These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** GZ316455	**Study Identifiers:** U1111-1131-0145, NCT01767714 **Study code:** AMD3100 (EFC12482)

Title of the study: A phase 3 multicenter, randomized, double-blind, placebo-controlled, comparative trial of plerixafor (0.24 mg/kg) plus G-CSF (10 µg/kg) versus G-CSF (10 µg/kg) plus placebo to mobilize and collect ≥5 × 10^6 CD34+ cells/kg in non-Hodgkin's Lymphoma (NHL) patients for autologous transplantation

Study center(s): 16 active centers in China

Study period:

Date first patient enrolled: 10/Apr/2013

Date last patient completed: 26/Nov/2014

Phase of development: Phase 3

Objectives:

Primary Objective: To determine if NHL patients mobilized with granulocyte-colony stimulating factor (G-CSF) (GRAN® only; 10 µg/kg/day) plus 0.24 mg/kg/day of plerixafor are more likely to achieve a target number of ≥5 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis than NHL patients mobilized with G-CSF (GRAN® only; 10 µg/kg/day) plus placebo.

Secondary Objectives:

- To evaluate the safety of G-CSF (10 µg/kg/day) plus plerixafor 0.24 mg/kg/day compared with G-CSF plus placebo
- To determine whether adding plerixafor to a standard G-CSF mobilization regimen increases the incidence of patients who achieve a minimum of 2 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis, compared with placebo
- To determine whether adding plerixafor to the standard mobilization regimen decreases the number of days of apheresis required to reach the targets of ≥5 × 10^6 CD34+ cells/kg and ≥2 × 10^6 CD34+ cells/kg, compared with placebo
- To determine whether adding plerixafor to the standard mobilization regimen improves the neutrophil and platelet engraftment, compared with placebo
- To assess pharmacokinetics (PK) and pharmacodynamics (PD) (CD34+ cell mobilization) of plerixafor in a subset of patients

Methodology:

Multicenter, randomized, double-blind, placebo-controlled, comparative study

Number of patients:

Planned: 100

Randomized: 100

Treated: 100

Evaluated:

Efficacy: 100

Pharmacodynamics: 31

Safety: 100

Pharmacokinetics: 32

Diagnosis and criteria for inclusion:

Patients with NHL who were in first or second complete remission (CR) or partial remission (PR), defined for the purpose of this study as complete or partial response following first- or second-line therapy, planned to have and were eligible for autologous HSC transplantation, and had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

Study treatments

Investigational medicinal product: Plerixafor

Formulation: A sterile, preservative-free, clear, colorless to pale yellow, isotonic solution in single-use, 2 mL glass vials. Each 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.

Route of administration: Subcutaneous (SC) injection

Dose regimen: 0.24 mg/kg/day in the evening between 10:00 PM and 11:00 PM on Day 4, up to a maximum of 4 doses till Day 7

Investigational medicinal product: Placebo for Plerixafor

Formulation: A preservative-free colorless solution for SC in single-use, 2 mL glass vials. Each vial contained 1.2 mL of 0.9% sodium chloride.

Route of administration: SC injection

Dose regimen: 0.24 mg/kg/day in the evening between 10:00 PM and 11:00 PM on Day 4, up to a maximum of 4 doses till Day 7

Noninvestigational medicinal product: G-CSF

Formulation: G-CSF (GRAN® only; 10 μg/kg/day; Kirin Kunpeng Biopharmaceutical Co.) was labeled with study-specific details and in accordance with specific country regulatory requirements.

Route of administration: SC injection

Dose regimen: 10 μg/kg/day for 4 mornings (4 doses) for mobilization, followed by another dose each morning before apheresis on days that the patient was to continue apheresis (up to 8 doses in total)

Duration of treatment: Patients received a mobilization regimen consisting of G-CSF for 4 days. On Day 4, patients were randomized to receive the IMP in a 1:1 ratio (either plerixafor or placebo). On Day 5, patients received a dose of G-CSF approximately 9 to 10 hours after IMP administration, followed by stem cell collection 1 hour later (± 15 minutes). Patients continued to receive the same regimen for a maximum of 4 days of apheresis. If patients achieved collection of ≥5 × 10^6 CD34+ cells/kg in <4 days of apheresis, apheresis could be discontinued at that point or the patient could continue to the maximum of 4 days of apheresis to pool additional cells. Treatments were completed until patients satisfied the criteria for transplantation or became eligible for the Open-label Rescue Period, in which the treatment was repeated beginning on the Day 1 of G-CSF after a minimum of 7-day rest period. Patients who entered the Rescue Period could receive maximum 16 doses of G-CSF, 4 doses of double-blind IMP, and 4 doses of open-label plerixafor, and could undergo a maximum of 8 apheresis procedures before ablative chemotherapy.

