Sponsor: Sanofi **Drug substance(s):** avalglucosidase alfa	**Study Identifiers:** IND: 109569, EudraCT/EU trial number: 2016-000942-77, NCT02782741, WHO: U1111-1178-4806 **Study code:** EFC14028

Title of the study:

A Phase 3 randomized, multicenter, multinational, double blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment naïve patients with late onset Pompe disease

Study center(s):

This study was conducted at 70 active sites (ie, sites which screened at least 1 participant) in 25 countries/regions worldwide (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Japan, Republic of Korea, Mexico, The Netherlands, Poland, Portugal, The Russian Federation, Spain, Switzerland, Taiwan, Turkey, United Kingdom, and United States of America). Of the 70 sites which screened participants, 56 enrolled at least 1 participant who was randomized to treatment with the investigational medicinal product and 1 center enrolled the pediatric participant directly in the extension treatment period (ETP).

Study period:

Study initiation date (first participant first visit): 02 November 2016

Study completion (last participant last visit): 31 May 2023

Study Status: Completed

Phase of development: Phase 3

Objectives:

Primary

- To determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position, as compared to alglucosidase alfa

Secondary

Key secondary objective

- To determine the effect of avalglucosidase alfa on functional endurance

Additional secondary objectives

- To determine the safety of avalglucosidase alfa
- To determine the effect of avalglucosidase alfa on Inspiratory muscle strength
- To determine the effect of avalglucosidase alfa on expiratory muscle strength
- To determine the effect of avalglucosidase alfa on lower extremity muscle strength
- To determine the effect of avalglucosidase alfa on quick motor function test
- To determine the effect of avalglucosidase alfa on health-related quality of life

Methodology:

This was a Phase 3, multicenter, multinational, randomized, double-blind, 12-month PAP study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa (both at 20 mg/kg qow) in treatment-naïve participants ages 3 years and above with LOPD, followed by an open-label extension. The study included 2 main periods: the blinded treatment period PAP and an open-label avalglucosidase alfa ETP for all participants, in which participants in the alglucosidase alfa arm were switched to avalglucosidase alfa treatment after 12 months. Participants were randomized in a 1:1 ratio with stratification factors based on baseline FVC (%predicted: <55% or ≥55%, gender, age, (<18 years and ≥18 years), and country (Japan and ex-Japan).

The duration of the study for each randomized participant (including the first pediatric participant) included an up to 14-day screening period (that may have been extended to a maximum of 8 weeks in prespecified situations), a 49-week blinded treatment period (PAP), an up to 96-week open-label treatment period (ETP) with avalglucosidase alfa for all participants regardless of prior randomization group, an up to 144-week (or until avalglucosidase alfa is approved in the participant's country, whichever came first) extended open-label treatment period (extended open-label avalglucosidase alfa long-term follow-up phase) for all participants and an up to 4-week post treatment observation period.

The duration of the study for the pediatric participant who was enrolled directly in the ETP included a 14-day screening period (extended to a maximum of 8 weeks in prespecified situations), an up to 96-week open-label treatment period (ETP) with avalglucosidase alfa, an up to 144-week (or until avalglucosidase alfa is approved in the participant's country, whichever came first) extended open-label treatment period (extended open-label avalglucosidase alfa long-term follow-up phase) and an up to 4-week post treatment observation period.

Number of participants (planned and analyzed):

A total of 96 participants were planned to be enrolled in this study. A total of 101 participants were enrolled and treated in 70 active sites, including a second pediatric participant who was included directly in the ETP in the 70th site, after enrollment in the PAP had been completed.

Diagnosis and criteria for inclusion:

Enrolled in this study were treatment-naïve participants with LOPD who had a confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations. The following criteria excluded participants from the study: the participant was <3 years of age, had known Pompe specific cardiac hypertrophy, was wheelchair dependent, was not able to ambulate 40 meters (approximately 130 feet) without stopping and without an assistive device, required invasive-ventilation (non-invasive ventilation was allowed), was not able to successfully perform repeated FVC measurements in upright position of ≥30% predicted and ≤85% predicted, or had previous treatment with immunomodulation, alglucosidase alfa, or any investigational therapy for Pompe disease.

