the daily number of CD34+ cells/kg harvested during apheresis presented by day of apheresis.

Transplantation parameters - Summary statistics of the number of CD34+ cells/kg infused. The number (%) of patients with PMN and PLT engraftment and time to engraftment are presented.

Durability - The number (%) of patients with durable engraftment at 100 days, 6 and 12 months post transplant.

Peripheral Blood CD34+ Cells and Fold Increase - Summary statistics of PB CD34+ cells/μL and fold increase in PB CD34+ cells/μL post-plerixafor compared to pre-plerixafor.

SAFETY:

Safety data are summarized for the Safety Population. The following safety parameters are tabulated:

Extent of Exposure -Summary statistics are provided for the following parameters:

- dose of G-CSF mobilization (before plerixafor) per day (μg) / body weight (kg)
- dose of plerixafor (μg) per day (μg) / body weight (kg)
- number of G-CSF administrations for mobilization (before plerixafor)
- number of G-CSF administrations on days of apheresis
- number of plerixafor administrations

Adverse Events (AEs) - Adverse events were coded in Medical Dictionary for Regulatory Activities version 13.1. All reported AEs are listed. Treatment emergent AEs (TEAEs) defined as AEs starting on or after the date of first dose of plerixafor, and starting before Day 1 of ablative chemotherapy are tabulated. Non treatment emergent AEs are listed only. Incomplete start dates were imputed following a conservative approach, i.e., in case of partially missing start date, assume an AE was treatment emergent. An overview table presents the number (%) of patients with AEs, SAEs, related AEs, AEs leading to discontinuation and severe AEs. An AE is defined as related, if the relationship is 'possible', 'probable', 'definite' or not provided. An AE is defined as severe, if the CTCAE grade is at least 3 or not provided.

Serious Adverse Events (SAEs) - The number (%) of patients with SAEs are presented by system organ class (SOC) and preferred term (PT). Patients can count for multiple PTs within a SOC, if they experienced

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multiple SAEs. If a patient experienced multiple SAEs with the same PT, this patient is only counted once in that PT.

Duration of SAEs - Median, minimum and maximum duration of SAEs are provided. Duration is provided for selected PTs: diarrhea, nausea, fatigue, injection site erythema, headache, arthralgia, dizziness, vomiting, insomnia, flatulence, injection site pruritus, and anxiety. If a patient experienced multiple events, the event with the longest duration was considered.

Deaths - All patients who died are listed. Minimum information to be provided is patient ID, start and stop date, SOC, PT, relationship, and severity.

Serious Adverse Events by relationship - The number (%) of patients with SAEs is presented by relationship, SOC and PT. Patients can count for multiple PTs within a SOC, if they experienced multiple related SAEs. If a patient experienced multiple related SAEs with the same PT, this patient is only counted once in that PT. For patients with multiple incidences of AEs within a PT, only the strongest relationship is counted.

Serious Adverse Events leading to discontinuation - A listing of patients, who discontinued due to an SAE, is presented.

Serious Adverse Events by severity - The number (%) of patients with SAEs is presented by severity, SOC and PT. Patients can count for multiple PTs within a SOC, if they experienced multiple severe SAEs. If a patient experienced multiple severe AEs with the same PT, this patient is only counted once in that PT. For patients with multiple incidences of AEs within a PT, only the highest severity is counted.

RESULTS:

DISPOSITION AND DEMOGRAPHY:

A total of 118 patients received at least 1 dose of investigational product. Overall, 105 (89%) patients received a transplant, 88 (70%) patients completed the study, and 89 (75%) patients completed the 12-month follow-up evaluations. One patient completed the 12-month follow-up, but experienced an SAE of disease recurrence (noted at the 12-month visit) and was recorded as having terminated from the study early due to this event. The majority of patients were White (93% overall); and 2% were either Black, Asian, Native Hawaiian or Other Pacific Islander, or Other. The majority of patients (90/118, 76%) were diagnosed with MM, followed by NHL (25/118, 21%), and HD (3/118, 2.5%).

EFFICACY:

Of 114 patients who underwent apheresis 110/114 (96%) achieved the minimum cell collection within 4 days of apheresis. By disease group, 20 (80%) of the NHL group and 88 (98%) of the MM group achieved the minimum cell collection. The number of patients who achieved the optimum target cell collection within 4 days of apheresis was 97/114 (85%). By disease group, 12 (48%) of the NHL group and 83 (92%) of the MM group achieved the optimum cell collection. The median number of days of apheresis required to achieve the minimum cell collection was 1 day (range: 1 to 3 days). The median number of days of apheresis required to optimum target cell collection was 1 day (range: 1 to 4 days). The mean total number of CD34+ cells collected was 8.25×10^6 CD34+ cells/kg (range: 0.1×10^6 to 24×10^6 CD34+ cells/kg). The lower proportion of patients reaching target cell collections compared with phase 3 studies where 60% of patients with NHL achieved $\geq 5 \times 10^6$ CD34+ cells/kg may be due to variation expected from the small sample size in MOZ00808 and that 4 patients with NHL stopped collection at the investigator's discretion prior to reaching the optimum

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target cell collection or the maximum of 5 aphereses. An additional factor which may have affected PB CD34+ cell yield was the extensive myelosuppressive nature of chemotherapy regimens that some patients received prior to the study as well as the number of these regimens and the number of cycles received. Overall, the mean fold-increase in PB CD34+ cell count associated with the first dose of plerixafor was 3.85 (range: 0.2 to 94.0) which was somewhat lower than observed in the phase 3 studies.

