Template of Study Results Summary for Public Disclosure – Interventional Studies

Sponsor: Sanofi **Drug substance(s):** avalglucosidase alfa (neoGAA, GZ402666)	**Study Identifiers:** U1111-1147-3439; NCT02032524; EudraCT number: 2013-003321-28 **Study code:** LTS13769

Title of the study:

An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease

Study center(s):

This study was conducted at 16 centers that enrolled participants in 7 countries: Belgium, Denmark, France, Germany, The Netherlands, United Kingdom, United States.

Study period:

Date first participant enrolled: 27-Feb-2014

Date last participant completed: 12-Dec-2022

Study Status: Completed

Phase of development: Phase 2

Objectives:

Primary:

- To assess the long-term safety and PK of avalglucosidase alfa in participants with Pompe disease who have previously completed an avalglucosidase alfa study.

Secondary:

- To assess the long-term effect of avalglucosidase alfa on pharmacodynamic variables to assess if the benefits of avalglucosidase alfa were maintained and to assess the time course of response.

Methodology:

This is an open label, multicenter, multinational extension study with repeated IV infusions of avalglucosidase alfa (neoGAA, GZ402666). The study population includes patients with Pompe disease who have completed the open-label study TDR12857 with avalglucosidase alfa. At the entry into the LTS13769 study, participants continued to receive the same dose as received in the TDR12857 study. After the dose of 20 mg/kg every other week, participants receiving initially the doses of 5 or 10 mg/kg qow had to provide consent to switch to the 20 mg/kg qow regimen for the remaining duration of the LTS13769 study; participants on 20 mg/kg continued with this dose. Results presented in the report combine the 2 periods of treatment of the 2 studies (Study TDR12857 and Study LTS13769).

Number of study participants:

Planned: the number of participants was determined by enrollment from other avalglucosidase alfa studies

Analyzed: 24 participants

Diagnosis and criteria for inclusion:

Patients with Pompe disease who previously completed an avalglucosidase alfa study.

Study products

Avalglucosidase alfa dose levels were: 5 mg/kg QOW, 10 mg/kg QOW, or 20 mg/kg QOW. Study treatment was administered by IV infusion.

Duration of study intervention:

Initially 26 weeks in TDR12857 and 6 years in LTS13769 plus an additional follow-up phase (until approval in applicable country or maximum of 2 years for UK, Germany, and Denmark)

Criteria for evaluation:

Primary:

Safety endpoints:

- Assessment of adverse events, including IARs and deaths
- Physical examination
- Clinical laboratory evaluations, including hematology, biochemistry, and urinalysis
- Vital signs
- Body weight
- 12-lead ECG
- Immunogenicity assessments

PK endpoints:

- C_{max}
- AUC_{last}
- AUC
- t_{last}
- $t_{1/2z}$
- CL
- Vd

Secondary:

Pharmacodynamic endpoints:

- Skeletal muscle MRI
- Skeletal muscle needle or open biopsy
- Urinary Hex4 level

Statistical methods:

Pharmacodynamic Analysis:

Descriptive statistics (including mean, SD, median, minimum, maximum, and 95% confidence intervals of changes) for both observed and change from baseline (and/or rebaseline, if specified) by study visit were provided for quantitative parameters, by group and by each participant group/dose level, unless otherwise specified. Qualitative results that were categorical were presented with number and percentage of participants in each category. If a linear trend in the change of a PD endpoint was observed, a longitudinal model was employed to model change from baseline over time.

Efficacy Analysis:

Secondary endpoints were summarized with both the FA set and the efficacy analysis set. Observed measurements, changes from baseline, and changes from rebaseline (LTS-switch participants only) to each applicable study time point in 6MWT (distance walked, actual and percent predicted) and PFT parameters (actual and percent predicted, supine and standing FVC, FEV1, MIP, MEP, and PEF) were summarized using summary statistics. 95% CIs are used to estimate the change from baseline at each study visit. Missing data were not imputed. Spaghetti plots showing participant data over time were presented.

Safety Analysis:

Descriptive statistics for actual values and changes from baseline were generated by time point for selected safety parameters of interest. Data was also plotted. For the purpose of analysis, baseline value was defined as the last value prior to the first dose of avalglucosidase alfa in the TDR12857 study.

Summary Results:

Demographic and other baseline characteristics:

Of the 24 participants enrolled in the TDR12857 study, 12 (50.0%) were male (3 [30.0%] in Group 1 and 9 [64.3%] in Group 2) and 12 (50%) were female (7 [70.0%] in Group 1 and 5 [35.7%] in Group 2). The majority of the participants in both groups were White (8 [80.0%] in Group 1 and 13 [92.9%] in Group 2).

