Sponsor: Sanofi **Drug substance:** GZ402668	**Study Identifiers:** U1111-1158-9815, NCT02313285, EudraCT Number 2014-001592-31 **Study code:** LTS14120
Title of the study: An open-label, long-term follow-up study of multiple sclerosis patients who participated in Genzyme-sponsored studies of GZ402668	
Study Center: This study was conducted at a single center that enrolled patients in Germany.	
Study period: Date first participant enrolled: 12 January 2015 Date last participant completed: 20 April 2022 Study Status: Completed	
Objectives: **Primary:** To assess the long-term safety of GZ402668 in patients with MS who received prior treatment during the TDU13475 or TDU14981 studies **Secondary:** • To assess the pharmacokinetics of GZ402668 in patients with MS • To assess the pharmacodynamics of GZ402668 in patients with MS • To assess the immunogenicity of GZ402668 in patients with MS	
Methodology: This study was an open-label, observational, long-term extension study. The study began at a single center and may have been expanded to a multicenter study, depending on the number of study centers necessary for the TDU13475 and TDU14981 studies. A patient entered the LTS14120 study without prior knowledge of his/her treatment assignment in the TDU13475 or TDU14981 clinical studies. Patients from the TDU13475 or TDU14981 studies were unblinded within approximately 6 months after entry into the LTS14120 study after which: •Patients who received placebo in TDU13475 or TDU14981 studies were discharged from the LTS14120 study. •Patients who received GZ402668 in TDU13475 or TDU14981 studies remained in the LTS14120 study for a total of 47 months. Patients were required to return to the study center on a monthly basis at which time laboratory assessments were performed for hematology, serum creatinine, liver enzymes, and urinalysis (with microscopy). Every 3 months, laboratory assessment for thyroid function testing, vital signs, and collection of information regarding AEs and concomitant medications were performed. Every 6 months, laboratory assessment for lymphocyte phenotyping, serum collection for future assessment of immune system markers, and EDSS assessments were performed. Every 12 months a cranial MRI was performed. Patients were instructed to call the study center between visits to report any AEs, including worsening MS. Additionally, to the above assessments, on Month 1, 2, and 3 the following assessments were performed, antidrug antibodies (ADA), GZ402668 serum concentrations, lymphocyte phenotyping (Months 1 and 3 only), serum collection for possible future assessment of immune system markers (Month 3 only), physical examination with vital signs and body weight, 12-lead ECG, and collection of information regarding AEs and concomitant medications. On Month 6 and 12, patients had an ADA assessment. On Month 9, patients had additional assessments for lymphocyte phenotyping, vital signs, and serum collection for future assessment of immune system markers.	

Number of participants:

The number of patients to be enrolled in the LTS14120 study was dependent on the number of patients enrolled in study TDU13475 or TDU14981, with up to 68 patients possibly enrolling based on the original planning.

The number of patients who enrolled in the LTS14120 study were:

- Sixteen patients who received placebo and were withdrawn from the study upon availability of treatment assignment after unblinding.
- Fifteen patients who received an intravenous (IV) dose of GZ402668, of whom 1 (6.7%) patient chose to withdraw from the study.
- Thirty-three patients who received a subcutaneous (SC) dose of GZ402668, of whom 3 (9.1%) patients chose to withdraw from the study, 1 (3.0%) patient withdrew due to an AE, and 1 (3.0%) patient was lost to follow-up.

All patients were included in the Safety and Efficacy populations, while placebo treated patients were excluded from the pharmacokinetic (PK) population.

Participant selection:

Patients were enrolled if they received an investigational medicinal product (IMP) administration (GZ402668 or placebo) in either the TDU13475 or TDU14981 studies and provided signed written informed consent according to the local regulations.

Study products:

The study was observational in nature and no IMP was administered.

Duration of study:

Not applicable.