Of the 105 patients who underwent transplantation 100/105 (95%) patients achieved PMN engraftment and 103/105 (98%) patients achieved PLT engraftment. Patients with lymphoma and MM usually have PMN engraftment within 12 days after transplantation, but it may occur as late as 21 days post transplant. The median number of days to PMN engraftment was 14 days (minimum 9 days, maximum 61 days). The median number of days to PMN engraftment (14 days) in MOZ00808 is longer than that observed in phase 3 studies (10 to 11 days) where all patients received G-CSF post-transplant. Approximately half (54%) of the patients who received a transplant in MOZ00808 did not receive G-CSF post-transplant, which may have influenced the number of days to PMN engraftment.

The median number of days to PLT engraftment was 18 days (minimum 0 days, maximum 61 days). A total of 18 patients did not engraft PMNs within 22 days post transplantation and there were 31 patients who did not achieve PLT engraftment within 22 days. However, only 2 patients failed to engraft PMNs and 1 patient failed to engraft PLTs at all. Some longer times to PLT engraftment (maximum 61 days) in MOZ00808 may have been influenced by some patients who returned home after PMN engraftment. In these cases blood samples for assessment of PLT engraftment would not have been taken daily, potentially giving an inflated number of days to PLT engraftment as the true date of engraftment could fall on a day when no assessment was made.

At 100 days post-transplant, 97/100 patients assessed had a durable graft, at 6 months 96/99 patients assessed had a durable graft, and 85/89 patients assessed had a durable graft at 12 months post-transplant. There were no reports of secondary graft failure. Twelve patients experienced disease progression or recurrence within 12 months post-transplant. Three patients received a second off-study allogeneic transplant during the 12 month follow-up period.

SAFETY:

This study provided plerixafor to 118 adult patients diagnosed with NHL, HD, or MM, 113 of whom were to receive treatment with an autologous peripheral stem cell transplant for the first time and 5 for the second time. Safety was assessed by the incidence of TEAEs/treatment emergent SAEs (TESAEs), serum chemistry tests, and hematological tests.

Forty-five (38%) of 118 patients reported TEAEs. The most frequently occurring TEAEs overall were (in order of decreasing frequency): diarrhea (9 patients), nausea (7 patients), and bone pain (5 patients). All other TEAEs occurred in less than 5 patients.

Overall, 22 patients experienced events of grade 1 severity, 15 patients experienced events of grade 2, 5 patients experienced events of grade 3, 2 patients experienced events of grade 4, and 1 patient experienced events of grade 5. The most common grade 1 or 2 TEAEs in order of decreasing frequency were: diarrhea (9 patients), nausea (7 patients), bone pain (5 patients), abdominal pain (4 patients), headache (4 patients), hypokalemia (4 patients), injection site erythema (4 patients), dizziness (3 patients), and vomiting (3 patients).

The frequency of TEAEs that were considered related to the study treatment was 24/118 (20%) patients. The most commonly occurring treatment-related TEAEs in order of decreasing frequency were: diarrhea (8 patients), injection site erythema (4 patients), nausea (4 patients), injection site reaction (3 patients),

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abdominal pain (2 patients), and vomiting (2 patients). All other treatment-related TEAEs were each experienced by 1 patient only. The majority of TEAEs that were considered related to the study treatment were grade 1 or 2, however 5 patients experienced events of grade 3 or 4 that were considered to be related to the study treatment: 1 patient experienced myocardial infarction (grade 3, SAE), 1 patient experienced myeloma relapse (grade 3, SAE), 1 patient experienced injection site reaction (grade 3, non-serious AE), 1 patient experienced both leukocytosis and PMN count increased (both grade 3 non-serious AEs), and 1 patient experienced non-serious AEs of procedural complication (grade 3), neutropenia (grade 4) and thrombocytopenia (grade 4).

Death was reported for 4 patients all of which occurred at least 46 days after the last dose of plerixafor and were not considered to be related to plerixafor. A total of 5 patients experienced TESAEs. These were myeloma occurrence (Grade 5), myocardial infarction (Grade 3), device (Hickman line) related infection (Grade 2), blood magnesium decreased (Grade 2), and deep vein thrombosis (Grade 1). Of these, 3 patients experienced serious, treatment-related AEs. Myocardial infarction (1 patient, MM), blood magnesium decreased (1 patient, NHL), myeloma recurrence (1 patient, MM). Two patients experienced TEAEs of which lead to study treatment discontinuation or modification. One patient experienced PLT count decreased (not related to plerixafor) and the second patient experienced blood magnesium decreased (possibly related to plerixafor).

Clinically significant laboratory findings observed in 2 or more patients were low potassium (4 patients - 3 at first apheresis time point, 1 of which was also low at screening. One patient at second apheresis), high WBC or ANC (3 patients - all at first apheresis time point), and low hemoglobin (2 patients - 1 at screening and first apheresis time points, the second at 12 month follow-up).

CONCLUSIONS:

[redacted]