Study products:

Investigational medicinal products: Avalglucosidase alfa and alglucosidase alfa.

Formulation:

- Avalglucosidase alfa: sterile, nonpyrogenic, lyophilized product, 100 mg
- Alglucosidase alfa: sterile, nonpyrogenic, white to off white, lyophilized cake or powder, 50 mg

Route of administration: Intravenous (IV).

Dose regimen: 20 mg/kg once every 2 weeks (qow).

Duration of study intervention:

Avalglucosidase alfa was administered by IV infusion every 2 weeks starting at Randomization Visit (Visit 2, Day 1/Day 2) continuing up to Visit 27/Week 49 for a total of 25 doses (PAP), followed by an open-label long-term period continuing up to 96-weeks for a total of 48 additional doses, followed by an extended open-label long-term period continuing up to 144-weeks for a total of up to 72 additional doses or until avalglucosidase alfa is approved in the participant's country, whichever came first. After the 100 participants were randomized, 1 additional pediatric participant was enrolled directly in the open-label long-term period with a 96-week duration (as described above), followed by an extended open-label long-term period continuing up to 144- weeks for a total of up to 72 additional doses or until avalglucosidase alfa is approved in the participant's country, whichever came first.

Alglucosidase alfa was administered by IV infusion every 2 weeks starting at Randomization Visit (Visit 2, Day 1/Day 2) continuing up to Visit 27/Week 49 for a total of 25 doses (PAP), followed by avalglucosidase alfa administered by IV infusion every 2-weeks in an open-label long-term period for up to 96-weeks for a total of 48 additional infusions, followed by an extended open-label long-term period with avalglucosidase alfa (same regimen) continuing up to 144-weeks for a total of up to 72 additional doses or until avalglucosidase alfa is approved in the participant's country, whichever came first.

Criteria for evaluation:

Primary

- Change from baseline to Week 49 in FVC (% predicted) in the upright position

Secondary

- Total distance (meters) walked during 6MWT
- AEs including SAE and AESI, and other safety information such as clinical laboratory data, vital signs, ECG, physical examination, weight, height, and immunogenicity.
- MIP and % predicted
- MEP and % predicted
- HHD: lower extremity summary score and individual muscle group and percent predicted from the muscle groups of Hip Flexion, Hip Extension, Hip Abduction, Hip Adduction, Knee Flexion, Knee Extension, Ankle Dorsiflexion, Ankle Plantar Flexion
- Total score of QMFT
- SF 12: the PCS and MCS scales from the survey

6MWT=6 Minute Walk Test ; ACE=angiotensin converting enzyme; AE=adverse event; AESI=adverse events of special interest; AUC0-last=area under the concentration-time curve from dosing (time 0) to the last measured concentration; Cmax=maximum concentration; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimension 5 Level; FVC=forced vital capacity; GAA=acid alpha-glucosidase; GMFM-88=Gross Motor Function Measure-88; GSGC= Gait, Stair, Gower's Maneuver, and Chair; HHD=hand-held dynamometry; MCS=mental component score; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; PCS=physical component score; PD=pharmacodynamics; PDIS=Pompe Disease Impact Scale; PDSS=Pompe Disease Symptom Scale; PGIC=Patient Global Impression of Change scale; QMFT=Quick motor function test; PedsQL=Pediatric Quality of Life Inventory; PK=pharmacokinetic(s); R-Pact=Rasch-built Pompe-specific activity scale; SAE=serious adverse event; SF-12=12-Item Short Form Health Survey.

Statistical methods:

Unless otherwise specified, efficacy analyses used the modified intention-to-treat (mITT) population, where participants were considered to be in the treatment group to which they were randomized. The mITT population included randomized patients who receive at least 1 infusion (partial or total). Corresponding supportive analysis were performed for per protocol (PP) population as well. Safety analyses used the safety population, where participants were analyzed according to treatment received. In PAP, safety population included randomized patients who receive at least 1 infusion in PAP. Patients who receive at least one infusion of avalglucosidase alfa in PAP were assigned to the avalglucosidase alfa arm for the PAP safety analysis purposes. In ETP, safety population included patients who receive at least 1 infusion in ETP and included 1 pediatric patient who was directly enrolled to ETP. Overall safety of avalglucosidase alfa was based on patients who receive at least 1 infusion during either PAP or ETP.