Duration of observation: This study consisted of a 30-day Screening Period, a G-CSF Mobilization Period (Day 1-4), an IMP Treatment and Apheresis Period (Day 4 to Day 8), a 24-Hour Follow-up Visit, a Chemotherapy, a Transplantation Period (within 2 months from the last apheresis), and a 30 Day Post-Transplantation Follow-up Visit, as well as an optional Open-label Rescue Period (up to 8 apheresis procedures) after a minimum of 7-day rest period post an initial Treatment and Apheresis Period.

Criteria for evaluation:

Efficacy:

Primary endpoint:

The difference between the treatment arms in the proportion of patients who met the target of ≥5 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis.

Secondary endpoints:

The proportion of patients who achieved ≥2 × 10^6 CD34+ cells/kg within 4 or fewer days of apheresis

Number of days of apheresis to collect ≥2 × 10^6 CD34+ cells/kg

Number of days of apheresis to collect ≥5 × 10^6 CD34+ cells/kg

The fold-increase in the number of circulating CD34+ following the first dose of plerixafor or placebo, with the first apheresis day (Day 5) value serving as the primary estimate

Total number of CD34+ cells collected

Time from transplantation to neutrophil engraftment and platelet (PLT) engraftment

Safety:

The safety analyses were based on the reported adverse events (AEs), clinical laboratory evaluations (serum chemistry, complete blood count with differential, urinalysis, CD34+ peripheral blood samples and CD34+ apheresis product samples), delayed platelet recovery, primary neutrophil graft failure and secondary graft failure, vital signs, physical examination findings, and review of patient's concomitant medications. Safety was assessed for all enrolled patients from the time of ICF sign-off until 30 days post transplantation. National Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 was used for the grade of AE severity. Delayed PLT recovery was defined as the failure to achieve a sustained platelet count ≥20×10^9/L within 30 days post transplantation (transplant day +30). Primary neutrophil graft failure was defined as the failure to achieve a sustained absolute neutrophil count (ANC) of ≥0.5×10^9/L within 30 days post transplantation (transplant day +30). Secondary graft failure was defined as confirmation of 1 of the following: a) PLT failure: after achieving primary PLT recovery of ≥20 ×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 required sustained PLT transfusion support; b) Neutrophil failure: after a sustained recovery of ANC ≥0.5 ×10^9/L, there was a subsequent decrease in ANC such that the ANC fell to <0.5×10^9/ L for at least 7 days regardless of growth factor support (defined by at least 2 consecutive ANC laboratory values obtained over at least 7 days). Delayed PLT recovery, primary neutrophil graft failure, and secondary graft failure were reported to the Sponsor as serious adverse events (SAEs).

Pharmacokinetics (PK):

The following PK parameters of plerixafor were calculated using a non-compartmental analysis (NCA) method: maximum plasma concentration observed (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration versus time curve from time zero to infinity (AUC), area under the plasma concentration versus time curve from time zero to 10 hours after dosing (AUC_{0-10}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the last observed concentration above the lower limit of quantification (LLOQ) (AUC_{last}), terminal elimination half-life ($t_{1/2z}$), apparent volume of distribution (V_z/F), and apparent total systemic clearance (CL/F).

Pharmacodynamics (PD): peripheral blood absolute CD34+ cell count. Fold increase (of baseline, pre-treatment) over time.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

PK: Venous blood samples for the determination of plerixafor plasma concentrations were collected at 0 hour (immediately prior to), at 0.25, 0.5, 1, 2, 4, 6, 8, and 10 hours post IMP dosing at approximately 10:00 PM on Day 4.The plasma concentrations of plerixafor were determined using a validated liquid chromatography-tandem mass spectrophotometry (LC-MS-MS) method, with the LLOQ of 5 ng/mL.

PD: Venous blood samples for PD analysis were collected at immediately prior to plerixafor or placebo administration (0 hour), 2, 4, 6, 8 and 10 hours post plerixafor or placebo dosing on Day 4. The peripheral blood CD34+ cell count were determined by flow cytometry.

Statistical methods:

Efficacy: The full analysis set (FAS) consisted of all randomized patients who received any amount of IMP; patients were analyzed according to the randomized treatment. FAS was the primary population for efficacy analysis, unless otherwise specified. The per-protocol (PP) population consisted of all randomized patients who received any amount of IMP, had completed the apheresis phase, and did not have any major protocol deviations that significantly impacted the assessment of efficacy.

