SYNOPSIS

NAME OF COMPANY		SUMMARY TABLE	FOR NATIONAL AUTHORITY
Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA	Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands	Referring to Part …… of the Dossier: Volume: Page: Reference:	USE ONLY:
NAME OF FINISHED PRODUCT **Mozobil®** NAME OF ACTIVE INGREDIENT **Plerixafor**			

TITLE OF STUDY:

A Multicenter, Randomized, Comparative, Patient-Blinded Study to Evaluate the Safety and Efficacy of G-CSF Alone Versus AMD3100 (240 µg/kg) Added to a G-CSF Mobilization Regimen in Adult Patients with Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD) or Multiple Myeloma (MM) Who Have Previously Failed Stem Cell Collections or Collection Attempts

INVESTIGATORS AND STUDY CENTERS:

[redacted]

PUBLICATION (REFERENCE):

Not applicable

STUDIED PERIOD:

First Patient Enrolled: 29 November 2007

Last Patient Completed: 23 June 2009

PHASE OF DEVELOPMENT: Phase 2

OBJECTIVES:

The primary study objective was to determine if patients reach a target of $\geq 2x10^6$ CD34+ cells/kg within 2 days of apheresis in NHL, HD, or MM patients who are documented poor mobilizers (i.e., patients who had undergone apheresis during their most recent collection attempt but failed to collect a sufficient number of cells) that have received a mobilization regimen of granulocyte colony-stimulating factor (G-CSF) with placebo or a mobilization regimen of G-CSF with AMD3100 (plerixafor injection; hereafter referred to as Mozobil®).

The secondary study objectives were:

1. To examine and compare the safety of both mobilization regimens, G-CSF plus Mozobil (240 µg/kg) and G-CSF plus placebo in NHL, MM and HD patients.
2. To measure the daily and total number of CD34+ cells harvested during apheresis.
3. To measure the number of days of apheresis needed to harvest $\geq 2x10^6$ CD34+ cells/kg.
4. To measure the number of days of apheresis needed to harvest $\geq 5x10^6$ CD34+ cells/kg.

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5. To determine the times of platelet (PLT) and polymorphonuclear leukocyte (PMN) engraftment.
6. To evaluate the durability of engraftment.
7. To determine if patients reach the Optimum Target of $\geq 5x10^6$ CD34+ cells/kg within 4 days of apheresis.

METHODOLOGY:

This was a Phase 2, multicenter, randomized, comparative, patient-blinded study of the safety and efficacy of Mozobil (240 µg/kg), used in addition to a standard G-CSF mobilization regimen, for the collection of peripheral blood (PB) stem cells for autologous transplantation in patients with NHL, HD, or MM who had failed previous collections or collection attempts with a mobilization regimen of chemotherapy with or without G-CSF.

Eligible patients were randomized on a 1:1 basis to one of two treatment groups: G-CSF plus Mozobil or G-CSF plus placebo. All patients initially received a mobilizing regimen of G-CSF (10 µg/kg in the morning) for 4 consecutive days. The nonpegylated form of G-CSF was used throughout the study and was supplied by the clinical site itself. Starting on Day 4 of G-CSF treatment, Mozobil (240 µg/kg) or placebo (saline supplied by the clinical site itself) was administered via subcutaneous injection in the evening prior to each day of apheresis. Apheresis was initiated 10 to 11 hours following each dose of Mozobil or placebo. The dosing regimen of G-CSF in the morning (approximately 1 hour prior to apheresis) and Mozobil or placebo in the evening was repeated for a minimum of 2 and a maximum of 7 aphereses, until a minimum of $2x10^6$ CD34+ cells/kg were collected (for patients receiving tandem transplant, a minimum of $4x10^6$ CD34+ cells/kg were collected).

Venous samples for complete blood count (CBC) and CD34+ cell counts were obtained immediately prior to each administration of Mozobil or placebo and within 30 minutes prior to the administration of G-CSF on each apheresis day. In addition, each apheresis product was also measured for CBC and CD34+ cell count. The number of PB CD34+ cells/µL was measured by fluorescence activated cell sorting (FACS) analysis for absolute and percent of CD34+ cells/total.

Irrespective of the randomized treatment group, patients who failed to collect $\geq 0.8x10^6$ CD34+ cells/kg in 2 aphereses or $\geq 2x10^6$ CD34+ cells/kg in 7 aphereses were offered a rescue arm with G-CSF plus Mozobil.