For all analyses, the avalglucosidase alfa treatment group was compared to the alglucosidase alfa group. While the primary comparison of interest is at 12 months (49 weeks), all summary statistics were computed and displayed by treatment group and each scheduled assessment time as well. Summary statistics for continuous variables included n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages were presented. Graphical displays were provided as appropriate. All efficacy endpoints were summarized descriptively at each study visit, as well as the last observation available during the PAP.

All efficacy analyses were performed based on the mITT population. Corresponding analysis was performed for PP population for the primary efficacy endpoint. If the pure intention-to-treat (ITT) (all randomized patients) population was different from the mITT population, a sensitivity analysis in this population was to be performed as well to assess the robustness of the results. In PAP analysis, the safety analyses were carried out with participants by the actual treatment received, irrespective of the treatment the participant was randomized to.

In ETP analysis and overall evaluation of avalglucosidase alfa safety, the safety analyses were carried out by the following 4 groups:

- Group 1 includes data in PAP and ETP among participants who received avalglucosidase alfa in PAP and ETP,
- Group 2 includes data in ETP among participants who received alglucosidase alfa in PAP and received avalglucosidase alfa in ETP,
- Group 3 includes data in PAP and/or ETP among participants who received avalglucosidase alfa in that period,
- Group 4 includes data in PAP and/or ETP among pediatric participants who received avalglucosidase alfa in that period.

Below are some changes following study database lock and posthoc analysis:

Due to a limited number of Hispanic participants, an ethnicity subgroup analysis of the primary efficacy endpoint was replaced by a region subgroup analysis. This change was not captured in the latest statistical analysis plan (SAP) amendment. An error was found in the SAP after database lock. This involved a reference equation to derive grip strength. The equation was corrected by replacing "/2.2" by "× 2.2":

- R: [-(age×.18)+(gender×16.90)+((weight/height2) ×.23)+31.33] × 2.20
- L: [-(age×.16)+(gender×16.68)+((weight/height2) ×.29)+26.60] × 2.20

'Baseline HHD % predicted score-by-visit interaction' was removed from the mixed model for repeated measures model for % predicted of HHD lower extremity muscle strength.

Another error was found in the SAP after DBL; "baseline-by-visit interaction" was inadvertently deleted in the sensitivity analysis of change from baseline in FVC (%predicted), based on a MMRM model including baseline FVC, age, gender, treatment group, visit, and treatment-by-visit interaction as fixed effects also.

Summary Results:

The study was initiated on 02 November 2016 before the Coronavirus Disease 2019 (COVID-19) pandemic started and was ongoing during the pandemic, however, was executed as planned. For this final CSR, a total of 44 participants missed 187 IMP infusions. PFT and 6MWT were not performed because of COVID-19 at Week 145, in 9 and 5 participants, respectively. Beyond Week 145 and up to Week 289, a total of 31 PFTs and 21 6MWTs were not performed due to COVID-19. Overall, because of COVID-19 49 participants missed a total of 79 PFTs and 37 participants missed a total of 45 6MWTs. However, overall, the impact of COVID-19 on the study was moderate during this reporting period. To note, the PAP period was conducted before the COVID 19 pandemic.

Demographic and other baseline characteristics:

All 95 participants who completed the PAP entered the ETP during which 51 participants continued with avalglucosidase alfa and 44 participants were switched from alglucosidase alfa to avalglucosidase alfa. A total of 80/100 participants completed the study as per protocol, including the 2 pediatric participants (the first participant was randomized in the PAP and a second participant entered ETP directly and has data until Week 97 at the time of data cut-off, corresponding to their end-of-treatment visit). However, 1 participant who did not complete EOS visit was reflected as an ongoing participant in the CRF.

