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Sponsor: Sanofi **Drug substance(s):** GZ402668	**Study Identifiers:** U1111-1184-8607, NCT02977533, 2016-002415-18 **Study code:** TDU14981

Title of the study: A randomized, double-blind, placebo-controlled study of safety, tolerability, pharmacokinetics and pharmacodynamics of a single subcutaneous dose of GZ402668 in men and women with progressive multiple sclerosis

Study center(s): One center in Germany

Study period:

Date first subject/patient enrolled: 30/Nov/2016

Date last subject/patient completed: 16/May/2018

Phase of development: Phase 1b

Objectives:

Primary:

To assess the safety and tolerability of GZ402668 after a single subcutaneous (SC) dose in men and women with progressive multiple sclerosis (MS).

Secondary:

To assess in men and women with progressive MS:

- The pharmacokinetic (PK) parameters of GZ402668
- The pharmacodynamics (PD) of GZ402668

Methodology: A Phase 1b, double-blind, randomized, placebo-controlled, single-dose study in men and women with progressive MS.

Number of patients:	Planned: 24 = 16 patients in Cohort 1 Part 1 (1a and 1b) and Part 2 (1c and 1d) and 8 optional patients in Cohort 2 Part 1 (2e) and Part 2 (2f). Cohort 2f was not conducted in this study.
	Randomized: 20
	Treated: 20
Evaluated:	
	Safety: 20
	Pharmacokinetics: 15
	Pharmacodynamics: 20

Diagnosis and criteria for inclusion: Male and female patients 18 to 65 years of age (inclusive), body weight >40.0 kg, and a diagnosis of progressive MS based on 2010 revision of McDonald criteria.

Study treatments

Investigational medicinal product: GZ402668

Formulation: Solution for injection

- Cohort 1 Part 1 (1a and 1b): dose 1; SC volume injected of 0.6 mL
- Cohort 1 Part 2 (1c): dose 2; SC volume injected of 1.0 mL
- Cohort 1 Part 2 (1d) and Cohort 2 (2e): intermediate dose; SC volume injected of 0.8 mL

Route(s) of administration: Subcutaneous injection in the abdominal area

Dose regimen: 1 single dose on Day 1

Investigational medicinal product: Placebo

Formulation: Solution for injection (1.0 mL)

Route(s) of administration: Subcutaneous injection in the abdominal area

Dose regimen: 1 single dose on Day 1

Non investigational medicinal product: Acyclovir

Formulation: 200 mg tablet

Route(s) of administration: Oral

Dose regimen: 200 mg twice daily from Day 1 to 28 days after IMP administration (evening of Day 28 was the last day for acyclovir administration)

Duration of treatment: 1 day

Duration of observation: Up to 8 weeks including screening (Days -28 to -2), a 4-week treatment period including 1 treatment day, and an end-of-study (EOS) visit 28 days after IMP administration (Day 29).

Criteria for evaluation:

Safety: Adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiogram (ECG), physical examinations, body temperature, body weight, biomarkers of autoimmunity, and local tolerability including erythema and edema peak diameter classification, Present Pain Intensity (PPI) data, and skin reaction data.

Pharmacokinetics: The following PK parameters were calculated using noncompartmental methods from serum GZ402668 concentrations: Maximum serum concentration observed (C_{max}), time to reach C_{max} (t_{max}), time corresponding to the last concentration above the upper limit of quantification (t_{last}), area under the serum concentration versus time curve (AUC), AUC from time zero to the t_{last} (AUC_{last}), terminal half-life associated with the terminal slope ($t_{1/2z}$), apparent total body clearance (CL/F), and volume of distribution at stead state (V_{ss}/F).

Pharmacodynamics/Efficacy: The primary PD parameter was lymphocyte phenotyping. The following lymphocyte populations were measured: lymphocyte panel, T cell subset panel, B cell subset panel, and dendritic/monocyte panel.

Statistical methods:

Safety

All safety analyses were performed using the safety population. All patients exposed to IMP (regardless of the amount administered) were included in the safety population. Evaluation of safety was based on the review of individual values and descriptive statistics (summary tables, graphics). The safety analysis focused on the treatment-emergent AEs (TEAEs) during the on-treatment phase, defined as the time interval from the administration of IMP up to the EOS visit (included). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1). The number (%) of patients who experienced TEAEs was summarized by primary system-organ class and preferred term, grade, and relationship to IMP administration. Potentially clinically significant abnormalities in clinical laboratory test results, vital signs, and ECG were flagged and summarized by treatment using frequency tables.

Pharmacodynamics/Efficacy

All PD analyses were performed using the PD population. All randomized patients who received at least 1 dose of IMP and who had at least 1 evaluable PD assessment were included in the PD population. The PD parameters were summarized by IMP dose and/or premedication regimen using descriptive statistics for each time point. The point estimate and 95% confidence interval (CI) was provided for the proportion of patients who depleted to pre-specified lymphocyte count levels relative to their baseline level by treatment group.