Criteria for evaluation:

Primary:

- Assessment of adverse events (AEs) including serious adverse events (SAEs) and adverse events of special interest (AESI)
- Physical examination
- Clinical laboratory evaluations including thyroid function, hematology, creatinine, urinalysis with microscopy
- Vital signs
- Electrocardiogram (ECG)

Secondary:

- GZ402668 serum concentrations
- Lymphocyte phenotyping: eg, CD3+, CD3+CD8+, CD3+CD4+, CD16+CD56+, CD19+, total lymphocyte counts; helper/suppressor ratio
- Anti-GZ402668 antibodies

Statistical methods:

Demographics and baseline characteristics were summarized using descriptive statistics by dose group.

Primary Analysis:

All patients in the extension study were evaluated for safety. A summary of safety was evaluated based on incidence, duration, grade/intensity, seriousness, and relationship of AEs to GZ402668, and on changes in physical examination, vital signs, and clinical laboratory results. The AEs are tabulated (numbers of events and incidence) by dose group. Other safety parameters are summarized using descriptive statistics.

All AEs were graded according to National Cancer Institute Common Terminology for AEs (NCI CTCAE version 4.0) and coded using the Medical Dictionary for Regulatory Activities version 24.1. The AEs from the LTS14120 study was analyzed as treatment-emergent AEs (TEAEs). Laboratory safety variables were converted into standard international units.

A detailed listing of patients who experienced TEAEs and SAEs is provided including severity and relationship to treatment, and outcome. Study day was computed relative to the start date of the LTS14120 study. A separate listing for patients who withdrew from the study due to AEs is provided.

Frequency distribution tables of TEAEs (incidence tables) are provided for the overview of TEAEs, as well as summary tables for TEAEs, AESIs, TEAEs related to IMP, TEAEs by maximal intensity, treatment-emergent SAEs, TEAEs leading to study discontinuation, and deaths.

For all laboratory variables, vital signs, and ECG variables, descriptive statistics for observed values and change from baseline are provided for each time point. These analyses were performed using central measurements for laboratory variables and ECG variables. Potentially clinically significant abnormality (PCSA) analyses were performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For laboratory variables, vital signs, and ECG variables, the incidence of patients with at least 1 PCSA were summarized and a listing of individual values for patients with PCSAs are provided. The number and percentage of patients with physical examination abnormalities across visits are provided.

Analysis of secondary endpoints:

Serum samples were collected for GZ402668 concentration evaluation from all patients once a month for 3 months from the start of the study. Serum samples from patients who received placebo treatment were not analyzed for GZ402668 concentration.

Individual GZ402668 serum concentrations by visit and descriptive statistics by visit are listed. Pharmacokinetic evaluation was not performed, because patients were not treated with GZ402668 during this study.

Pharmacodynamic parameters were summarized using descriptive statistics at each time point, including assessment of observed values and change from baseline. A descriptive analysis of lymphocyte repopulation was performed, including T-cell recovery (especially CD4+ and CD8+ counts) and changes in B-cell (CD19+ lymphocyte) numbers.

The ADA status (negative, positive, inconclusive) and titer categories ($\leqslant$ 800, 1600 to 6400, and $\geqslant$ 12800) were described overtime using frequencies with the sample status and titers listed.

Summary:

Demographic and other baseline characteristics:

Of the patients administered IMP in the TDU13475 and TDU14981 studies, the following number of patients were enrolled patients in the LTS14120 study: 15 patients who were administered an IV dose of IMP (IV groups: 1 mg [3 patients]; 3.5 mg [3 patients]; 12 mg [9 patients]), 33 patients who were administered a SC dose of IMP (SC groups: 12 mg [6 patients]; 36 mg [12 patients]; 48 mg [6 patients]; 60 mg [9 patients]), and 16 patients who were administered placebo. All enrolled patients were included in the Safety and Efficacy populations, while placebo treated patients were excluded from the PK population.