Of the 96 participants (including the second pediatric participant who entered into ETP directly) enrolled in the ETP (ETP population), there were no major imbalances noted in the baseline demographic characteristics between the treatment groups and population characteristics.

The mean age (SD) of all participants in the mITT population was 48.1 years (14.2). The mean (SD) age at Pompe disease diagnosis was 44.73 years (14.74) and 48.16 years (14.64) in the avalglucosidase alfa and alglucosidase alfa groups, respectively. The mean (SD) age at first symptoms of Pompe disease was 32.94 years (16.58) and 37.73 years (15.74) in the avalglucosidase alfa and alglucosidase alfa groups, respectively. The mean (SD) time from Pompe disease diagnosis to first infusion of study treatment was 15.60 months (32.06) and 26.52 months (59.86) in the avalglucosidase alfa and alglucosidase alfa groups, respectively. The mean (SD) time from first symptom of Pompe disease to first infusion of study treatment was 160.36 months (131.71) and 151.78 months (120.90) in the avalglucosidase alfa and alglucosidase alfa groups respectively. Overall, key efficacy parameters in the PAP were well balanced between avalglucosidase alfa and alglucosidase alfa groups. respectively.

Exposure:

During the PAP, a mean (SD) of 24.8 infusions (0.5) of avalglucosidase alfa and 22.8 infusions (5.8) of alglucosidase alfa were administered per participant. The median duration of exposure to avalglucosidase alfa and alglucosidase alfa was 11.53 months and 11.50 months, respectively.

The mean total infusions given per patient in participants who received avalglucosidase alfa in both the PAP and ETP (Group 1) were: 99.5 total infusions (in PAP + ETP) and 74.6 infusions (in ETP); and 70.9 total infusions were given per participants who switched from alglucosidase alfa to avalglucosidase alfa in the ETP (Group 2). The mean total infusions given per patient in participants who received avalglucosidase alfa in either PAP or ETP (Group 3) was 85.9 infusions. The 2 pediatric participants (Group 4) received 93 infusions and 48 infusions, respectively. In the ETP, the median duration of exposure to avalglucosidase alfa Group 1 was 35.48 months, Group 2 was 30.75 months, and 41.72 months in Group 3. The duration of exposure for 2 pediatric participants (Group 4) was 22.6 and 44.2 months.

Efficacy results:

The totality of efficacy data demonstrates substantial improvements of avalglucosidase alfa over alglucosidase alfa (the standard of care treatment for Pompe disease) for clinically meaningful outcome measures for Pompe disease participants. The study shows favorable results on its primary study endpoint % predicted FVC and has met the primary objective of demonstrating non-inferiority of avalglucosidase alfa compared to alglucosidase alfa on its primary study endpoint % predicted FVC change from baseline at Week 49 (LS mean difference of 2.43%; 95% CI of -0.13, 4.99); the lower boundary of 95% CI of -0.13 far exceeded -1.1 (the predefined NI margin).

The primary endpoint was also measured for superiority. Superiority statistical significance was not achieved for the avalglucosidase alfa arm (p=0.0626) while the effect of avalglucosidase alfa treatment was numerically better than alglucosidase alfa. Since superiority was not reached, formal testing was stopped per the testing hierarchy and p-values for secondary endpoints are provided at the nominal level (without multiplicity adjustment).

In the participants continuing with avalglucosidase alfa, at Week 145 (n=44), median % predicted FVC was 65.05, resulting in a 2.74 observed median increase from baseline, and at Week 169 (n=37), median % predicted FVC was 63.96, resulting in a 1.61 observed median increase from baseline, showing a maintained benefit compared with baseline. In participants who had switched from alglucosidase alfa to avalglucosidase alfa, median % predicted FVC was 59.54 at Week 145 (n=33) resulting in a 0.37 observed median increase from baseline, and at Week 169 (n=30), median % predicted FVC was 56.32, resulting in a 1.47 observed median increase from baseline. A stabilization was observed after the switch with similar values to the avalglucosidase alfa group at Week 145 and at Week 169. After Week 169 more variability was observed due to the limited number of participants since most participants had completed the study.