Analysis of primary efficacy endpoint: the primary efficacy endpoint, the proportion of patients who met the target of ≥5 × 10^6 CD34+ cells/kg in 4 or fewer days of apheresis during the regular IMP treatment and apheresis period based on the central laboratory values of CD34+ cell counts, was analyzed using Pearson's chi-square test (unstratified), uncorrected for continuity. The difference in the proportions between treatment arms and the corresponding 95% confidence intervals (CI) was provided using pooled variance. For sensitivity analysis, primary endpoint was also analyzed based on local laboratory value and based on PP population.

Analyses of secondary efficacy endpoints: central lab values were used for all the secondary efficacy endpoints analysis. If severe missing rate was observed for central lab values, a sensitivity analysis was conducted using local lab values.

The proportion of patients who achieved ≥2 × 10^6 CD34+ cells/kg within 4 or fewer days of apheresis: the calculation algorithm of this variable was the same as for the primary endpoint except that 2 × 10^6 CD34+ cells/kg was used as the target threshold criterion.

Number of days of apheresis to collect ≥2 × 10^6 CD34+ cells/kg: this time-to-event variable was tested for treatment effect by use of an un-stratified log-rank statistic. A supportive analysis was conducted using Cox's PH regression model with Efron's tie handling method, parameterized to include fixed effect terms for treatment and study center and the hazard ratio and its 95% CI were provided. Kaplan-Meier curves were estimated per treatment group.

Number of days of apheresis to collect ≥5 × 10^6 CD34+ cells/kg: the calculation algorithm of this variable was the same as for number of days of apheresis to collect ≥2 × 10^6 + cells/kg, but using ≥5 × 10^6 CD34+ cells/kg as the threshold criterion.

The fold-increase in the number of circulating CD34+ following the first dose of plerixafor or placebo, with the first apheresis day (Day 5) value serving as the primary estimate: this variable was calculated using the following formula:

Fold-increase = Pre-G-CSF CD 34+ cells/μL on Day x / Pre-G-CSF CD 34+ cells/μL on Day x-1. Calculations were made for Days 5, 6, 7, and 8 with the value for Day 5 serving as the primary estimate. Treatment arm differences in fold-increase at each apheresis day were tested by 2-sample t-tests independently.

Total number of CD34+ cells collected: the value of this variable was calculated as the sum of all central laboratory daily values collected over the 4 days of apheresis (Day 5 to Day 8). Daily values on days of apheresis in rescue treatment were not included. Two-sample t-test was used to compare the difference in the total number of CD34+ cells collected between treatment groups.

Time from transplantation to neutrophil engraftment and PLT engraftment: these 2 time-to-event variables were analyzed in a manner similar to the number of apheresis days required to achieve the target number of CD34+ cells, including only those patients who underwent transplant.

Only primary endpoint was controlled by a two-sided type I error rate of 0.05. Therefore, multiplicity adjustment was not applicable in this study.

Safety: Safety data was summarized for the safety analysis set, which included all randomized patients who received plerixafor or placebo. Patients were analyzed according to the actual treatment received. The safety analysis was based on the reported AEs and other safety information, including clinical laboratory evaluations, vital signs, and review of patient's concomitant medications. The primary focus of AE reporting was on treatment-emergent adverse events (TEAEs). The summary of safety results was presented by treatment group (plerixafor and placebo).

PK: The following PK variables were summarized using descriptive statistics on PK population: $AUC_{0\text{-}10}$, AUC_{last}, AUC, C_{max}, t_{max}, $t_{1/2z}$, V_z/F, CL/F.

PD: Peripheral CD34+ cells at specified time points were summarized using descriptive statistics by treatment group on PD population.

Summary:

Population characteristics:

One-hundred (100) Chinese NHL patients were randomized and received IMP. All randomized patients were included in FAS of efficacy population. The population was balanced between the 2 groups of treatment (plerixafor and placebo), with 50 patients in each group. There were 3 and 9 patients in the plerixafor and placebo group, respectively, who discontinued the treatment and/or apheresis prematurely due to AEs, poor compliance to protocol and other reasons. Three (3) patients in the plerixafor group and 13 patients in the placebo group entered the rescue period.

Patients across treatment groups had comparable demographic characteristics at baseline. The disease characteristic of the population included in the study was representative of Chinese NHL patients, and generally similar between the plerixafor group and placebo group. The mean peripheral blood (PB) CD34+ cell counts before randomization were also similar in the 2 treatment groups.