All enrolled patients were white with mostly males in the placebo group (10 [62.5%] patients), females in the IV group (9 [60.0%] patients), and a near equal distribution in the SC group (16 [48.5%] males and 17 [51.5%] females, respectively).

The mean (standard deviation [SD]) age and baseline weight of patients were 51.8 (8.1) years and 77.54 (14.79) kg in the placebo group, 54.0 (7.2) years and 71.63 (13.02) kg in the IV groups, and 52.0 (8.5) years and 75.72 (11.44) kg in the SC groups. The mean (SD) baseline body mass index of patients was 25.68 (4.58) kg/m^2 in the placebo group, 25.69 (5.69) kg/m^2 in the IV groups, and 25.77 (3.87) kg/m^2 in the SC groups.

More patients had secondary progressive MS in the placebo group (11 [68.8%] patients), the IV group (11 [73.3%] patients), and the SC group (21 [63.6%] patients) than primary progressive MS (placebo group: 5 [31.3%] patients; IV group: 4 [26.7%] patients; and SC group: 12 [36.4%] patients).

Safety results:

One (3.0%) patient in one of the SC groups (at 48 mg) had a fatal TEAE of septic shock after having a TEAE of pulmonary sepsis, both of which were considered as not related by the Investigator. This event appeared in the context of a prolonged stay in hospital after a cardiogenic shock due to a myocardial infarction, on Day 1255 after the single dose of GZ402668. The same patient experienced the onset of Basedow's disease, which was the only autoimmune related event, of known class effects of anti-CD52 drugs, that occurred during the whole observation period.

Treatment-emergent SAEs were reported for 1 (6.3%) patient in the placebo group; 3 (20.0%) patients in the IV groups, and 19 (57.6%) patients in the SC groups. The most commonly reported SAEs were MS relapse (1 [6.7%] patient [IV] and 11 [33.3%] patients [SC]), MS (0 patient [IV] and 2 [6.1%] patients [SC]), and road traffic accident (1 [6.7%] patient [IV] and 1 [3.0%] patient [SC]). All other SAEs were each reported for 1 patient. Only 1 (3.0%) patient in the 60 mg SC group had a treatment-emergent SAE of urinary tract infection that was considered treatment-related by the Investigator.

The majority of patients in the placebo group had at least 1 TEAE reported (14 [87.5%] patients) with 7 (43.8%) patients having a treatment-related TEAE. Near all patients who received IMP (IV or SC) had at least 1 TEAEs reported (15 [100%] patients [IV] and 32 [97.0%] patients [SC]) with most having at least 1 treatment-related TEAE reported (13 [86.7%] patients [IV] and 30 [90.9%] patients [SC]).

The most commonly reported (>18%) TEAEs by PT in the placebo group were nasopharyngitis (5 [31.3%] patients) and dizziness (3 [18.8%] patients).

Overall, the most commonly reported TEAEs by PT (> 30%) in the IV or SC groups were nasopharyngitis (14 [93.3%] patients [IV] and 29 [87.9%] patients [SC]), urinary tract infection (6 [40.0%] patients [IV] and 14 [42.4%] patients [SC]), MS relapse (2 [13.3%] patients [IV] and 13 [39.4%] patients [SC]), headache (6 [40.0%] patients [IV] and 7 [21.2%] patients [SC]), back pain (5 [33.3%] patients [IV] and 6 [18.2%] patients [SC]), pyrexia (5 [33.3%] patients [IV] and 4 [12.1%] patients [SC]), and fall (2 [13.3%] patients [IV] and 12 [36.4%] patients [SC]).

The most frequently reported TEAEs (>18%) considered treatment-related by the Investigator were nasopharyngitis (11 [73.3%] patients [IV] and 20 [60.6%] patients [SC]) and urinary tract infection (3 [20.0%] patients [IV] and 6 [18.2%] patients [SC]).