The following key results were observed for secondary efficacy endpoints:

- In the PAP, the LS mean change (SE) in 6MWT (distance walked in meters), a measure of functional endurance, from baseline to Week 49 was 32.21 (9.93) in the avalglucosidase alfa group and 2.19 (10.40) in the alglucosidase alfa group; the difference was 30.01 (nominal p=0.0405), showing an improvement with avalglucosidase alfa, compared to alglucosidase alfa. In the participants continuing with avalglucosidase alfa, at Week 145 (n=45), mean 6MWT (meters) (SD) was 432 (114.91), resulting in a 24.89 meter mean increase from baseline and at Week 169 (n=37), mean (SD) 6MWT was 435.28 (119.34), resulting in a 26.51-meter increase from baseline, showing a maintained benefit compared to baseline. In participants who had switched from alglucosidase alfa to avalglucosidase alfa, mean 6MWT (meters) (SD) was 374.96 (135.49) at Week 145 (n=35) resulting in a -4.11 meter mean change from baseline and at Week 169 (n=32), mean 6MWT was 368.14 (139.32) resulting in a -9.41 meter mean change from baseline. After the switch to avalglucosidase alfa, a stabilization was observed in the alglucosidase alfa group with sustained baseline levels at Week 145 and Week 169. After Week 169 more variability was observed due to the limited number of participants since most participants had completed the study.
- In the avalglucosidase alfa group, there were 2 participants at Weeks 13, 25, 37, and 49 in the PAP with decreased use of assistive walking device from baseline compared to no incidence in the alglucosidase alfa group.
- The effect on MIP and MEP is better evaluated in the post-hoc sensitivity analysis after the removal of 4 participants who were excluded due to an implausible MIP/MEP value of 200 cm H2O at baseline. In the PAP, the LS mean change (SE) in MIP (% predicted) from baseline to Week 49 was 8.71 (2.08) in the avalglucosidase alfa group and 4.33 (2.19) in the alglucosidase alfa group; the resulting difference was 4.38 (95% CI: -1.64, 10.39). The LS mean (SE) in MEP (% predicted) from baseline to Week 49 was 10.97 (2.84) in the avalglucosidase alfa group and 8.35 (2.97) in the alglucosidase alfa group; the difference was 2.61 (95% CI: -5.61, 10.83). In the ETP, participants who switched from alglucosidase alfa to avalglucosidase alfa, the mean (SD) change in MIP (% predicted) from baseline was 6.79 (12.73) at Week 145 and 9.04 (15.61) at Week 169 and the mean (SD) change in MEP (% predicted) from baseline was 9.70 (15.03) at Week 145 and 15.29 (23.70) at Week 169. For participants who continued with avalglucosidase alfa during the ETP, the mean (SD) change in MIP (% predicted) from baseline was 8.51 (14.07) at Week 145 and 8.96 (17.45) at Week 169 and the mean (SD) change in MEP (% predicted) from baseline was 15.89 (19.64) at Week 145 and 18.54 (17.51) at Week 169. Participants maintained a benefit compared to baseline. After Week 169 more variability is observed due to the limited number of participants since most participants completed the study.

