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Sponsor: Sanofi **Drug substance(s):** GZ402668	**Study Identifiers:** U1111-1155-6252, NCT02282826, 2014-001591-61 **Study code:** TDU13475

Title of the study: A randomized, double-blind, placebo-controlled study of safety, tolerability, pharmacokinetics and pharmacodynamics of ascending single intravenous and subcutaneous doses of GZ402668 in men and women with progressive multiple sclerosis (TDU13475).

Study center(s): 1 center in Germany.

Study period:

Date first subject/patient enrolled: 30/Oct/2014

Date last subject/patient completed: 10/Mar/2016

Phase of development: Phase 1

Objectives:

Primary objective:

- To assess the safety and tolerability of GZ402668 after ascending single intravenous (IV) and subcutaneous (SC) doses in men and women with progressive multiple sclerosis.

Secondary objectives:

- To assess in men and women with progressive multiple sclerosis:
  - The pharmacokinetic (PK) parameters of GZ402668 after ascending single IV doses,
  - The pharmacodynamics (PD) of GZ402668 after ascending single IV doses,
  - The PK parameters of GZ402668 after ascending single SC doses,
  - The PD of GZ402668 after ascending single SC doses.

Methodology: Double-blind, randomized, placebo-controlled, sequential ascending single dose study, including 3 IV dose cohorts (4 patients per cohort; active/placebo = 3:1) and an additional IV cohort at the pharmacologically active dose, defined by lymphocyte depletion. After review of IV data, SC administration could begin with 3 SC ascending dose cohorts.

At each dose escalation, the tolerability profile was reviewed and the need for any premedication was assessed.

Number of patients: Planned: 40 (up to 48 patients, if cohort(s) were to be repeated)

Randomized: 44

Treated: 44

Evaluated:

Safety: 44

Pharmacokinetics: 33 (patients receiving placebo were not included)

Pharmacodynamics: 44

Diagnosis and criteria for inclusion: Male and female patients with progressive multiple sclerosis, age 18 to 65 years, inclusive.

Study treatments

Investigational medicinal product: GZ402668 solution for injection

Route(s) of administration: IV (infusion over 4 hours) or SC.

Dose regimen: Five ascending single doses administered in a single administration in dose 1, 2 and 3 IV cohorts and dose 3 SC group, or divided administration for dose 4 and 5 SC cohorts using multiple injection sites.

Investigational medicinal product: Matching GZ402668 placebo

Route(s) of administration: IV (infusion over 4 hours) or SC.

Dose regimen: Single doses administered identically to GZ402668.

Non investigational medicinal product: Acyclovir

Formulation: Tablets.

Route(s) of administration: Oral.

Dose regimen: 200 mg twice daily from Day 1 to Day 28.

Duration of treatment: Single dose

Duration of observation: Up to 8 weeks, including screening (up to 4 weeks [28 days]), treatment period (investigational medicinal product administration to the last assessment; 4 weeks including 1 treatment day [5 days hospitalization, 4 ambulatory visits]). Enrollment in a separate safety follow-up study (LTS14120) for monthly laboratory assessments was required (duration of up to 6 months for patients receiving placebo and 4 years for patients receiving GZ402668).

Criteria for evaluation:

Interim analysis: Blinded safety data through at least Day 10 of each dose cohort were assessed to guide dose escalation decisions. Safety data included adverse events (AEs), biochemistry (including liver and kidney function tests) and hematology laboratory results, 12-lead electrocardiogram (ECG), blood pressure, body temperature, respiratory rate and heart rate, and cytokines. Pharmacodynamic data (ie, lymphocyte phenotyping through Day 10) was also reviewed to guide decision to dose escalation and determine the pharmacologically active dose (ie, substantial acute and sustained depletion of circulating lymphocytes), which was repeated in an additional 8 patients. After each cohort completed the observation period, the cohort was formally unblinded in order to allow only the patients who received GZ402668 to continue in the safety follow-up study and to release the placebo treated patients.