Efficacy results:

With respect to the primary efficacy endpoint in the FAS population, based on the central laboratory values, a significantly greater number of patients in the plerixafor group achieved ≥5 x 10^6 CD34+ cells/kg in 4 or fewer days of apheresis compared with the placebo group (62.0% versus 20.0%). The estimated treatment effect (ie, the difference in proportions between the treatment groups) was 42.0% (95% CI: 24.6% to 59.4%, p< 0.0001), which was statistically significant. The same was also true for sensitivity analyses conducted using the local laboratory values and in the PP population.

With respect to the secondary efficacy endpoints, statistically significant difference in proportions between the treatment groups was observed for patients reaching the target of ≥2 x 10^6 CD34+ cells/kg (88.0% in the plerixafor group versus 66.0% in the placebo group; treatment effect 22.0% [95% CI: 6.1% to 37.9%]; p=0.0090).

The number of apheresis days to collect ≥2 × 10^6 CD34+ cells/kg was significantly shorter in the plerixafor group, as the median time to reach the target CD34+ cell count was 1.0 day (95% CI: not calculated) in the plerixafor group, compared with 2.0 days (95% CI: 2.00 to 3.00) in the placebo group. Patients in the plerixafor group were 1.703 times more likely to achieve the target CD34+ cell count than those in the placebo group (hazard ratio: 1.703, 95% CI: 1.039 to 2.79, p=0.0001). The same was also true for the target CD34+ cell count of ≥5 × 10^6 CD34+ cells/kg, where the median time to reach the target was 2.0 day (95% CI: 2.00 to 3.00) in the plerixafor group, while was not estimable in the placebo group since less than half of the patients in that group reached the target in 4 days of apheresis. Patients in the plerixafor group were 6.123 times more likely to achieve the target cell count than those in the placebo group (hazard ratio: 6.123, 95% CI: 2.51 to 14.93, p<0.0001).

There was a 4.07-fold increase (median: 3.65, range: 1.2-10.4) in PB CD34+ cells in the plerixafor group compared with a 1.95-fold increase (median: 1.61, range: 0.6-6.5) in the placebo group over the 24-hour period from the day prior to the first apheresis to just before the first apheresis. The mean number of circulating PB CD34+ cells on Day 5 (the first day of apheresis) was statistically significantly greater in the plerixafor group compared with the placebo group (mean ± SD: 70.5±66.6 cell/μL versus 26.5±18.1 cell/μL, p<0.0001).

The mean total number of CD34+ cells collected (cells/kg) was also statistically significantly higher in patients in the plerixafor group compared with the placebo group (6232979.9 versus 3257586.5, p<0.0001).

In patients who underwent transplantation, there was no statistically significant difference between the 2 treatment groups in the days to neutrophil engraftment (10.0 days in each group, p=0.1027) and PLT engraftment (19.0 days in the plerixafor group versus 17.0 days in the placebo group, p=0.4067).

Pharmacodynamics results:

A total of 32 patients were enrolled in the PD sub-study, and data from 31 patients were available for PD analyses (13 patients in the plerixafor group and 18 patients in the placebo group). The PB CD34+ cell count generally did not change over time following the placebo treatment on Day 4, while 2.1 to 2.7-fold increases of the PB CD34+ cell count from baseline (pre-dose) were observed from 2 to 10 hours post plerixafor dosing on Day 4, with the maximum fold change achieved at 8 hours post dosing.

Safety results:

One (1) patient allocated to the placebo group received 1 dose of plerixafor on Day 4, and was included in the plerixafor group for the safety analysis. The safety population consisted of 100 patients, with 51 patients and 49 patients in the plerixafor group and placebo group, respectively.

The occurrences of TEAEs (all grades) were comparable in the 2 treatment groups, with 32 patients (62.7%) in the plerixafor group versus 31 patients (63.3%) in the placebo group. IMP related TEAEs were more frequently reported in patients in the plerixafor group than in the placebo group (6 patients [11.8%] versus 3 patients [6.1%]). There was neither TEAE leading to death nor treatment-emergent SAE reported.

There was no unexpected TEAE reported. TEAEs of any grades in the system organ class (SOC) of nervous system disorders, gastrointestinal disorders, as well as general disorders and administration site conditions were more frequently reported in patients in the plerixafor group than in the placebo group. The most frequently reported TEAEs by preferred term (PT) in the plerixafor group were pyrexia (6 patients [11.8%]), nausea (4 patients [7.8%]), as well as dizziness, paraesthesia and diarrhea (3 patients [5.9%] for each PT), all of which were Grade 1-2 events. The most frequent TEAEs by PT in the placebo group were platelet count decreased (9 patients [18.4%]), as well as thrombocytopenia and hypokalaemia (8 patients [16.3%] each). The relative higher incidence of these TEAEs was likely due to more apheresis days experienced by patients in the placebo group than in the plerixafor group.