- In the PAP, the LS mean change (SE) in HHD (lower extremity muscle strength) (composite score) from baseline to Week 49 was 260.69 (46.07) in the avalglucosidase alfa group and 153.72 (48.54) in the alglucosidase alfa group; the difference was 106.97 (95% CI: -26.56, 240.50). In the ETP, participants who switched from alglucosidase alfa to avalglucosidase alfa, the mean (SD) change in HHD composite summary score of the lower extremity muscle strength from baseline at Week 145 was 137.72 (362.75). For participants who continued with avalglucosidase alfa during the ETP, the mean (SD) change in HHD composite summary score of the lower extremity muscle strength from baseline at Week 145 was 186.95 (573.00). This showed improvements at Week 145 compared with baseline.
- In the PAP, the LS mean change (SE) in the motor function scale specific for Pompe disease QMFT (total score) from baseline to Week 49 was 3.98 (0.63) in the avalglucosidase alfa group and 1.89 (0.69) in the alglucosidase alfa group; the difference was 2.08 (95% CI: 0.22, 3.95), showing an improvement with avalglucosidase alfa, compared to alglucosidase alfa. In the ETP, participants receiving alglucosidase alfa and switching to avalglucosidase alfa had a mean (SD) total score for QMFT of 42.15 (12.65) at Week 145 with a mean (SD) change from baseline value of 1.56 (5.85). Participants who continued with avalglucosidase alfa had a mean (SD) total score for QMFT of 46.22 (10.02) at Week 145 with a mean (SD) change from baseline value of 5.20 (5.49). This showed improvements at Week 145 compared with baseline.
- In the PAP, for SF-12, the LS mean change (SE) for PCS score from baseline to Week 49 was 2.37 (0.99) in the avalglucosidase alfa group and 1.60 (1.07) in the alglucosidase alfa group; the difference was 0.77 (95% CI: -2.13, 3.67). For the MCS score, the LS mean change (SE) in SF-12 from baseline to Week 49 was 2.88 (1.22) in the avalglucosidase alfa group and 0.76 (1.32) in the alglucosidase alfa group; the difference was 2.12 (nominal p=0.2427). In the ETP, participants switching to avalglucosidase alfa had a mean (SD) PCS score of 39.67 (8.53) at Week 145 with a mean (SD) change from baseline value of 3.60 (7.38). They had a mean (SD) MCS score of 50.88 (8.91) at Week 145 with a mean (SD) change from baseline value of -0.30 (10.11). At Week 145, participants who continued with avalglucosidase alfa had a mean (SD) PCS score of 40.90 (7.87) with a mean (SD) change from baseline value of 4.50 (7.00) and had a mean (SD) MCS score of 47.98 (9.22) with a mean (SD) change from baseline value of -0.23 (7.48). These results showed an improvement in SF-12 PCS scores and stabilization of SF-12 MCS scores from baseline in participants who switched from alglucosidase alfa to avalglucosidase alfa in the ETP.

In both pediatric participants, an improvement in FVC (% predicted), 6MWT, MIP, MEP, HHD, and QMFT was observed in the avalglucosidase alfa group from Baseline to Week 289 for the first pediatric participant and from Baseline to Week 97 for the second pediatric participant, consistent with results observed in adult participants.

Study results were stable for the efficacy parameters at Week 169 with a small number of the parameters that showed improvement compared to the baseline. After Week 169 more variability is observed due to the limited number of participants since most participants completed the study.

Safety results:

Treatment-emergent AEs were consistent with the known safety profile of alglucosidase alfa as well as the underlying disease.

The following key results were observed for safety endpoints:

- The incidence of TEAEs in the PAP was 86.3% in the avalglucosidase alfa group and 91.8% in the alglucosidase alfa group; in the ETP was 100% in Group 1 and 97.7% in Group 2.
- The proportion of participants with TESAEs was lower in the avalglucosidase alfa (15.7%) than the alglucosidase alfa (24.5%) group in the PAP. In the ETP, the proportion of participants with TESAEs was slightly lower in Group 1 (27.5%) than Group 2 (31.8%).
- Three participants died during the study including one participant on alglucosidase alfa died due to acute myocardial infarction (unrelated) in the PAP and two additional participants who switched from alglucosidase alfa to avalglucosidase alfa died in the ETP, one due to adenocarcinoma pancreas (unrelated) and the other due to pneumonia and bronchospasm (unrelated). None of the pediatric participants died during the study.