Safety: Patients were monitored for safety via collections of AEs/treatment-emergent AEs (TEAEs) spontaneously reported by the patients or observed by the Investigator, including IARs (TEAEs between IV infusion/SC injection + 24 hours), physical examination and body weight; injection site skin assessment; standard clinical laboratory evaluations (hematology, biochemistry, coagulation, urinalysis with microscopy, thyroid function tests); vital signs (oxygen saturation; respiratory rate; blood pressure, supine and standing; heart rate, supine and standing); cardiac evaluation (12-lead ECG, telemetry, and Holter monitoring); anti-drug antibodies (anti-GZ402668 antibodies); and serum cytokines (interleukin 6 [IL-6], tumor necrosis factor alpha [TNFα], interferon gamma [IFNγ], interleukin 1 beta [IL-1β]). Local tolerability was assessed at defined time points and with defined criteria. If there were multiple sites of SC injection, the maximum grading was to be recorded. Skin reactions of mild intensity or worse (graded separately as mild, moderate and severe as defined in the FDA guidance on assessment of vaccine) were concurrently reported as AEs for each injection site (AE/TEAEs intensity was evaluated using the NCI CTCAE version 4.0, published 28 May 2009).

Pharmacokinetics: The following PK parameters were calculated for GZ402668 serum concentrations using noncompartmental methods: maximum serum concentration observed (C_{max}), time to reach C_{max} (t_{max}), area under the serum concentration versus time curve calculated from time zero to the real time corresponding to the last concentration above the limit of quantification (AUC_{last}), area under the serum concentration versus time curve extrapolated to infinity (AUC), terminal half-life associated with the terminal slope ($t_{1/2z}$), volume of distribution at steady state after single IV infusion dose (V_{ss}), total body clearance after IV infusion (CL), volume of distribution at steady state after single SC dose (V_{ss}/F), and apparent total body clearance of a drug after SC administration (CL/F), systemic bioavailability after SC administration (F), calculated as the ratio of the mean AUC normalized by dose relative to the highest IV dose 3.

Pharmacodynamics: Lymphocyte phenotyping, including measurement of T-lymphocyte subsets, B-lymphocytes subsets, and innate cells (ie, natural killer [NK], monocyte, and dendritic cells).

Exploratory efficacy: Although efficacy was not adequately assessed due to the size and duration of this study, some efficacy parameters were collected prior to treatment to allow an exploratory assessment in the long term follow-up study (LTS14120). Cranial magnetic resonance imaging with and without gadolinium and a patient disability evaluation (via Expanded Disabilitiy Status Scale) were performed at baseline. Relapse assessment was conducted over the course of the study (to be provided in the clinical study report).

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples for the determination of GZ402668 concentrations in serum were collected at the following times: predose (prior to start of administration) and at 2, 4, 8, 24, 36, 48, 72, and 96 hours after the start of administration. Samples were also collected on Days 7, 10, 15, and 29 (end of study [EOS]).

GZ402668 concentrations were determined in serum using a validated enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification of 0.123 µg/mL.

Pharmacodynamics sampling times and bioanalytical methods:

Samples for lymphocyte phenotyping, including measurement of T-lymphocyte subsets, B-lymphocytes subsets, and innate cells (ie, NK, monocyte, and dendritic cells) were collected at baseline (Day 1, predose [prior to start of administration]) and at EOS. Samples were collected for lymphocyte panel assessment only at the following times: screening, at 6, 12, 24, 48, and 72 hours after the start of administration, and Days 7, 10, and 15.

Changes in lymphocyte populations were measured after GZ402668 administration using flow cytometry and standard cell surface markers to characterize the time course of lymphocyte depletion and repopulation.

Statistical methods:

Safety: The safety evaluation was based upon the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables, graphics). All the safety analyses were performed using the safety population.

