## SYNOPSIS

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

Long-term Observational Follow-up Study of a Multicenter, Randomized, Double blind, Placebo-controlled, Comparative Trial of AMD3100 (240 µg/kg) Plus G CSF (10 µg/kg) Versus G-CSF (10 µg/kg) Plus Placebo to Mobilize and Collect ≥6 × $10^6$ CD34+ Cells/kg in Multiple Myeloma Patients for Autologous Transplantation

**INVESTIGATORS/STUDY SITES:**

[redacted]

**PUBLICATION (REFERENCE):**

None

| **STUDIED PERIOD (FOR PATIENTS ENROLLED IN THE LTF STUDY):**<br>**Date First Patient Consented:** 12 June 2006<br>**Date of Last Patient Out:** 29 July 2011 | **PHASE OF DEVELOPMENT:**<br>Phase 3 follow-up |
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**OBJECTIVES:**

The objective of this long-term observational study is to assess OS, PFS, and relapse rates of patients treated with at least 1 dose of study treatment (placebo or plerixafor) for a period of 5 years following the first dose of study treatment (placebo or plerixafor) in Study AMD3100-3102.

**METHODOLOGY:**

This was a long-term, 5-year observational follow-up study to the pivotal AMD3100-3102 study (A Multicenter, Randomized, Double-blind, Placebo-controlled, Comparative Trial of AMD3100 [240 µg/kg]) plus granulocyte-colony stimulating factor (G-CSF) [10 µg/kg] Versus G-CSF [10 µg/kg] Plus Placebo to Mobilize and Collect ≥6 × 106 CD34+ Cells/kg in Multiple Myeloma Patients for Autologous Transplantation). No investigational drug was administered in this follow-up study.
The intent of this follow-up study was to obtain survival and disease outcome information for all patients in Study AMD3100-3102 (hereafter, referred to as Study 3102). The study population consisted of patients who had previously received at least 1 dose of study treatment (placebo or plerixafor) in Study 3102. This population also includes all patients who failed stem cell collection and elected to enter a rescue procedure (open label plerixafor).

After enrollment into Study AMD3100-3102-LTF (hereafter, referred to as Study 3102-LTF), patients were followed-up every 6 months at the study site or via telephone and at each follow-up contact, occurrence and date of occurrence of disease progression/relapse and/or death was recorded. For patients who did not enroll into Study 3102-LTF, information regarding their status was obtained from Study 3102 records and from Study 3102-LTF registration forms, if provided, as detailed in the Clinical Study Report (CSR).
Two annual updates providing interim summaries of OS, PFS, and relapse rates were previously generated based on follow-up data received at 3 and 4 years from the last patient's first study drug treatment

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(placebo or plerixafor).

**NUMBER OF PATIENTS (PLANNED AND ANALYZED):**

Out of the 294 patients enrolled in Study 3102, a total of 163 patients were contacted and enrolled into Study 3102-LTF. Study 3102 patients who did not enroll into Study 3102 LTF contribute data that is limited to that collected during Study 3102 and/or Study 3102 LTF registration form information.

**MAIN CRITERIA FOR INCLUSION/EXCLUSION:**

**Inclusion Criteria:**

All patients who provided a signed informed consent and received at least 1 dose of study treatment (placebo or plerixafor) in Study 3102.

**Exclusion Criteria:**

None

**DOSE/ROUTE/REGIMEN (TEST ARTICLE):**

Not applicable

**REFERENCE TREATMENT:**

Not applicable

**DURATION OF TREATMENT:**

Not applicable

**CRITERIA FOR EVALUATION:**

**EFFICACY:**

The efficacy variables in this study were OS, PFS, and relapse rate. Efficacy analyses were based on these variables for all patients who were treated in Study 3102. Data for these outcomes were collected from Study 3102, Study 3102-LTF Registration Forms and Study 3102-LTF as detailed in the CSR. In addition, best response to ablative therapy in Study 3102 was recorded on the 3102LTF Disease History case report form.

**SAFETY:**

Safety monitoring (disease progression and death are efficacy parameters in this study) was not required since investigational drugs were not administered during the long-term observational study.

Exposure to G-CSF and study drug (placebo or plerixafor) administration during mobilization in Study 3102 was summarized by treatment group in this study report.

**STATISTICAL METHODS:**

**POWER AND SAMPLE SIZE:**

The results from this study are purely observational in nature. As such, there is no specific sample size requirement for this study.

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**ANALYSIS SETS:**

**Full Analysis Set**: Patients in Study 3102 were randomized to receive treatment with G-CSF + placebo or G-CSF + plerixafor. The full analysis set (FAS) consisted of all patients who received at least 1 dose of placebo or plerixafor in Study 3102, regardless of entering rescue or receiving post-transplant cyto-reductive chemotherapy.

Patients in the FAS were assigned to 1 of the 2 treatment groups depending on exposure to plerixafor in Study 3102. Patients never exposed to plerixafor and only exposed to placebo were assigned to the "placebo" group and the first exposure to placebo was the reference date for outcome analyses. Patients exposed to plerixafor regardless of exposure to placebo were assigned to the "plerixafor" group and the first exposure to plerixafor was the reference date for outcome analyses.

All rescue patients were included in the FAS and assigned to the "plerixafor" treatment group as all were exposed to plerixafor (either during Study 3102 period or the rescue period, or both). The earliest receipt of plerixafor was considered the reference date for outcome analyses.

**FAS Non-Cyto-Reductive population:** This set, considered the Primary Population, included all patients who received at least 1 dose of study drug (placebo or plerixafor) and did not receive post-transplant cyto reductive chemotherapy.