Following stem cell collection by apheresis, patients underwent ablative chemotherapy before transplantation. Following transplantation, G-CSF (5 µg/kg) was started on Day 5 or Day 6 and continued until PMN engraftment (absolute neutrophil count [ANC] was $\geq 0.5x10^9$/L for 3 days or $\geq 1.0x10^9$/L for 1 day).

Patients were seen for follow-up at 100 days (±7 days), 6 months (±7 days) and 12 months (±7 days) after transplantation to evaluate PMN and PLT engraftment (PLT $\geq 20x10^9$/L without a transfusion in the previous 7 days) and graft durability.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Up to 30 patients (15 patients per treatment group) were originally planned for this study. However, since the implementation of the original protocol changes in standard apheresis practices in Germany meant it was considered unethical to perform 2 aphereses in patients to prove their "poor mobilization" status. Furthermore, the availability of additional data in a similar patient population from other clinical investigations indicated that no additional medical knowledge would be gained from continuing the study. Therefore, the study was limited to the 5 patients enrolled at the time of implementation of Protocol Amendment 4 (dated 03 December 2008). Of these, 2 patients were randomized to the G-CSF plus Mozobil treatment group and 3 patients were randomized to the G-CSF plus placebo treatment group.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

The inclusion criteria, which were re-evaluated prior to Mozobil dosing, were:

1. Aged 18 to 78 years.
2. Eligible to undergo autologous transplantation.
3. Diagnosis of NHL, HD or MM (patients with plasma cell leukemia or other leukemias, including Chronic Lymphocytic Leukemia, were excluded).
4. In the last collection attempt prior to entry into this trial, the patient had failed to collect $0.8x10^6$ cells/kg in at least 2 apheresis sessions or $2x10^6$ cells/kg in 4 apheresis sessions using a mobilization regimen of chemotherapy, with or without G-CSF.

   NOTE: The complete history of the failed collection and/or collection attempts, including the mobilization regimen, apheresis yield(s), and/or PB CD34+ cell count(s) were documented and submitted to Genzyme prior to enrollment and randomization.
5. A minimum of a 7-day interval between last collection attempt and randomization.
6. Performance status, Eastern Cooperative Oncology Group of 0 or 1.
7. Cardiac, pulmonary and renal function deemed clinically adequate to be able to undergo mobilization and transplant.
8. ≥21 days between the last cycle of chemotherapy (e.g., cyclophosphamide) and randomization (thalidomide, dexamethasone, and other corticosteroids, Rituxan and Velcade were not considered prior chemotherapy for the purpose of this study).
9. The patient had recovered from all acute toxic effects of prior chemotherapy.
10. White blood cell $>2.5x10^9$/L.
11. ANC $>1.5x10^9$/L.
12. PLT count $>75x10^9$/L.
13. Adequate renal function as demonstrated by serum creatinine ≤2.2 mg/dL or creatinine clearance (24 hr urine collection) >60 mL/min.
14. Serum Glutamate Oxaloacetate Transaminase, Serum Glutamate Pyruvate Transaminase and total bilirubin <2.5 × upper limit of normal (ULN).
15. No active Hepatitis A, B or C infection.
16. Signed informed consent.
17. All patients must agree to use a highly effective method of contraception (including both female patients of child-bearing potential and male patients with child-bearing potential partners). Effective birth control included: a) birth control pills, depot progesterone, or an intrauterine device **PLUS** one barrier method, or b) two 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 Mozobil with hormonal

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contraceptives is not known.

The exclusion criteria, which were re-evaluated prior to Mozobil dosing, were:

1. A co-morbid condition which, in the view of the Investigators, rendered the patient at high risk from treatment complications.
2. A residual acute medical condition resulting from prior chemotherapy.
3. Received thalidomide, dexamethasone or corticosteroids, Rituxan and Velcade within 7 days prior to randomization.
4. Brain metastases or carcinomatous meningitis.
5. Active acute or chronic infection or anti-infective therapy within 7 days of randomization.
6. Fever (temperature >38°C).
7. Hypercalcemia (>1 mg/dL above the ULN).
8. Known to be HIV-positive.
9. Pregnant and nursing females.
10. Patient unwilling to implement adequate birth control (including both female patients of child-bearing potential and male patients with child-bearing potential partners).
11. Patients who previously received experimental therapy within 4 weeks of randomization or who were currently enrolled in another experimental protocol during the Mobilization phase.
12. Patients who had failed a previous collection attempt within 7 days or less from randomization.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Mozobil (supplied as solution of 20 mg/mL) administered by subcutaneous injection (240 µg/kg/day); Batch Number: [redacted].