Numbers of patients experiencing relapse during the on-treatment period were to be provided by treatment group.

Pharmacokinetics

All PK analyses were performed using the PK population. All randomized patients who received at least 1 dose of IMP and who had at least 1 evaluable PK assessment were included in the PK population. Patients who received placebo were not included in the PK population. The PK parameters of GZ402668 were summarized by descriptive statistics for each treatment. A dose effect was assessed with a linear fixed-effect model for $t_{1/2z}$ and dose proportionality was assessed with an empirical power model for C_{max}, AUC_{last}, and AUC.

Summary:

Population characteristics:

A total of 20 patients were randomized in 5 cohorts; 4 patients in each cohort (3 GZ402668:1 placebo). All patients were treated and completed the study.

The demographic characteristics at baseline were similar across all cohorts. Overall, the mean age of the safety population was 54.1 years (standard deviation [SD]: 7.2, range across cohorts was 30 to 63 years), 55.0% of patients were male, all patients were Caucasian/White (100%), mean body mass index (BMI) was 25.77 kg/m² (SD: 5.30, range across cohorts was 18.1 to 37.2 kg/m²). The mean EDSS score was 4.8 (SD: 1.3) and the majority of patients (13, 65.0%) had secondary progressive MS, with 7 patients (35.0%) having primary progressive MS. The mean time since first diagnosis was 8.85 years (SD: 6.40, range across cohorts 1.0 to 20.0 years).

Safety results:

All patients who received GZ402668 experienced at least 1 TEAE over the course of the study. One patient experienced a severe TEAE (clear cell renal cell carcinoma) during the study which was reported as an adverse event of special interest (AESI) and serious adverse event (SAE). The event was not considered to be related to the IMP. One patient experienced alanine aminotransferase (ALT) increased that was reported as an AESI and was not considered to be related to the IMP.

Four out of 15 patients (26.7%) reported severe (Grade 3) TEAEs following GZ402668 administration. The TEAEs of 3 out of the 4 patients who had severe (Grade 3) TEAEs, were macular, maculo-papular, or urticarial exanthemas (rashes). Because these rashes covered more than 30% of the body surface area, they were deemed severe (Grade 3), despite causing only mild to moderate discomfort to the patients.

A total of 172 TEAEs were reported with 160 TEAEs in the GZ402668 group and 12 TEAEs in the placebo group. Of the total 172 TEAEs, 75 (approximately 44%) were considered related to IMP administration, especially those expected IARs due to CD52-lytic cytokine and histamine release of depleted blood cells, such as fevers, chills, pruritus, and rashes.

All TEAEs occurred between start time of IMP administration up to 6 days postdose. The most commonly reported TEAE was injection site erythema followed by body temperature increased and headache, and none of these TEAEs were reported by patients following placebo administration.

The overall incidence of all IMP-related TEAEs and severity of the events across the GZ402668 groups showed no clear relationship with increasing dose. The incidence of TEAEs related to IMP administration was similar between the dose 1 and the intermediate dose of GZ402668, and a lower incidence was reported following the dose 2 of GZ402668. Following administration of GZ402668 dose 2 a lower incidence of mild (Grade 1) and moderate (Grade 2) TEAEs were reported compared to the dose 1 and the intermediate dose GZ402668 groups; however, a higher percentage of patients reported a higher incidence of severe (Grade 3) TEAEs in the dose 3 GZ402668 group.

There was a clear relationship in the incidence and severity of certain TEAEs expected to be reported following GZ402668 administration, between the varying premedication regimens in different cohorts. After an optimized premedication regimen was introduced into the study, beginning with the second patient in Cohort 1c, none of the patients dosed with the intermediate dose of GZ402668 developed IMP-related pruritus or rash. The premedication regimen in Cohorts 1d and 2e ameliorated the severity of expected TEAEs such as rash, erythema, and increased body temperature compared to premedication regimens of naproxen and methylprednisolone alone administered to patients in Cohorts 1a and 1b, and 1 patient in Cohort 1c, respectively.

A total of 14 out of 15 patients (93.3%) reported 73 treatment-emergent injection-associated reactions (IARs) following administration of GZ402668. A total of 3 out of 5 patients (60.0%) reported 4 treatment-emergent IARs following administration of placebo. Frequency and severity of IMP-associated cutaneous IARs (pruritus, rashes), caused by cytokine and histamine release by the desired PD effect of blood cell depletion, was observed to be GZ402668 dose-dependent and related to the selected premedication regimen. Both, the frequency and severity of commonly reported TEAEs, such as, rash, erythema, and increased body temperature, was ameliorated by premedication regimens of methylprednisolone and ranitidine in combination with either levocetirizine or fexofenadine in comparison to premedication regimens of either naproxen or methylprednisolone administered alone.

