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Sponsor: Sanofi **Drug substances:** GZ316455	**Study Identifiers:** U1111-1152-4403, NCT02221479 **Study code:** ACT13710

Title of the study: A randomized, open-label, two-arm parallel group, comparative study for assessing the clinical benefit of subcutaneous injection of Plerixafor plus G-CSF for mobilization and collection of peripheral hematopoietic stem cells in Japanese patients with multiple myeloma

Study center(s): 5 sites in Japan

Study period:

Date first patient enrolled: 14/Oct/2014

Date last patient completed: 07/Jul/2015

Phase of development: 2

Objectives:

Primary objective:

- To determine if a higher proportion was observed in multiple myeloma (MM) patients who mobilized with G-CSF plus plerixafor 240 µg/kg (GP) achieved a targeted number of ≥ 6 × 10^6 CD34+ cells/kg in 2 or fewer days of apheresis than MM patients mobilized with G-CSF alone (G).

Secondary objectives:

- To evaluate the safety of the GP arm compared to the G arm in MM patients.
- To compare the 2 treatment arms with respect to the number of patients who achieved a minimum of 2 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis.
- To compare the 2 treatment arms with respect to the number of days of apheresis required to reach the target of ≥ 6 × 10^6 CD34+ cells/kg.

Exploratory Study Objectives:

- To assess the PK of plerixafor (optional: PK assessment was implemented in principle, except patients unavailable to agree to participate in PK assessment).

Methodology: Randomized, open-label, 2-arm parallel group, comparative study

Number of patients:

Planned: 14

Randomized: 14

Treated: 14

Evaluated:

Efficacy: 14

Safety: 14

Pharmacokinetics: 14

Diagnosis and criteria for inclusion: Japanese patients with histological or pathological diagnosis of MM age 20 to 75, in their first or second complete response or partial response, and signed a written informed consent prior to performance of any study-related procedures.

Study treatments

Investigational medicinal product: Plerixafor

Formulation: Single-use vial was filled to deliver 1.2 mL of the sterile solution that contained 24 mg of plerixafor and 5.9 mg of sodium chloride in water for injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Route of administration: Subcutaneous (SC) route

Dose regimen: Plerixafor 240 µg/kg administered once daily

Noninvestigational medicinal product: Filgrastim

Formulation: Pre-filled syringe of or solution filgrastim 400 µg/m^2

Route of administration: Subcutaneous route

Dose regimen: Filgrastim 400 µg/m^2 once daily

Duration of treatment: Up to 8 days

Duration of observation: Up to 75 days

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- Primary endpoint was defined as proportion of patients who achieved a collection of ≥ 6 × 10^6 cells/kg CD34+ cells in ≤ 2 days of apheresis

Secondary Endpoint:

- Proportion of patients who achieved a collection of a minimum target of 2 × 10^6 cells/kg CD34+ cells in ≤ 4 days of apheresis
- Number of days of apheresis to collect 6 × 10^6 cells/kg CD34+ cells
- Number of days of apheresis to collect 2 × 10^6 cells/kg CD34+ cells
- Total number of CD34+ cells/kg collected over up to 4 apheresis
- The average number of CD34+ cells count per day
- The relative increase (ratio) of PB CD34+ cell count (cells/µL) between the following successive time points:
  - from Day 4 morning to Day 5 morning for both arm
  - from Day 4 morning to Day 4 evening, and from Day 4 evening to Day 5 morning for GP arm only

Safety:

Safety was assessed by the monitoring of AEs, clinical laboratory measurements (hematology, clinical chemistry, and coagulation), vital signs and physical examinations.

Pharmacokinetics:

Summary statistics of plerixafor plasma concentrations

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Plerixafor concentrations in plasma were determined at pre-defined time points (Day 4 PM and Day 5 AM) for patients who agreed to participate in the PK assessment.

Statistical methods:

Analysis population

Efficacy population:

The efficacy evaluable population was defined as those patients who were randomized and completed at least 1 apheresis yield of CD34+ cells during the initial treatment period. Those patients considered a treatment failure due to the early discontinuation after the G-CSF administration and before apheresis were included in this population.

Safety population:

The safety population was defined as the patients who received any amount of study treatment in the initial treatment period, analyzed according to the treatment actually received. If the patient received any amount of plerixafor in the initial treatment period, the patient was treated as a patient in the GP arm during the initial treatment period.

Rechallenged efficacy population:

The rechallenged efficacy population was defined as the rechallenged patients who were registered and had completed at least 1 apheresis yield of CD34+ cells during the rescue period. Those patients considered a treatment failure due to the early discontinuation after G-CSF administration before apheresis during the rescue period were included in this population. The rechallenged safety population was defined as the rechallenged patients who received any amount of study treatment during the rescue period.

Primary Analysis of efficacy primary endpoint

The analysis for efficacy primary endpoint was to calculate the treatment success proportion for each treatment group. 90% CI was also presented using Clopper-Pearson methods. The analysis was performed on the efficacy population.