For AEs, frequency distributions of TEAEs classified by Medical Dictionary for Regulatory Activities (version 18.1) system organ class and preferred term were tabulated by dose cohort.

Counts of patients with potentially clinically significant abnormalities (PCSAs, version 24 May 2014) in clinical laboratory, ECG, and vital sign evaluations were summarized by dose cohort for each parameter.

Summary plots (mean ± standard deviation [SD]) of raw data and changes from baseline were generated by dose cohort for selected parameters, including serum cytokines, vital signs, Holter monitoring, and ECG.

For local tolerability data, descriptive statistics of the individual erythema and edema data, as well as maximum pain intensity and other skin reactions, were provided by treatment.

For anti-drug antibody (ADA) data, descriptive statistics of the individual anti-GZ402668 antibody titer values and a summary of the number and percent of patients who seroconverted and time to conversion were provided for anti-GZ402668 antibodies by treatment group and overall.

Pharmacokinetics: Pharmacokinetic parameters of GZ402668 were summarized by descriptive statistics for each dose level and by route of administration. Dose effect was assessed using a linear fixed effects model on log-transformed $t_{1/2z}$ for IV infusion. Dose proportionality was assessed using a log-transformed power model on C_{max} and AUC_{last} for IV infusion.

Pharmacodynamics: Each PD variable was summarized by descriptive statistics and plots by scheduled time for each dose cohort, on raw data and change from baseline.

Summary:

Population characteristics:

A total of 44 patients were randomized in 7 cohorts (3 GZ402668:1 placebo in each of 3 IV cohorts, 6 GZ402668:2 placebo in 1 additional IV cohort, and 6 GZ402668:2 placebo in each of 3 SC cohorts). All patients were treated.

The demographic characteristics at baseline were similar across all cohorts with the exception that the mean (standard deviation [SD]) time since first diagnosis was higher in the IV cohorts (16.92 [8.41] years) than in the SC cohorts (7.69 [7.86] years). Overall, for the IV cohorts, the mean age of population was 54 years (SD: 6.3, range across cohorts was 38 to 64 years), 55.0% of patients were female, all patients were Caucasian (100%), mean body mass index (BMI) was 25.80 kg/m² (SD: 5.07, range across cohorts was 17.6 to 38.2 kg/m²) and mean Expanded Disability Status Scale (EDSS) score was 5.6 (SD: 1.7). Overall, for the SC cohorts, the mean age of population was 50 years (SD: 9.4, range across cohorts was 21 to 61 years), 50.0% of patients were female, all patients were Caucasian (100%), mean BMI was 25.64 kg/m² (SD: 3.08, range across cohorts was 19.2 to 29.5 kg/m²) and mean EDSS score was 5.6 (SD: 1.3).

Safety results:

No deaths, treatment-emergent serious adverse events, or grade 3 or higher AEs were reported with GZ402668. One treatment-emergent SAE (urinary retention) was reported in placebo group belonging to dose 4 SC cohort.

A higher percentage of patients receiving GZ402668 via SC administration versus IV administration reported experiencing at least 1 event of headache (60% of IV patients versus 67% of SC patients) as well as increased body temperature (40% of IV patients versus 78% of SC patients), asthenia (33% of IV patients versus 39% of SC patients), muscle spasticity (20% of IV patients versus 33% of SC patients). A significant percentage of patients in the GZ402668 SC groups experienced injection site erythema (83%) and injection site edema (39%) compared to 7% of IV patients. A larger percentage of patients in GZ402668 IV groups experienced nausea (40% IV patients versus 17% of SC patients), dizziness (20% IV patients versus 11% SC patients), tachycardia, fatigue, and vomiting (27% IV patients versus 11% SC patients), as compared to patients who received GZ402668 SC. These comparisons are not comprehensive, and other smaller frequency differences between the IV and SC active treatments exist.