- Nine participants discontinued the study due to TEAEs. In the PAP, four participants in the alglucosidase alfa group discontinued the study due to acute myocardial infarction (led to participant's death), arthritis, dyspnoea (IAR), and urticaria (IAR). In the ETP, two participants who remained on avalglucosidase alfa discontinued due to ocular hyperemia and erythema in one participant (both IARs), and acute myocardial infarction in another (unrelated); 3 participants who switched from alglucosidase alfa to avalglucosidase alfa discontinued due to adenocarcinoma pancreas (unrelated), respiratory distress (IAR) and urticaria (IAR).
- Protocol-defined IARs were experienced by fewer participants in the avalglucosidase alfa (25.5%) group compared to the alglucosidase alfa group (32.7%) in the PAP. In the ETP, fewer participants who remained on avalglucosidase alfa (Group 1, 23.5%) experienced protocol-defined IARs compared to participants who switched from alglucosidase alfa to avalglucosidase alfa (Group 2, 50.0%). Most participants experienced protocol-defined IARs during the infusion. The number of participants experiencing protocol-defined IARs decreased with time.
- One participant experienced anaphylaxis during avalglucosidase alfa infusion reporting TESAEs of respiratory distress and tongue edema (severe each), and 5 nonserious TEAEs of erythema, dysphagia, generalized edema, and chest discomfort (severe each), and nausea (mild) in the ETP. The reaction led to treatment discontinuation.
- Five pregnancies were reported during the study including two pregnancies in the PAP treated with alglucosidase alfa and three in the ETP with 1 pregnancy in Group 1 and 2 pregnancies in Group 2. The outcome of three pregnancies was normal live birth and for the remaining two was abnormal termination.
- The AESIs of ALT and AST increased were associated with concomitant conditions such as adenocarcinoma pancreas, cholecystitis or other causes such as alcohol consumption in some participants and most had no clinical correlation. None of the pediatric participants reported AESIs of ALT or AST increased.
- Similar incidence of laboratory or ECG related PCSAs were observed in both groups in the PAP; and similar results were observed in the ETP (for Groups 1 and 2 and in pediatric participants).
- The two pediatric participants did not experience any treatment-related SAEs or AESIs, including IARs.
- ADA titers were lower in the avalglucosidase alfa group and similar rates of SAEs and IARs at peak titers were observed between both treatment groups. Overall, the frequency of IARs and hypersensitivity in participants increased with increasing peak titer category.
- Thirteen participants received in total 402 home infusions and out of these, one participant experienced nonserious IARs (flushing and eyelid oedema) and 5 participants experienced nonserious unrelated TEAEs during the home infusions. There were no medication errors reported during the home infusions.
- In conclusion, the safety profile of avalglucosidase alfa was consistent with the alglucosidase alfa safety profile and was possibly more favorable.

Pharmacokinetic results:

Avalglucosidase alfa PK parameters in the second pediatric participant directly enrolled in the ETP appeared similar at Day 1 and Week 49, indicating no apparent accumulation after 20 mg/kg qow dosing. At Week 49, his/her terminal half-life was of 1.0 hour, the systemic plasma clearance of 1.50 L/h, and the volume of distribution was of 2.17 L.

Pharmacodynamic results:

Overall, higher changes in Hex4 levels from baseline were observed in the avalglucosidase alfa group in comparison to the alglucosidase alfa group. This positive effect was maintained in avalglucosidase alfa participants who had reached Week 145 and with available data, and enhanced in those who switched from alglucosidase alfa to avalglucosidase alfa treatment after Week 49.

Immunogenicity results:

A small number of participants (7 participants) had HSAT in the study with four participants who switched from alglucosidase alfa to avalglucosidase alfa and three participants who received avalglucosidase alfa in PAP and ETP. Five out of 7 participants experienced IARs, the majority nonserious and mild in intensity.

The percentages of treatment-naïve participants (Group 1) who developed NAbs are similar to those switched from alglucosidase alfa to avalglucosidase alfa (Group 2). None of the pediatric participants (Group 4) tested NAb positive post baseline for enzyme activity inhibition or cellular uptake.

The majority of participants developed ADA to avalglucosidase alfa which was anticipated given clinical experience with alglucosidase alfa and both sharing a common protein sequence. During ETP, ADA titers continued to decrease with time, with an increase in the number of participants who tolerized. Previous exposure to alglucosidase alfa appeared provide a degree of attenuation of immunologic response. Variable impact on PK, PD, and efficacy measures was observed among high titer participants; however, in most participants there was no clinically significant effect of ADA on efficacy. The incidence of IARs increased with higher ADA titers but were manageable with current clinical practices. The results from the ETP further extend the findings reported from the PAP.

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