DURATION OF TREATMENT:

Patients in this study received once-daily treatment with Mozobil (240 µg/kg) or placebo for a minimum of 2 and a maximum of 7 consecutive days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Placebo (subcutaneous injection of normal saline) was used as the comparator. Saline was provided by the clinical site. The volume of placebo administered was determined using the same calculation as for Mozobil to ensure the same volume for injection.

CRITERIA FOR EVALUATION:

EFFICACY:

The efficacy of Mozobil was demonstrated by the ability to mobilize and collect stem cells. The primary efficacy endpoint was the binary response variable categorizing whether the patient was able to mobilize a minimum of at least $2x10^6$ CD34+ cells/kg within 2 days of apheresis.

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Supporting efficacy analyses included:

1. The number of daily and total number of CD34+ cells harvested during apheresis.
2. The number of days of apheresis required to reach $\geq 2x10^6$ CD34+ cells/kg.
3. The number of days of apheresis required to reach $\geq 5x10^6$ CD34+ cells/kg.
4. The number of days to PMN engraftment and to PLT engraftment.
5. Durable engraftment at 100 days post-transplant.
6. Optimum Target of $\geq 5x10^6$ CD34+ cells/kg within 4 days of apheresis.

SAFETY:

Safety was evaluated by adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, vital sign parameters and physical examination findings.

STATISTICAL METHODS:

As a consequence of the reduction in the number of patients enrolled in the study following implementation of protocol amendment 4, no statistical analysis or comparison between treatment groups could be performed for any endpoint. Instead, raw and derived data of all patients were listed and assessed on an individual patient basis. No summary tables were created and no P-values or confidence intervals were calculated due to the small number of patients.

SUMMARY – CONCLUSIONS

A total of 5 patients were enrolled in the study. Of these, 2 patients were randomized to the G-CSF plus Mozobil treatment group and 3 patients to the G-CSF plus placebo treatment group.
All 5 patients in the study were white females and met the study entry criteria of being between 18 and 78 years of age. In the G-CSF plus Mozobil group, 1 patient had MM and 1 patient had HD. In the G-CSF plus placebo group, 2 patients had MM and 1 patient had peripheral T-cell lymphoma. All patients had failed to collect at least $0.8x10^6$ cells/kg using a chemotherapy mobilization regimen in their last collection attempt prior to entry into this study.

EFFICACY:

Both patients in the G-CSF plus Mozobil group mobilized sufficient PB CD34+ cells to proceed to transplant: 1 patient after the first planned treatment and 1 patient after rescue treatment. One patient in the G-CSF plus placebo group also mobilized sufficient PB CD34+ cells after the first planned treatment to proceed to transplant. The other 2 patients in the G-CSF plus placebo group terminated the study early due to mobilization failure (both patients underwent rescue therapy with G-CSF plus Mozobil prior to withdrawal but failed to mobilize sufficient numbers of PB CD34+ and were withdrawn).

Of the 3 patients who proceeded to transplant, 1 patient in the G-CSF plus Mozobil group had achieved the optimum target of $\geq 5x10^6$ CD34+ cells/kg within 4 days of apheresis. All 3 patients who proceeded to transplant achieved PLT and PMN engraftment, and all 3 patients had durable grafts and were alive at 12-months follow-up.

SAFETY:

Both patients in the G-CSF plus Mozobil group and 2 of the 3 patients in the G-CSF plus placebo group experienced at least one AE during the study. One patient in the G-CSF plus placebo group did not

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experience any AEs.

The types of AEs reported were similar in each treatment group. Injection site reactions (redness, swelling or inflamed site) were reported for both patients in the G-CSF plus Mozobil group and 1 of the 3 patients in the G-CSF plus placebo group. Diarrhea was reported as an AE by 1 of the 2 patients in the G-CSF plus Mozobil group and in 2 of the 3 patients in the G-CSF plus placebo group. Edema of the lower extremities was reported as an SAE in 1 patient in the G-CSF plus Mozobil group, while 1 patient in the G-CSF plus placebo group experienced an AE of edema limb (pretibial). All AEs were of mild or moderate intensity with the exception of a severe event of hypokalemia in 1 patient in the G-CSF plus placebo group.

One SAE was reported during the study: 1 patient in the G-CSF plus Mozobil group experienced an SAE of edema of lower extremities that was considered by the investigator to be possibly related to study treatment. No events of interest were reported during the study and no patients discontinued due to an AE.

Reported changes in laboratory parameters were consistent with the known and expected effects of Mozobil treatment, G-CSF treatment, and apheresis.

CONCLUSIONS:

[redacted]