**EFFICACY:**

The primary efficacy endpoints for this study were OS and PFS. Patients were observed for survival and disease status for a total follow-up period of up to 5 years from the first study drug treatment in Study 3102. Survival outcome data were collected from Study 3102, Study 3102-LTF, and from the Study 3102-LTF Registration Forms (details provied in the SAP), and disease status data were collected from Study 3102-LTF and from the Study 3102-LTF Registration Forms. Patients who have not died or progressed/relapsed, or for whom the date of the contributing event was not known, were censored on the date on which they were last documented to be alive without a report of disease progression/relapse; therefore, enrolled patients are censored on the last date reported in Study 3102-LTF while non-enrolled patients are censored on the last date reported in Study 3102 or on the Registration Form. These endpoints (OS and PFS) were estimated using the Kaplan-Meier (K-M) method. The number of observed and censored events were summarized.

Secondary analyses included overall relapse rate for a total follow-up period of up to 5 years from the first study drug treatment in Study 3102 and best response to ablative therapy in Study 3102.

The overall relapse rate and the best response was summarized per treatment group. The summaries were restricted to the patients entering the LTF study.

**SAFETY:**

Since investigational drugs were not administered in this observational study, no safety analyses were conducted other than exposure.

The FAS Non-Cyto-Reductive group was used for the safety analysis. Exposure to G-CSF and study drug (placebo or plerixafor) administration during mobilization in Study 3102 was summarized by treatment group in this clinical study report. For rescue patients, all exposure to G-CSF and plerixafor during both Study 3102 period and the rescue period were included; exposure to any placebo treatment was not included.

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**RESULTS:**

**DISPOSITION:**

Of the 294 Primary Population patients, 142 were placebo patients and 152 were plerixafor patients (7 of the 152 patients were placebo patients in the original Study 3102 randomized treatment assignment but received plerixafor during open label rescue).

- 163/294 (55%) patients (72 placebo and 91 plerixafor) were contacted and enrolled into the Study 3102-LTF study.
- 131/294 (45%) patients did not enroll into the Study 3102-LTF study.

The Registration Form captured the reason (i.e., patient died, was lost to follow up after Study 3102, or refused to participate) why patients did not enroll into the Study 3102-LTF study. Overall, the distribution of reasons for not enrolling in the Study 3102-LTF study appears comparable between the plerixafor and placebo treatment groups.

- A total of 40 (14%) patients died (20 placebo, 20 plerixafor) during and after Study 3102 and therefore, were not enrolled into Study 3102-LTF. These patients contribute complete survival data for OS and PFS analyses; however, relapse/progression was not captured for each patient.
- The remaining 91/294 (31%) patients (50/142 [35%] placebo and 41/152 [27%] plerixafor) did not enroll in the Study 3102-LTF for the below reasons:
    - 45 patients (25 placebo, 20 plerixafor) were lost to follow up during or after Study 3102.
    - 27 patients (14 placebo, 13 plerixafor) were at sites that declined to participate in the study.
    - 18 patients (10 placebo, 8 plerixafor) declined to participate.
    - 1 patient in the placebo group declined for unknown reason.

In summary, follow-up is complete for all 294 patients in the Primary Population.

**EFFICACY:**

Survival and disease progression data for all 294 patients in Study 3102 were collected from various sources and used for analysis of primary endpoints (overall survival [OS] and progression-free survival [PFS]).

- Median OS analysis, median OS was not reached for either the placebo or plerixafor groups. The estimated 12, 24, 36, 48, and 60 month OS probabilities for the placebo and plerixafor groups are estimated at 0.96 and 0.95, 0.87 and 0.87, 0.77 and 0.77, 0.67 and 0.70, and 0.64 and 0.64, respectively. The assessment of OS over 5 years has shown that there is no statistically significant difference (Log Rank p = 0.936; Wilcoxon p= 0.970) between the two groups.
- Median PFS analysis, median PFS was reached for the placebo (34 months) and plerixafor (26 months) groups. The estimated 12, 24, 36, 48, and 60 month PFS probabilities for the placebo and plerixafor groups are estimated at 0.88 and 0.83, 0.63 and 0.57, 0.46 and 0.38, 0.34 and 0.24, and 0.30 and 0.17, respectively. A non-statistically significant (Log Rank p = 0.061; Wilcoxon p= 0.138) trend for patients treated with plerixafor to have a shorter PFS than those receiving placebo was observed.
- Median triple endpoint (defined as death, progression/relapse, or introduction of alternative therapies used for the treatment of Multiple Myeloma [e.g., maintenance therapy], was reached at 20 months for both placebo and plerixafor groups. The estimated 12, 24, 36, 48, and 60 month triple endpoint probabilities for the placebo and plerixafor groups are estimated at 0.64 (both groups), 0.43 and 0.42, 0.28 and 0.27, 0.19 and 0.16, and 0.14 and 0.11, respectively. No statistically significant difference was observed in the triple endpoint (Log rank p=0.752, Wilcoxon p=0.944).

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relapse rate and best response to Study 3102 treatment were secondary endpoints.

- Overall relapse rate was in line with PFS and higher in the plerixafor group (60%) than the placebo group (42%). Given the potential limitations of the data collection for this endpoint, overall relapse rate analysis may not represent an accurate picture of the actual relapse rates of patients in Study 3102.
- Best response to Study 3102 treatment (provided by a limited number of patients) was similar between the placebo and plerixafor groups with CR being the most common response.

**SAFETY:**

Safety monitoring, other than disease progression or death (which are efficacy parameters in this study), was not required since investigational drugs were not administered during the long-term observational study.

Exposure to G-CSF and study drug (placebo or plerixafor) administration during mobilization in Study 3102 was summarized by treatment group and presented in the CSR.

**CONCLUSIONS:** [redacted]