Among the 21 participants who completed the TDR12875 study, 19 were consented and enrolled in the long-term safety LTS13769 study.

The mean age at Pompe disease diagnosis was 43.3 and 36.3 years in Groups 1 and 2, respectively. The number of participants with confirmed Pompe disease family history was 40.0% and 42.9% in Groups 1 and 2, respectively. In Groups 1 and 2, 2/10 participants (20.0%) and 3/14 participants (21.4%), respectively, used some kind of walking device at baseline.

Exposure:

In TDR12857/LTS13769 overall, there were 3450 total infusions. A total of 1340 and 2110 qow IV infusions of 5, 10, or 20 mg/kg avalglucosidase alfa were administered to participants in Groups 1 and 2, respectively. The median duration of exposure to avalglucosidase alfa was 411.2 weeks for Group 1 combined and 402.2 weeks for Group 2 combined (a range of 16 to 454 weeks). The median number of infusions per participant was 178.0 for Group 1 and 188.0 for Group 2 (a range of 8 to 225, overall) and the median average biweekly dose received was 15.4 mg/kg for Group 1 and 17.5 mg/kg for Group 2 (a range of 4 to 20 mg/kg, overall).

Overall, 10 participants in Group 1 received 134.0 IV infusions and 14 participants in Group 2 received 150.7 infusions of avalglucosidase alfa. The difference is mainly driven by the fact there were more participants enrolled in Group 2. Nine (90.0%) participants in Group 1 and 14 (100%) participants in Group 2 had compliance ≥80%.

Pharmacodynamics

Skeletal muscle MRI results: Overall, the participants' results from muscle mass index, CSA, Dixon Fat Fraction, and water T2 (with and without B1 mapping) were generally stable for the duration of the study. Typically, patients in this population would be expected to have declines in these areas due to disease progression, which may suggest that avalglucosidase alfa treatment may contribute to muscle preservation.

Skeletal muscle glycogen content results:

Across all Group 1 participants, the mean (SD) muscle glycogen level in the left quadriceps was 3.7% (3.6%; N=4) at baseline with similar levels at Week 27 of 2.9% (1.5%; N=3). The mean (SD) muscle glycogen level in the right quadriceps was 7.5% (8.8%; N=6) at baseline with reduced levels at Week 27 of 6.6% (7.1%; N=6) with a change from baseline of -0.9% (2.4%).

Across all Group 2 participants, the mean (SD) muscle glycogen level in the left quadriceps was 6.9% (8.6%; N=11) at baseline with reduced levels at Week 27 of 4.0% (4.7%; N=7) with a change from baseline of -1.7% (4.2%). The mean (SD) muscle glycogen level in the right quadriceps was 3.9% (2.3%; N=2) at baseline with levels at Week 27 of 6.0% (3.3%; N=2) with a change from baseline of 2.0% (1.0%). Overall, biopsies collected from the majority of Group 1 and Group 2 participants represented mild disease with low levels of accumulated glycogen making it difficult to histopathologically evaluate the effect of avalglucosidase alfa on total or lysosomal glycogen.

Urine glucose tetrasaccharide levels: In Group 1, mean reductions from baseline in urinary Hex4 concentrations were observed over time in all treatment groups. The mean (SD) at baseline was 7.0 (3.9) mmol/mol in the 5 mg/kg group, 13.0 (4.8) mmol/mol in the 10 mg/kg group, and 5.4 (4.3) mmol/mol in the 20 mg/kg group. The greatest mean (SD) reduction was 8.5 mmol/mol (SD not calculable) at Week 442 in the 5 mg/kg group, 12.5 mmol/mol (SD not calculable) at Week 416 in the 10 mg/kg group, and 4.4 (SD not calculable) mmol/mol at Week 234 in the 20 mg/kg group. In Group 2, mean reductions from baseline in urinary Hex4 concentrations were observed in the 10 mg/kg and 20 mg/kg groups, with an increase followed by reduction from baseline in the 5 mg/kg group. The mean (SD) at baseline was 7.0 (3.8) mmol/mol in the 5 mg/kg group, 3.9 (1.9) mmol/mol in the 10 mg/kg group, and 7.5 (8.3) mmol/mol in the 20 mg/kg group. The greatest mean (SD) reduction was 5.9 (0.1) mmol/mol at Week 260 in the 5 mg/kg group, 2.9 (1.2) mmol/mol, 2.9 (1.7) mmol/mol, and 2.9 (SD not calculable) mmol/mol at Week 234, Week 260, and Week 416, respectively in the 10 mg/kg group, and 10.5 (11.7) mmol/mol at Week 390 in the 20 mg/kg group.

