

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

<p>Sponsor: Sanofi</p> <p>Drug substance(s): ALEMTUZUMAB</p>	<p>Study Identifiers: UTN: U1111-1171-7939; NCT number: NCT02583594; EudraCT Number: 2015-002550-12</p> <p>Study code: TDU14260</p>
<p>Title of the study: A phase 1, exploratory, randomized, open-label, 2-arm study to characterize the pharmacodynamics, pharmacokinetics, safety, and tolerability of alemtuzumab 12 mg administered subcutaneously or intravenously in patients with progressive multiple sclerosis (TDU14260)</p>	
<p>Study center(s): 1 study center in Spain</p>	
<p>Study period: Date first participant enrolled: 30 November 2015 Date last completed: 1 March 2021 Study Status: Completed</p>	
<p>Phase of development: Phase 1</p>	
<p>Objectives:</p> <p>Primary objective: To characterize the pharmacodynamic (PD) profile of 2 treatment courses of alemtuzumab 12 mg administered by subcutaneous (SC) injection and 2 treatment courses of alemtuzumab administered by intravenous (IV) infusion in patients with progressive multiple sclerosis (ProgMS).</p> <p>Secondary objectives:</p> <ol style="list-style-type: none"> To characterize the pharmacokinetic (PK) profiles of alemtuzumab administered by SC injection or IV infusion to patients with ProgMS. To characterize the safety and tolerability of alemtuzumab administered by SC injection or IV infusion to patients with ProgMS. 	

<p>Methodology:</p> <p>This was a Phase 1, exploratory, single-center, randomized, open-label, parallel group, descriptive clinical trial in patients with ProgMS.</p>
<p>Number of participants:</p> <p>Planned: 24 Randomized: 24 Treated: 24 in period 1, 21 in period 2</p> <p>Evaluated:</p> <p>pharmacodynamics: 24 in period 1, 21 in period 2 Safety: 24 in period 1, 21 in period 2, 20 in safety monitoring phase Pharmacokinetics: 24 in period 1, 21 in period 2</p>
<p>Diagnosis and criteria for inclusion: Male or female adults (age ≥ 18) with a diagnosis of MS based on 2010 revision of McDonald criteria and diagnosis of progressive MS, including primary progressive MS and secondary progressive MS.</p>
<p>Study products</p> <p>Investigational medicinal product(s): GZ402673 (alemtuzumab)</p> <p>Formulation: Concentrate for solution. Each single-use vial contains 12 mg alemtuzumab (10 mg/mL; total extractable volume 1.2 mL)</p> <p>Route(s) of administration: SC injection or IV infusion in a supervised medical setting</p> <p>Dose regimen:</p> <p>SC injection of 12 mg/day on 5 consecutive days (initial course; total dose 60mg), followed by a second course (12 mg/day on 3 consecutive days; total dose 36 mg) administered 12 months after the initial course.</p> <p>Or</p> <p>Intravenous infusion (after dilution) of 12 mg/day on 5 consecutive days (initial course; total dose 60 mg), followed by a second course (12 mg/day on 3 consecutive days; total dose 36 mg) administered 12 months after the initial course.</p>
<p>Duration of treatment: 5 days for initial course and 3 days for second course (12 months after the initial course)</p> <p>Duration of observation: Approximately 61 months</p>
<p>Criteria for evaluation:</p> <p>Primary endpoint Pharmacodynamics: change from Baseline in the CD3+ lymphocyte subset after SC or IV administration.</p> <p>Secondary endpoint Pharmacodynamics: Changes from Baseline in CD3+CD8+, CD3+CD4+, CD19+, and CD16+CD56+ lymphocyte subsets, total lymphocyte count, and helper/suppressor ratio after SC or IV administration. Pharmacokinetics:</p> <ul style="list-style-type: none"> • Serum alemtuzumab parameters after SC administration: C_{max}, F[SC], T_{max}, AUClast, AUC, t_{1/2z}, • Serum alemtuzumab parameters after IV administration: C_{max}, T_{max}, AUClast, AUC, t_{1/2z}.

Safety:

- Safety assessments including the following for all patients:
 - Occurrence, seriousness, grade/intensity, relationship to study drug, time of onset and resolution, and outcome of serious adverse events (SAEs) and adverse events (AEs).
 - Occurrence, seriousness, grade/intensity, relationship to study drug, time of onset and resolution, and outcome of the following adverse events of special interest (AESIs)
- Autoimmune mediated conditions including, but not limited to:
 - Immune thrombocytopenic purpura (ITP).
 - Nephropathies including anti-glomerular basement membrane (GBM) disease.
 - Cytopenias.
 - Thyroid disorders.
 - Autoimmune Hepatitis.
 - Acquired Hemophilia A.
- Hemophagocytic lymphohistiocytosis (HLH).
- Serious infections including serious opportunistic infections [eg, Listeria infections, Cytomegalovirus (CMV), Epstein-Barr Virus (EBV)], HPV associated with cervical dysplasia.
- Malignancy.
- Pneumonitis.
- Progressive Multifocal Leukoencephalopathy (PML).
- Temporally associated* pulmonary alveolar hemorrhage.
- Temporally associated* myocardial ischemia, myocardial infarction.
- Temporally associated* stroke.
- Temporally associated* cervicocephalic arterial dissection.
- * Temporally associated: 1 to 3 days after last infusion
 - Changes in hematological parameters.
 - Vital sign collection.
 - Immunogenicity (anti-alemtuzumab antibody titers).
 - Safety parameters by route of administration:
 - For patients receiving alemtuzumab via SC administration, local tolerability at the injection site was assessed, including occurrence, seriousness, grade/intensity, relationship to study drug, time of onset and resolution, and outcome of any reactions. Pain intensity was assessed by a subset of the McGill Pain Questionnaire after each injection.
 - For patients receiving alemtuzumab via IV administration, the occurrence, seriousness, grade/intensity, relationship to study drug, time of onset and resolution, and outcome of infusion associated reactions (IARs) was assessed.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetic samples were collected on:

- Initial treatment course: pre-dose, 2, 4, and 8 hours after first dose start, pre-dose to second, third, and fourth dose, predose, 2, 4, 8, 24, 48, 72, and 96 hours after fifth dose start.
- Second treatment course: pre-dose, 2, 4, and 8 hours after first dose start, pre-dose to second dose, pre-dose, 24, 48, 72, and 96 hours after third dose start.