There were few AESIs reported. One patient receiving SC dose 5 experienced 1 AESI of elevated liver enzymes, compared to 2 patients with elevated liver enzyme findings at the dose 2 and dose 3 (with ibuprofen premedication) GZ402668 IV. There were 2 AESIs of reduced platelets in the GZ402668 IV groups only.

Local tolerability as assessed by FDA criteria revealed singular mild events in the GZ402668 IV group, but several in the SC groups of mostly moderate nature. One event of erythema >12 cm in diameter in the dose 3 SC group was deemed severe as defined by FDA guidance criteria. This was reported concurrently as a mild TEAE using CTCAE criteria and resolved without sequelae.

For both the IV and SC groups, the increases in highest mean levels of cytokine appeared to be dose dependent (except for the dose 3 GZ402668 IV group with CS premedication). The highest mean levels of cytokines were noted for the highest doses of drug (IV dose 3 with ibuprofen premedication and SC dose 5 with ibuprofen prophylaxis). The mean maximal levels of IL-6, TNFα, and IL-1β cytokine were considerably lower in all SC groups including the dose 5 SC group with ibuprofen prophylaxis as compared to the dose 3 IV group with ibuprofen premedication; however, the mean maximal levels of INFγ measured in the highest doses of each IV and SC administration were similar.

There were few PCSA for laboratory assessments, vital signs, blood pressure (primarily orthostatic pressure), and ECG either in patients administered GZ402668 via IV or SC administration.

ADA results

Low-titer ADA were detected postdose in GZ402668 IV and SC cohorts with a similar incidence. ADA positivity was not clearly dose dependent, but median and maximum titers were substantially higher in the 2 highest dose cohorts although not linearly dose dependent.

Anti-drug antibodies were not detected prior to IV or SC administration in any of the patients receiving placebo or GZ402668.

Treatment-induced ADAs were detected in 4/15 patients (26.7%) receiving GZ402668 via IV administration (1/3 patient [33.3%] in the dose 1 and 3/6 patients [50.0%] in the dose 3 ofGZ402668 IV with ibuprofen).

Treatment-induced ADAs were detected in 7/18 patients (38.9%) receiving GZ402668 via SC administration (2/6 patient [33.3%] in the dose 3, 3/6 patients [50.0%] in the dose 4, and 2/6 patients [33.3%] in the dose 5 GZ402668 SC groups).

In all patients who developed ADA, they were detectable at 28 days, the only posttreatment sampling time point. Persistence of all ADAs was classified as indeterminate as there was no follow-up sampling during the study.

Pharmacokinetic results:

Intravenous administration

Following a single IV infusion dose, maximum GZ402668 serum concentrations were mostly observed at the end of infusion, after which they appeared to decline biexponentially. After the dose 3, the mean $t_{1/2z}$ was approximately 11 days; the mean CL was 27.6 mL/h; and the mean V_{ss} was 8.64 L. The exposures (C_{max} and AUC_{last}) increased much more than dose proportionally from dose 1 to dose 2, while increased roughly dose proportionally from dose 2 to dose 3

	Mean ± SD (Geometric Mean) [CV%] of GZ402668 Parameters		
	IV dose 1	IV dose 2	IV dose 3[b]
N	3	3	9
C_{max} (µg/mL)	0.227 ± 0.0737	0.687 ± 0.248	2.54 ± 0.494
	(0.219) [32.5]	(0.653) [36.1]	(2.50) [19.4]
t_{max}[a] (h)	4.10 (4.03 - 4.10)	4.05 (4.03 - 8.17)	4.08 (4.00 - 8.00)
AUC_{last} (µg•h/mL)	2.13 ± 2.18	68.5 ± 35.2	356 ± 96.1
	(1.52) [102.4]	(60.9) [51.4]	(344) [27.0]
$t_{1/2z}$ (h)	NC ± NC	231 ± 145	256 ± 72.3
	(17.5) [NC]	(206) [62.5]	(248) [28.2]
AUC (µg•h/mL)	NC ± NC	NC ± NC[d]	466 ± 123
	(NC) [NC]	(NC) [NC]	(451) [26.4]
CL (mL/h)	NC ± NC	NC ± NC[d]	27.6 ± 8.32
	(NC) [NC]	(NC) [NC]	(26.6) [30.2]
V_{ss} (mL)	NC ± NC	NC ± NC[d]	8640 ± 1340
	(NC) [NC]	(NC) [NC]	(8560) [15.5]

[a] Median (Min - Max).