Most patients in the IV groups had TEAEs considered mild (Grade 1) to moderate (Grade 2) in severity while Grade ≥ 3 TEAEs were reported for more patients in the SC groups (4 [26.7%] patients [IV] compared with 19 [57.6%] patients [SC]) with most patients having TEAEs of Grade 3 severity reported. Most Grade 4 and Grade 5 TEAEs were reported for the patient who died. Other Grade 4 TEAEs were reported for 1 patient each, either ischemic stroke or road traffic accident.

Adverse events of special interest were only reported in the SC groups (4 [12.1%] patients). The AESIs were clear cell renal cell carcinoma, thyroid mass, Basedow's disease, and goiter, each reported for only 1 (3.0%) patient.

There were no clinically meaningful patterns or trends identified in vital signs parameters over time or between treatment groups.

Overall, few patients (≤ 3 patients) had a PCSA for reported the vital signs parameters of systolic blood pressure, diastolic blood pressure, and heart rate during the treatment emergent period (including patients who received placebo). However, ≥ 4 patients had a PCSA related to weight reported in both the IV and SC groups:

- ≥ 5% decrease from baseline: 5/15 (33.3%) patients (IV) and 9/33 (27.3%) patients (SC), as well as 2/16 (12.5%) patients who received placebo.
- ≥ 5% increase from baseline: 4/15 (26.7%) patients (IV) and 15/33 (45.5%) patients (SC), as well as 2/16 (12.5%) patients who received placebo.

There were no clinically meaningful patterns or trends identified in ECG parameters over time or between treatment groups.

Overall, few patients (≤ 3 patients) had a PCSA reported for most ECG parameters during the treatment emergent period (including patients who received placebo). However, ≥ 4 patients had a PCSA related the following parameters:

- QRS interval > 110 msec: 0/15 patients (IV) and 5/33 (15.2%) patients (SC), as well as 3/16 (18.8%) patients who received placebo.
- QTcB > 450 msec: 4/15 (26.7%) patients (IV) and 1/33 (3.0%) patient (SC), as well as 1/16 (6.3%) patient who received placebo.

No QTcB or QTcF results of >480 msec or increase of > 60 msec from baseline were reported, although an increase from baseline of]30-60] msec was reported for the QTcF results (1/15 [6.7%] patient [IV]) and for the QTcB results (1/15 [6.7%] patients [IV] and 1/16 [6.3%] patients [placebo]).

Abnormal physical examination results for the neurological system were reported for most patients at all planned assessments (from 68.8% up to 100%) while other site/system abnormalities were reported from 33.3% up to 78.8% of patients at any given assessment.

Overall, the laboratory results were varied over time and between the treatment groups with no notable trends observed. However, the mean white blood cell results tended to decrease from baseline over the Month 1 to Month 3 period, whereafter the results slowly trended upwards.

The number of patients with a PCSA in the laboratory parameters were low (≤ 3 patients), except for:

- Hemoglobin decrease from baseline of ≥ 20 g/L: 4/15 (26.7%) patients (IV) and 6/33 (18.2%) patients (SC), and 0/16 patients who received placebo.
- Monocytes > 0.7 × 109/L: 5/15 (33.3%) patients (IV) and 20/33 (60.6%) patients (SC), as well as 2/16 (12.5%) patients who received placebo.
- Eosinophils > 0.5 × 109/L or > upper limit of normal (ULN) (if ULN ≥ 0.5 × 109/L): 0/15 patients (IV) and 4/33 (12.1%) patients (SC), as well as 1/16 (6.3%) patients who received placebo.
- Creatinine ≥ 30% change from baseline: 2/15 (13.3%) patients (IV) and 4/33 (12.1%) patients (SC), and 0/16 patients who received placebo.

- Thyrotropin < lower limit of normal (LLN): 5/15 (33.3%) patients (IV) and 7/32 (21.9%) patients (SC), and 0/11 patients who received placebo.

Pharmacokinetic results:

Serum concentrations were below the lower limit of quantitation (LLOQ) of 0.123 µg/mL at all 3 visits in 16 patients. Serum concentrations were measurable and above LLOQ at all 3 visits in 9 patients, at both the Months 1 and 2 visits in 6 patients, at only Month 1 visit in 17 patients.