TEAEs leading to study treatment and/or apheresis discontinuation were more frequently reported in the placebo group than in the plerixafor group (7 patients [14.3%] versus 1patient [2.0%]), with the most frequently reported events as platelet count decreased (5 patients in the placebo group). All but 1 of the events were considered by the Investigator as not related to the IMP.

One (1) patient in the plerixafor group died due to progressive disease during the post-treatment period.

Neither primary neutrophil graft failure nor secondary graft failure was reported, but 7 patients (3 in the plerixafor group and 4 in the placebo group) were reported to have “delayed platelet recovery” during the post-treatment period, which were considered as SAEs per protocol. All but 1 of the SAEs were considered by the Investigator as not related to the IMP.

In analyses of laboratory results, with respect to hematology, the baseline mean values for neutrophils and white blood cell were similar in the 2 treatment groups, and there were mean increases at 24 hours after last apheresis in both groups. Although the mean value of neutrophils at 24 hours and increases from baseline were greater in the placebo group than in the plerixafor group, due to a high value of neutrophil count recorded for 1 patient in the placebo group 24 hour after last apheresis, the median value of neutrophils at 24 hours and increases from baseline were greater in the plerixafor group than in the placebo group as expected. For platelet count, the decrease from baseline to 24 hours was observed in both treatment groups. Although the mean value was higher in the placebo group at baseline, it became lower at 24 hours compared with the plerixafor group, and the mean decrease at 24 hours from baseline was more profound in the placebo group than in the plerixafor group. The majority of patients in each treatment group had platelet count values within the normal range at baseline, and shifted from within the normal range to below LLN at 24 hours due to apheresis. The most common Grade 3 or 4 abnormal hematologic event was platelet count decreased, which was reported in a total of 29 patients in the 2 treatment groups, and more frequently reported in the placebo group than in the plerixafor group at Grade 3 or 4 (17 patients [34.7%] versus 12 patients [23.5%]).

With respect to serum chemistry, the mean value of liver function parameters ALT, AST and ALP at baseline were comparable in the 2 treatment groups. Mean increase from baseline in ALP was observed in both groups. Small increases from baseline in ALT and AST were also observed in both groups, and the mean increases in ALT and AST were higher in the placebo group than in the plerixafor group. A few more patients in the placebo group compared with plerixafor group had ALT values shifted from Grade 0 at baseline to Grade 1-2 at 24 hours. The mean value of renal function parameters and electrolytes at baseline were comparable in 2 treatment groups and there were no marked changes from baseline noted in both groups. The most common Grade 3 or 4 abnormal serum chemistry event was hypokalemia, which was reported in a total of 8 patients in the 2 treatment groups, and more frequently reported in the plerixafor group than in the placebo group at Grade 3 (6 patients [12.2%] versus 2 patients [4.2%]).

Only infrequent potentially clinically significant abnormality (PCSA) values were reported for blood pressure and heart rate during the TEAE and post-treatment period, and none of the vital signs that met the criteria for PCSA was associated with any clinically relevant manifestations.

Pharmacokinetic results: A total of 32 patients were enrolled in the PK assessment, with 14 and 18 patients treated with plerixafor and placebo, respectively. Following a single subcutaneous administration of 0.24 mg/kg plerixafor to NHL patients, maximum plasma concentrations were reached at a median t_{max} of 0.47 hours and declined with mean terminal half-life of 3.61 hours. Mean plasma C_{max}, AUC_{0-10}, AUC_{last}, AUC, CL/F and V_z/F were 786 ng/mL, 2580 ng.h/mL, 2580 ng.h/mL, 3010 ng.h/mL, 5.73 L/h and 29.0 L, respectively.

Summary table: mean ±SD (geometric mean) [CV%] of plerixafor PK parameters (n = 14)

C_{max}	t_{max}[a]	$t_{1/2z}$	AUC_{0-10}	AUC_{last}	AUC	CL/F	V_z/F
(ng/mL)	(h)	(h)	(ng•h/mL)	(ng•h/mL)	(ng•h/mL)	(L/h)	(L)
786 ± 205	0.47	3.61 ± 1.31	2580 ± 424	2580 ± 424	3010 ± 711	5.73 ± 1.27	29.0 ± 8.98
(764) [26.0]	(0.22 - 1.00)	(3.44) [36.2]	(2550) [16.5]	(2550) [16.5]	(2940) [23.7]	(5.60) [22.1]	(27.7) [30.9]

[a] Median (Min - Max)

Issue date: 08-Mar-2017