Analysis of main efficacy secondary endpoints

Minimum success proportion defined as a proportion of patients who achieved a collection of ≥ 2 × 10^6 CD34+ cells/kg in ≤ 4 days and 90% CI was presented for each treatment group. Number of days of apheresis to collect 6 × 10^6 cells/kg CD34+ cells was analyzed using Kaplan-Meier method. Total number of CD34+ cell count collected over up to 4 apheresis, and the average number of CD34+ cells count per day were summarized using descriptive statistics. The raw data and the relative increase of PB CD34+ cell count at each time point were summarized using descriptive statistics

Analysis of safety endpoints

TEAEs were summarized with respect to frequency, incidence, intensity /severity (as graded by NCI CTCAE v4.03). All AEs were coded using the Medical dictionary for regulatory activities (MedDRA) system. Other analyses of safety endpoints including laboratory test, and vital sign are summarized using descriptive statistics.

Summary:

Population characteristics: The number of male and female patients was comparable at 8 (57.1%) and 6 (42.9%) respectively. All patients were Asian. The mean age was 59.5 years (range: 38 to 71).

Efficacy results: For the primary efficacy endpoint, more patients on the GP arm (5/7 patients, 71.4%) achieved a collection of ≥ 6 × 10^6 cells/kg CD34+ cells in ≤ 2 days of apheresis than on the G arm (0/7 patients). Of the 2 patients on the GP arm who did not achieve the primary efficacy endpoint, 1 patient achieved more than 5 × 10^6 cell/kg CD34+ cells on Day 1, and the other patient achieved 4.95 × 10^6 cell/kg CD34+ cells in 2 days. These two patients discontinued due to a reason other than AEs from treatment with plerixafor.

All patients on the GP arm and 6/7 patients (85.7%) on the G arm achieved a collection of 2 × 10^6 cells/kg CD34+ cells in ≤ 4 days of apheresis. The median time to collect ≥ 6 × 10^6 cells/kg was 2.0 days for GP arm while no patients achieved the target on the G arm. For the GP arm, the cumulative success probability was (95%CI) 0.143 (0.000 to 0.402) on Day 1 and 0.829 (0.524 to 1.000) on days 2 through 4.The median time to collect ≥ 2 × 10^6 cells/kg was 1.0 days for GP arm and 2.0 days for the G arm.

The mean (SD) for the total number of CD34+ cells up to 4 apheresis was 7.55 (2.32) x 10^6 cells/kg for the GP arm and 3.67 (1.25) x 10^6 cells/kg for the G arm and the mean (SD) average number of CD34+ cells per day was 4.13 (1.08) x 10^6 cells/kg for the GP arm and 0.92 (0.31) x 10^6 cells/kg for G arm. The median (range) relative increase in venous blood CD34+ cells/µL from the morning of Day 4 to the morning of Day 5 was 5.01 (3.4 to 8.9) for the GP arm and 1.95 (0.6 to 2.5) for the G arm. For the GP arm, the median (range) relative increase in venous blood CD34+ cells/µL from the morning of Day 4 to the evening of Day 4 was 1.67 (1.1 to 3.0) and 3.32 (1.6 to 6.8) from the evening of Day 4 to the morning of Day 5.

Safety results: A total of 10 patients experienced a TEAE, including 6 patients (85.7%) in the GP arm and 4 (57.1%) in the G arm. For all 6 patients in the GP arm with TEAEs, the events were considered by the Investigator to be related to the study treatment and for 2 of 4 the patients with a TEAE in the G arm, the events were related to either G-CSF alone or plerixafor.

The incidence of TEAEs (all grades) was 85.7 % in the GP arm vs 57.1 % in the G alone arm. No patients had Grade 4 or 5 TEAEs, and 3 patients had 4 Grade 3 TEAEs. The incidence of treatment-related TEAEs was higher in the GP arm (6/7 [85.7%]) than in the G arm (2/7 [28.6 %]). In the GP arm, the most frequently reported TEAEs were back pain (5 [71.4%]), headache (2 [28.6%]), and diarrhea (2 [28.6%]). No serious AEs were reported in the GP arm, and 2 serious AEs (Grade 3 decreased appetite and Grade 3 hepatic function abnormal) considered related to G-CSF were reported for 1 patient in the G arm.

No deaths, pregnancies, vasovagal TEAEs, systemic allergic reactions, symptomatic overdoses or discontinuations for AEs were reported.

In conclusion, the TEAEs observed in the GP arm of this study in Japanese patients with MM were consistent with the known safety profile of plerixafor.

Pharmacokinetic results: Participation in PK testing was optional in this study, and plasma concentration results were only available for 4 patients with sparse sampling. Following a single SC administration of plerixafor to four patients, plasma concentrations were the highest at 30-60 minutes and declined to approximately 1/5 at 9-10 hours. Variability in plasma concentrations between patients was low to moderate.

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