There were a total of 5 clinically relevant abnormalities observed; 2 in clinical laboratory evaluations of biochemistry (ALT increased and GGT increased), 2 in vital signs (hypertension and decreased blood pressure), and 1 in ECG parameters (ECG QT prolongation). Of these abnormalities, 2 were considered related to GZ402668, with the remaining either considered not related or in patients who received placebo.

Several subjects experienced elevated body temperatures throughout the study. A total of 8 out of 15 subjects (53.3%) who received GZ402668 had a body temperature ≥38°C during the study, with 3 out of 15 subjects (20.0%) having a body temperature >39°C. A higher number of subjects in Cohorts 1a and 1b (GZ402668 dose 1), and 1c (GZ402668 dose 2) had body temperatures >39°C compared to Cohorts 1d and 2e (GZ402668 intermediate dose). This suggests the effect of increased body temperature was ameliorated with the premedication given to subjects in Cohorts 1d and 2e.

Pharmacodynamic results:

Lymphocyte depletion is the principal desired PD effect of GZ402668. Lymphocyte depletion was observed following administration of GZ402668 at all dose levels, confirming the desired biological activity of GZ402668. The maximal extent of depletion was substantial in all GZ402668 dose groups, with mean absolute lymphocyte count decreases from baseline >90% following the dose 1 (93.8%), the intermediate dose (93.5%), and the dose 2 (98.0%). Across all GZ402668 dose groups after the maximal depletion, lymphocyte recovery occurred around Day 7, however all mean lymphocyte counts were still lower than baseline at the EOS visit.

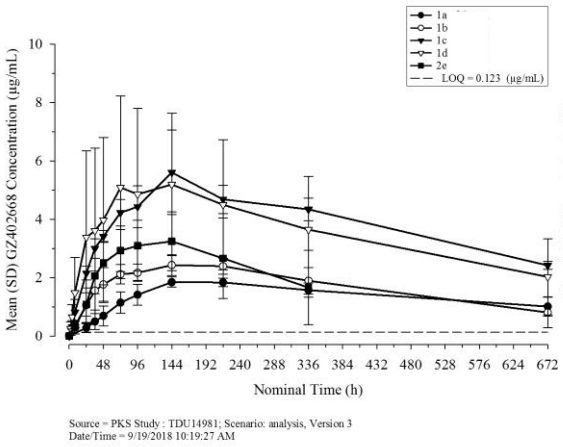
A similar effect was observed in the T-reg cell subpopulation, with substantial depletion in all GZ402668 dose groups; maximal mean decreases from baseline of 96.9%, 97.9%, and 99.5% following the dose 1, the intermediate dose, and the dose 2 of GZ402668, respectively. However, when given as a percentage of CD4+ cells, T-reg cells were increased at the EOS visit compared with baseline in all GZ402668 groups. The maximal mean increase was observed following GZ402668 dose 2; rising from 7.787% at baseline to 40.040% at EOS (approximately 414% increase). No percentage increase in T-reg cells was observed in the placebo group.

On-study assessment of MS relapse was performed and it was confirmed that no patients experienced relapse during the study. Treatment efficacy in terms of prevention of MS relapses will be assessed in the ongoing long-term follow-up study, LTS14120.

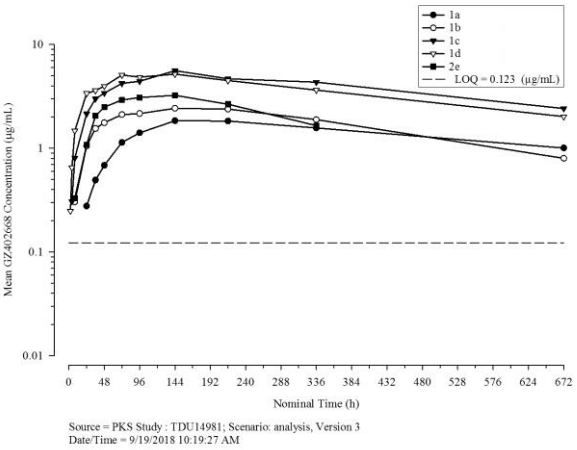
Pharmacokinetic results:

Mean GZ402668 serum concentration time profiles are illustrated in the figure below.

Cartesian scale



Semi-logarithmic scale



Following a single SC dose 1, intermediate dose or dose 2, GZ402668 was absorbed slowly into the systemic circulation (median tmax of 72 to 217 hours) and eliminated slowly with measurable serum concentrations up to the last sampling time of 672 hours (28 days).

There was no significant effect of dose on t1/2z (p=0.487) and the geometric mean t1/2z pooled across all doses was 297 hours (approximately 12 days).

Over the 1.67-fold dose range of dose 1 to dose 2, GZ402668 exposure increased in more than a dose-proportional manner.

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