Concentration below LLOQ were treated as zero for calculation of descriptive statistics.

The mean concentration in patients from the 12 mg IV group at Month 1 was 0.1211 µg/mL which declined to below LLOQ at Month 2. The mean concentration in patients from the 1 and 3.5 mg IV groups were below LLOQ at all visits.

The mean concentration in patients from the 12 mg SC group at Month 1 was 0.26 µg/mL which declined to below LLOQ by Month 2. Mean concentrations at Month 1 from the 36, 48, and 60 mg SC groups were 0.6907, 1.0688, and 1.5456 µg/mL, respectively, which declined gradually to 0.0318, 0.1937, and 0.2451 µg/mL, respectively, at Month 3.

Pharmacodynamic results:

Mean leukocytes levels were slightly lower than baseline in placebo and near baseline in 1 mg IV, 3.5 mg IV, and 12 mg SC groups. Mean leukocyte levels at Month 1 in the 12 mg IV (4.322 cells/nL), 36 mg SC (4.436 cells/nL), and 60 mg SC (5.613 cells/nL) groups were lower than baseline which increased to levels above the LLN, near to baseline values of 6.433, 5.920, and 7.501 cells/nL, respectively, at the end of the study. Mean leukocyte levels in the 48 mg SC group were low (5.270 to 7.362 cells/nL) during the study period, but above the LLN, compared to baseline where the levels were increased (15.412 cells/nL).

Mean lymphocyte levels were near baseline levels in the placebo and 1 mg IV dose groups. Mean lymphocyte levels were low at Month 1 in the 3.5 mg IV (1.09739 cells/nL) group which returned to near baseline levels of 2.18300 cells/nL by the end of the study. In other dose groups (12 mg IV, 12, 36, 48, and 60 mg SC), lymphocyte levels were low at Month 1 (0.52029, 0.77856, 0.34153, 0.48888, and 0.30388, respectively) and gradually increased to levels above the LLN, but stayed below baseline levels by the end of the study (1.47551, 0.99145, 1.15985, 1.28384, and 1.46865 cells/nL, respectively).

Mean T-cells were slightly lower or near baseline in placebo and 1 mg IV dose groups. Mean T-cells were low at Month 1 in the 3.5 mg IV (0.59350 cells/nL) group which returned to near baseline by the end of the study (1.46765 cells/nL). In other dose groups (12 mg IV, 12, 36, 48, and 60 mg SC), T-cells were low at Month 1 (0.16805, 0.43714, 0.09311, 0.19683, 0.04246 cells/nL, respectively) and gradually increased to lower than baseline levels by the end of the study (0.88794, 0.66620, 0.59720, 0.73524, and 0.89614 cells/nL, respectively).

Mean T-reg CD4 T-cells were near baseline in placebo group. Mean T-reg CD4 T-cells at Month 1 were low in 1, 3.5, and 12 mg IV, 12, 36, 48, and 60 mg SC (0.04051, 0.02187, and 0.00873, 0.01944, 0.00634, 0.01198, and 0.00348 cells/nL, respectively) which increased but remained lower than baseline levels at the end of study (0.06610, 0.04690, and 0.04057, 0.04530, 0.03235, 0.04950, and 0.04116 cells/nL, respectively).

Other results:

Overall, most patients (≥ 69.7%) in the combined IV and SC groups remained ADA negative. All ADA positive patients in the groups and most of the ADA positive patients in the SC groups had a titer of ≤ 800. A titer of 1600 to 6400 was only reported in the SC groups by ≤ 2 patients at any given time point. A titer of ≥ 12800 was only reported for 1 (33.3%) patient in the 36 mg SC group at Month 1 assessment.

Over the 12-month assessment period, the number of patients with a positive result decreased over time in both the IV and SC groups.

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