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Sponsor: Sanofi **Drug substance(s):** GZ316455	**Study Identifiers:** U1111-1152-4309, NCT02221492 **Study code:** ACT12781

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 non-Hodgkin lymphoma

Study center(s): 15 sites in Japan

Study period:

Study initiation date (first patient enrolled): 25/Nov/2014

Date last patient completed: 28/Mar/2016

Phase of development: 2

Objectives:

Primary objective

- To determine if a higher proportion was observed in non-Hodgkin Lymphoma (NHL) patients who mobilized with granulocyte-colony stimulating factor (G-CSF) plus plerixafor 240 µg/kg (GP) achieved a target number of ≥5 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis than NHL patients mobilized with G-CSF alone (G).

Secondary objective(s)

- To evaluate the safety of the GP arm compared to the G arm in NHL patients
- To compare the 2 treatment groups 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 groups with respect to the number of days of apheresis required to reach the target of ≥5 × 10^6 CD34+ cells/kg

Exploratory objective

- To assess the pharmacokinetics (PK) - optional

Methodology:

Randomized (1:1), open-label, 2-arm parallel group, comparative study

Number of patients**:**

Planned: 30

Randomized: 32

Treated: 32

Evaluated:

Efficacy: 32

Safety: 32

Pharmacokinetics: 8

Diagnosis and criteria for inclusion:

Japanese patients with histological or pathological diagnosis of NHL 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 contains 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)

Dose regimen: Plerixafor 240 µg/kg administered once daily

Noninvestigational medicinal product: G-CSF (Filgrastim)

Formulation: Pre-filled syringe / Solution for injection

Route of administration: Subcutaneous

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 efficacy endpoint

- Proportion of patients who achieved a collection of ≥5 × 10^6 CD34+ cells/kg in ≤4 days of apheresis

Secondary efficacy endpoints

- Proportion of patients who achieved a collection of a minimum target of 2 × 10^6 CD34+ cells/kg in ≤4 days of apheresis
- Number of days of apheresis to collect ≥5 × 10^6 CD34+ cells/kg
- Number of days of apheresis to collect ≥2 × 10^6 CD34+ cells/kg
- Total number of CD34+ cells/kg collected over up to 4 apheresis
- The relative increase (ratio) of peripheral blood (PB) CD34+ cell count (cells/µL) between the following successive time points:
  - From the morning of Day 4 to the morning of Day 5, 6, 7, and 8, for both arms.
  - From the morning of Day 5 to the morning of Day 6, from the morning of Day 6 to the morning of Day 7, and from the morning of Day 7 to the morning of Day 8, for both arms.
  - From the morning of Day 4 before G-CSF administration to the evening of Day 4 before plerixafor administration, and from the evening of Day 4 before plerixafor administration to the morning of Day 5 before G-CSF administration, for the GP arm only.

Safety:

Safety was assessed by the monitoring of adverse events (AEs), clinical laboratory measurements (hematology, clinical chemistry, and coagulation), vital signs, and physical examinations during the period from the signature of the informed consent until the end of the follow up.

Pharmacokinetics (exploratory) : 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. Plasma samples were analyzed for the concentration of plerixafor using a validated liquid chromatography-tandem mass spectrophotometry method.

Statistical methods:

The study period was divided into two periods exclusively based on the timing of the data collection. The initial treatment period is defined as the time from the informed consent to the 30-day follow-up visit, or the first day of radiotherapy or ablative chemotherapy, or the first dose of G-CSF administration in rescue procedure (only if the patient enters the rescue procedure), whichever occurs earlier. The rescue period is defined as the time from the first G-CSF administration after receipt of the 2nd informed consent, up to the 30-day follow-up visit, or the first day of radiotherapy or ablative chemotherapy, whichever occurs earlier.

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. However, those patients considered a treatment failure due to the early discontinuation after the G-CSF administration and before apheresis were included in this population as an exception to the above definition.

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.

Re-challenged population:

The re-challenged efficacy population was defined as the re-challenged patients who were registered and had completed at least 1 apheresis yield of CD34+ cells during the rescue period. However, 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 re-challenged safety population was defined as the re-challenged patients who received any amount of study treatment during the rescue period as the exception of the above definition.

Primary Analysis

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

Analysis of secondary efficacy endpoints

Minimum success proportion defined as a proportion of patients who achieved a collection of ≥2 x 10^6 CD34+ cells/kg in ≤4 days and 90% CI was presented for each treatment group. Number of days of apheresis to collect 5 x 10^6 CD34+ cells/kg 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 individual data and the relative increase of PB CD34+ cell count at each time point were summarized using descriptive statistics

Analysis of safety endpoints

For the safety analysis, treatment-emergent adverse events (TEAEs) were summarized with respect to incidence, intensity /severity (as graded by NCI CTCAE v4.03). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Other analyses of safety endpoints including laboratory test, and vital sign are summarized using descriptive statistics.