[b] Data includes IV cohorts 3 and 3b, as there were no appreciable differences in PK between these 2 cohorts.

[c] Not calculated due to insufficient concentration time data points for the terminal phase.

[d] Not calculated due to AUC_{ext} >30%.

NC = Not calculated.

Subcutaneous administration:

After a single SC dose, GZ402668 was absorbed with a median t_{max} of 6.0 to 7.5 days and the mean $t_{1/2z}$ was approximately 13 days. Mean serum GZ402668 C_{max} and AUC values increased approximately proportionally in the dose range of dose 3 to dose 5. The bioavailability was about 100% at SC doses 3 and 4 and about 82% at SC dose 5.

	Mean ± SD (Geometric Mean) [CV%] of GZ402668 Parameters		
	SC dose 3	SC dose 4	SC dose 5
N	6	6	6
C_{max} (µg/mL)	0.938 ± 0.300	2.71 ± 0.621	4.01 ± 0.409
	(0.893) [32.0]	(2.64) [22.9]	(3.99) [10.2]
t_{max}[a] (h)	145.24 (139.75 - 263.52)	144.41 (96.00 - 216.93)	181.82 (145.83 - 217.77)
$t_{1/2z}$ (h)	308 ± 104	315 ± 117	312 ± 130
	(288) [33.9]	(289) [37.2][b]	(290) [41.8]
AUC_{last} (µg•h/mL)	369 ± 105	937 ± 348	1730 ± 526
	(355) [28.5]	(864) [37.2]	(1650) [30.4]
AUC (µg•h/mL)	553 ± 144	1510 ± 368	1900 ± 266
	(539) [26.1]	(1470) [24.4]	(1880) [14.0]
CL/F (mL/h)	22.9 ± 7.06	25.0 ± 6.89	32 1 ± 4.67
	(22.3) [30.8]	(24.4) [27.5]	(31.8) [14.6]
V_{ss}/F (mL)	NC ± NC	NC ± NC	NC ± NC
	(NC) [NC]	(NC) [NC]	(NC) [NC]
F (%)	119	108	81.5

[a] Median (Min - Max).

NC = Not calculated.

Pharmacodynamic results:

Lymphocyte depletion is the principal desired PD effect of GZ402668. Dose dependent lymphocyte depletion was observed in IV and SC groups, confirming the desired biological activity of GZ402668. The maximal extent of depletion was dose related and very substantial in all GZ402668 dose groups, with mean absolute lymphocyte count decreases from baseline >90 % in the dose 3 IV (97.5%), dose 4 and dose 5 SC (92.2 and 95.4%) groups. Lymphocyte recovery began earlier in lower dose groups that showed less complete depletion. The mean absolute lymphocyte count decreases from baseline on Day 15 was still >90% in the dose 5 SC group, and over 80% in the dose 3 IV and the dose 4 SC groups. The mean absolute lymphocyte count decreases from baseline on Day 29 was still >80% in dose 5 SC and dose 3 IV groups and close to 80% in dose 4 SC group.

Comparison of the PD response to GZ402668 administration by IV or SC administration leads to some general conclusions.

- Lymphocyte depletion occurs after IV or SC administration of GZ402668.
- The time course of lymphocyte depletion tends to be more rapid after IV than SC administration.
- In the groups that received identical administered amounts of GZ402668 (ie, the dose 3 groups IV and SC), less lymphocyte depletion occurred after SC administration.
- Similar increase in the relative proportion of $CD4^+$ Treg were seen after IV or SC administration.