Efficacy

Overall, participants remained stable on treatment over time, with variations on performance in six minute walk test, forced vital capacity, forced expiratory volume, maximum expiratory pressure, maximum inspiratory pressure, and peak expiratory flow due to age and comorbidities.

Safety results:

Overall, all 24 participants (100.0%) experienced at least 1 treatment-emergent adverse event (TEAE) during the study, with a total of 1163 TEAEs reported. The majority of the TEAEs and SAEs are reflective of the underlying disease and other associated comorbidities due to participants' age. Overall, 9 participants (37.5%) experienced a total of 39 SAEs, and 1 participant experienced 6 TEAEs which led to permanent treatment discontinuation. One participant in Group 1 had a fatal TEAE of acute respiratory failure during the post treatment period on Study Day 2143, 56 days after the last dose of IMP. Overall, there were 41 protocol-defined infusion associated reactions (IAR) reported in 7 participants, and 60 algorithm-defined IAR events reported in 14 participants. One participant in Group 1 had two AEs of arthralgia that were considered to be severe cutaneous and potential immune-mediated reactions. Two participants had TEAEs that matched standardized Medical Dictionary for Regulatory Activities Queries (SMQ) for anaphylaxis. Both recovered and one participant was withdrawn from the study. Of the 2 participants who received home infusions (32 home infusions in 1 participant and 36 in the other), 1 participant experienced 1 TEAE (cough). There were significant reductions overall in alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase.

As expected with administration of ERT, of the treatment naïve participants, 90.0% (9 of 10 participants) developed treatment-emergent ADA of which 80.0% (8 participants) were persistent and 1 participant tolerized, becoming ADA negative over time. Of the treatment experienced participants, 42.9% (6 of 14 participants) developed treatment-emergent ADA, with 4 participants that were ADA negative at study entry who developed treatment induced ADA and 2 participants who made a boosted response (treatment-boosted ADAs were pre-existing ADAs which were boosted at least two titer steps from baseline following administration of the study drug). Overall, 15 of 24 participants (62.5%) developed treatment-emergent ADA. Of these, 13 participants were treatment-induced and 5 participants had pre-existing ADA, of which 2 developed a treatment boosted response. Of the 13 participants with treatment-induced ADA, 2 were considered transient, 10 were considered persistent, and 1 participants tolerized, becoming ADA negative over time. The overall median peak titer for the treatment naïve participants was 1600 (range of 200 to 51200) and a median peak titer of 400 (range of 100 to 12800) for the experienced participants. The median time to seroconversion from date of first infusion was 8.1 weeks (mean [SD]: 8.3 [2.1] weeks) for treatment naïve participants (Group 1) and 32.6 weeks (mean [SD]: 57.7 [72.5] weeks) for treatment experienced participants(Group 2)

Overall, the incidence of TEAEs were similar between the treatment naïve and treatment experienced participants. There was a trend for lower IARs and hypersensitivity in the treatment experienced group (21.4% and 42.9%, respectively) compared to the treatment naïve participants (40.0% and 60.0%, respectively).

Overall, 5 of 10 treatment naïve participants developed NAb that inhibited cellular uptake and 5 participants developed NAb that inhibited catalytic activity. Detection of NAb from first infusion was a median of 170.9 days for inhibition of cellular uptake and 298.4 days for inhibition of catalytic activity. Two of 14 treatment experienced participants developed NAb: one catalytic inhibition and the other inhibition of cellular uptake. Time to development of inhibition was similar to the naïve participants. In Group 1, the treatment naïve participants receiving 5 or 10 mg/kg drug had NAb cellular uptake transiently detected at 1 to 2 time points, while the persistence of NAb positivity was variable with the 20 mg/kg group. Two of the 3 participants receiving 20 mg/kg were intermittently positive for several time points, and 1 participant was persistent. The 2 treatment experienced participants in Group 2 had detectable NAb at only a single time point. In Group 1, 2 NAb positive participants experienced an SAE, 3 NAb positive participants experienced hypersensitivity AEs, and 2 NAb positive participants experienced a protocol or algorithm-defined IAR. In Group 2, 1 NAb positive participant experienced a hypersensitivity AE. No evident impact of ADA Peak Titer has been observed on Hex4 level in participants and no evident impact of over time by anti-avalglucosidase alfa ADA status has been observed on exploratory efficacy endpoints in participants.

Pharmacokinetic results:

Participants previously treated with alglucosidase alfa exhibited avalglucosidase alfa PK similar to naïve participants. After 20 mg/kg qow, mean $t_{1/2}$ was around 1.6 to 1.8 hours. Mean systemic plasma clearance was around 1.0 L/h and mean steady-state volume of distribution ranged from 3.1 to 3.9 L.

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