Summary:

Population characteristics:

A total of 32 Japanese patients were randomized and received at least 1 dose of study treatment (G-CSF only [G] or G-CSF plus plerixafor [GP]). Three patients in the GP arm and 5 patients in the G arm did not complete study treatment during the initial treatment period. One patient in the GP arm and 2 patients in the G arm discontinued due to AEs. Five patients in the G arm, who failed collection thresholds (ie, did not collect at least 0.8 x 10^6 CD34+ cells/kg after 2 days of apheresis or who did not achieve at least 2 x 10^6 CD34+ cells/kg in 4 apheresis days), subsequently had a rescue procedure (re-challenged patients).

There was no substantial difference between the 2 treatment groups. The mean age was 56.2 years in the GP arm and 57.5 years in the G arm, respectively. The numbers of male patients were more than female in both treatment groups.

Most patients had stage III or IV disease at baseline. All patients were complete response (CR) or partial response (PR). Mean time from initial diagnosis to randomization was 24.21 months in the GP arm and 10.84 months in the G arm, respectively.

Efficacy results:

For the primary efficacy endpoint, 9 of 16 (56.3%; 90% CI, 33.34% to 77.33%) patients in the GP arm achieved a collection of ≥5 × 10^6 cells/kg CD34+ in ≤4 days of apheresis, while 1 of 16 (6.3%; 90% CI, 0.32% to 26.40%) patient achieved this target in the G arm (treatment difference of 50.0% [90%CI: 23.04 to 76.96]; odds ratio of 13 [90% CI: 3.02 to 88.33]).

Fifteen out of 16 (93.8%; 90% CI, 73.60% to 99.68%) patients in the GP arm achieved a collection of ≥2 × 10^6 CD34+ cells/kg within 4 apheresis days and 5 of 16 (31.3%; 90% CI, 13.21% to 54.83%) in the G arm.

The median number of apheresis days to achieve a collection of ≥5 × 10^6 CD34+ cells/kg was 3.5 days in the GP arm and the cumulative success probability and the 95% CI were 0.125 (0.000 to 0.287) on Day 1, 0.250 (0.038 to 0.462) on Day 2, 0.500 (0.255 to 0.745) on Day 3, and 0.600 (0.337 to 0.863) on Day 4. Only one patient in the G arm achieved the target cell dose on Day 2.

Safety results:

For study treatment (plerixafor), the mean cumulative dose of study drug/body weight was 762.74 µg/kg with an average of 3.2 days of administration in the GP arm. For G-CSF, there were similar exposure between the GP arm and the G arm.

In the safety population, 81.3% (13 of 16) of the patients in the GP arm and 75.0% (12 of 16) of the patients in the G arm experienced at least 1 TEAE. A total of 75.0 % (12 of 16) of the patients in the GP arm and 68.8% (11 of 16) of the patients in the G arm experienced at least 1 TEAE considered to be related to study treatment (plerixafor and/or G-CSF).

A total of 25.0% (4 of 16) of the patients in the GP arm and 18.8% (3 of 16) of the patients in the G arm experienced at least 1 TEAE which was ≥Grade 3. A total of 6.3% (1 of 16) of the patients in the GP arm and 6.3% (1 of 16) of the patients in the G arm experienced at least 1 TEAE which was ≥Grade 3 and considered to be related to study treatment as per investigator judgment.

The TEAEs (all grades) occurring in ≥2 patients in the GP arm were the following: back pain (9 of 16, 56.3%); platelet count decreased (4 of 16, 25.0%); headache, diarrhea, and nausea (3 of 16, 18.8% each); and arthralgia (2 of 16, 12.5%). Headache, diarrhea, nausea, arthralgia, and platelet count decreased reported more frequently in the GP arm than in the G arm by 2 or more patients are expected TEAEs with plerixafor.

Back pain was reported similarly in both groups; 9 patients in the GP arm and 8 patients in the G arm. These patients were considered related to study treatment (plerixafor and/or G-CSF). Only 1 reported TEAE of back pain was considered related to both plerixafor and G-CSF in the GP arm, because the back pain occurred during the G-CSF and plerixafor administration period. The remaining back pain occurred during G-CSF mobilization period and was considered not related to plerixafor.

There were no meaningful differences between the treatment arms with respect to specific laboratory parameters. An exception to this was neutrophil counts in which the median increase in the GP arm was slightly higher than in the G arm as one would expect with plerixafor. The occurrence of all grades of electrolyte abnormalities was similar between the treatment arms. All Grade 3 and Grade 4 electrolyte abnormalities resolved.

The most frequently reported ≥Grade 3 TEAE was platelet count decreased which developed in 3 patients in the GP arm and 1 patient in the G arm. Differences between the two treatment arms with respect to hematologic factors are not considered clinically meaningful.

The number of patients with at least 1 PCSA for BP and HR during treatment period was low and consistent between the 2 treatment groups.

One patient (platelet count decreased: Grade 2) in the GP arm and 2 patients (hypoxia: Grade 3 and fatigue: Grade 2) in the G arm had early treatment discontinuation due to TEAEs.

There were no deaths during the study.

There were no treatment emergent serious adverse events (SAEs) in the GP arm.

Pharmacokinetic results: Following a single SC administration of plerixafor to 8 patients, plasma concentrations were the highest at 30 to 60 minutes and declined to approximately 1/6 of the maximum mean concentration at 9 to 10 hours. Variability in plasma concentrations between patients was low to moderate.
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