Pharmacodynamics samples were collected on P1V2, P1V19, P1V21, P1V24, P1V27, P2V30, P2V39, P2V41, P2V44, P2V47 and P2V50.

Statistical methods:**Primary analysis:**

The primary PD parameter, CD3+ lymphocyte subset after SC and IV administration, was summarized using descriptive statistics at each time point, including assessment of observed values and change from Baseline.

Secondary analysis:

The secondary PD parameters for SC and IV administration were summarized using descriptive statistics at each time point, including assessment of observed values and change from Baseline.

Analysis of pharmacokinetic variables:

Serum PK parameters were summarized using descriptive statistics and also analyzed using noncompartmental methods.

Analysis of Safety data:**• Adverse events:**

The primary analysis of adverse event reporting was on treatment-emergent adverse events (TEAEs). The reporting period was defined as the time from the first administration of IMP to the end of the study.

TEAEs were tabulated (numbers of events and incidence) by seriousness, grade/intensity, relationship to study drug, and by treatment group. AE leading to treatment discontinuation, deaths, SAEs, injection site reaction (ISR) after SC administration, IAR after administration, and AESIs were also tabulated.

• Clinical laboratory evaluations:

Hematological parameters were summarized using descriptive statistics at each time point, including assessment of observed values and change from Baseline.

• Vital signs:

Vital signs were summarized using descriptive statistics at each time point, including assessment of observed values and change from Baseline. Vital signs changes during and immediately following SC and IV administration from pre-treatment were summarized.

• Immunogenicity:

Anti-alemtuzumab antibody titers were summarized using descriptive statistics at each time point, including assessment of observed values and change from Baseline.

Summary Results:**Population characteristics:**

- 29 patients were screened; 5 patients were screening failures.
- 24 (82, 8%) patients were randomized: 16 assigned to SC arm, 8 to IV arm. Patients' demographics and characteristics at baseline were similar in the 2 treatment arms.

Treatment course 1:

- All 24 patients completed treatment course 1: 16 in SC arm and 8 in IV arm.
- During period 1 and before starting the second treatment course, 3 patients (1 in SC arm and 2 in IV arm) discontinued the study due to patient's personal decision.

Treatment course 2:

- 21 patients were treated with treatment course 2: 15 in SC arm and 6 in IV arm.
- All 21 patients completed the second course of treatment.
- All 21 patients completed period 2 (month 24).

Safety monitoring phase:

- 14 patients completed safety monitoring phase: 8 in SC arm and 6 in IV arm.

pharmacodynamics:

In both arms (SC/IV) lymphocyte CD3+ cell count decreased over time following the first course of alemtuzumab treatment. The mean (SD) of change from baseline at month 1 was -1284.07 (447.895) in the SC arm and -1059.29 (200.315) in the IV arm. The lower CD3+ levels were achieved at month 1 in both arms. After month 1, lymphocyte counts repopulated until month 12. The Mean (SD) of CD3+ cell count at month 12 was 598.688 (396.172) in the SC arm and 528.143 (330.946) in the IV arm. After the second alemtuzumab treatment course, lymphocyte counts decreased again. The mean (SD) of CD3+ cell count at month 13 was 89.667 (70.496) in the SC arm and 129.333 (102.981) in the IV arm and repopulated again until month 24.

Depletion across all lymphocyte subpopulations, including T cells, B cells, NK cells, and various subsets thereof, was observed in both arms.

Both SC and IV formulations showed lymphocyte count depletion by 30 days after administration. Lymphocyte repopulates over time. Lymphocyte values generally were recovering towards baseline levels during the first year after treatment. After the second course of alemtuzumab administration, both SC and IV formulations showed lymphocyte count depletion again by 30 days. After month 13, lymphocyte count repopulated again towards baseline until month 24.

Safety results:

All (100%) patients reporting at least 1 TEAE following SC and IV administration in both treatment arms.

No unexpected adverse events were noted.

Seven treatment-emergent SAEs occurred in 3/16 patients (18.8%) in the SC arm. Two treatment-emergent SAEs occurred in 2/8 patients (25.0%) in the IV arm. Seven AESIs occurred in 5/16 patients (31.3%) in SC arm. Three AESIs occurred in 3/8 patients (37.5%) in IV arm.

No TEAE leading to permanent treatment discontinuation or death. Tolerability in both treatment arms was as expected.

Pharmacokinetic results:

Following either route of administration, serum concentrations increased with consecutive daily dosing within each treatment course, reaching a maximum after the last dose within that course. Following IV treatment, alemtuzumab concentration were measurable during the entire sampling period (22 days) and declined slowly with a $t_{1/2z}$ of 6.79 days (N=1). Following SC treatment, alemtuzumab was absorbed slowly into the systemic circulation (median t_{max} of ~ 6 days) and eliminated slowly with measurable serum concentrations up to the last sampling time of 22 days. Lower concentrations were obtained after SC administration compared to IV, with a bioavailability of 32%.

Issue date: 1-Mar-2022