2 ABSTRACT

Title

A Prospective Safety Sub-Registry to Assess Anaphylaxis and Severe Allergic Reactions, and Severe Cutaneous and Systemic Immune-Mediated Reactions with Alglucosidase Alfa Treatment (AGLU06909/LTS13930)

Keywords

Alglucosidase alfa, Pompe disease, Safety Sub-registry, anaphylaxis, severe allergic reactions, infusion-associated reactions

Rationale and background

Alglucosidase alfa (Myozyme® and Lumizyme®), a recombinant human acid-α glucosidase (rhGAA), is approved in more than 86 countries or regions for all patients with a confirmed diagnosis of Pompe disease.

Treatment with alglucosidase alfa has resulted in events of anaphylaxis and immune-mediated reactions in some patients. Anaphylactic and severe allergic reactions have been observed during and up to 3 hours after starting the alglucosidase alfa infusion. Immune-mediated reactions have been observed several weeks to 3 years after initiation of alglucosidase alfa infusion. Consequently, participants in this Safety Sub-Registry study were planned to be followed prospectively for 4 years.

Research question and objectives Study

The objectives of this Safety Sub-Registry study were to collect uniform and meaningful data on patients with Pompe disease who experience anaphylaxis, severe allergic reactions, and/or signals of severe cutaneous and/or systemic immune-mediated reactions following treatment with alglucosidase alfa.

Study design

Prospective, exploratory, observational, 4-year longitudinal sub-registry study of patients enrolled in the Pompe Registry who received or planned to receive enzyme replacement therapy (ERT) with alglucosidase alfa at or prior to enrollment

Setting

- Site and participant selection: This voluntary Safety Sub-Registry study consisted of prospective collection of participants' data following treatment with alglucosidase alfa.
- Overall participation status: The Safety-Sub-Registry study enrolled 110 patients with Pompe disease at 18 active centers in 6 countries/regions.

- Data collection: Data were collected on the Pompe Registry (Main Registry) or Safety Sub-Registry electronic case report form (eCRF).
- Safety data collection: Protocol-specified AEs, laboratory assessments, and vital sign data were recommended to be collected via spontaneous reporting as per the treating physician's standard-of-care.

Participants and study size, including dropouts

A total of 110 participants were enrolled in the study; 77 participants completed 4 years of follow-up and 33 participants discontinued study participation.

Variables and data sources

- **Data management, review, validation:** The Safety Sub-Registry database was extracted from the Pompe Registry database. AE data as specified in the protocol were systematically collected and monitored/underwent source data verification (SDV) in the Registry database for those Registry patients who were voluntarily enrolled in the Safety Sub-Registry study.
- **Statistical considerations:** Descriptive analyses were performed on the patient data recorded until the database lock date (07 June 2021) for this final report.
- **Variables and evaluation criteria:** Medical Dictionary for Regulatory Activities (MedDRA) v24.0 was used to code each AE into its system organ class (SOC) and the preferred terms (PT). Tables of AEs present (1) Any AE; (2) primary SOC(s); and (3) the PT(s) that fall under each SOC. A patient can experience more than one AE within each of these independent categories. If this occurs, the maximal intensity AE(s) (ie, mild, moderate, or severe) or the related event(s) (ie, related, not related) are counted once within each independent category. For this final analysis, the number of participant having experienced serious/not serious and related/not related AEs were also summarized once for each independent category of age at Pompe symptom onset categories (ie, ≤1 year; >1 and ≤2 years; >2 and ≤12 years; >12 and ≤18 years; >18 years; and missing age at symptom onset).
- **Data analyses:** The safety analyses include the analyses for Anaphylaxis, Hypersensitivity, and Immune-Mediated Reactions which were conducted using the same strategies used in the Periodic Benefit Risk Evaluation Report. Standardized MedDRA Queries (SMQs) were used for Anaphylaxis and Hypersensitivity. For Immune-Mediated Reactions, a combination of SMQs and PTs were used including the Vasculitis SMQ and Severe Cutaneous Reaction SMQ plus the following PTs: Glomerulonephritis, Nephrotic syndrome, Proteinuria, Hematuria, Serositis, Myocarditis, Skin lesion, Arthralgia, Arthritis, Myalgia, Arthropathy, Lymphadenopathy, Serum sickness, Type III immune complex mediated reaction, and Influenza like illness. Preferred terms falling in these groups were included in each analysis. Potential effects on specific AE occurrences in relation to the status and timing of IgG antibody (in participants with evaluable samples) and of baseline CRIM (in participants' age at symptom onset ≤12 months) were summarized descriptively.

Results

- **Overall participation status:** Participants came from 18 sites (2 to 10 from each site) in 6 countries/regions, including United States (31), Italy (30), Belgium (22), Taiwan (10), Germany (9), and Czech Republic (8).
- **Participation per period of the study:** The safety population included all 110 participants enrolled in the study.
- **Descriptive data:** The median age of the 110 participants at enrollment was 46.0 (range 0 to 82) years. Approximately equal numbers of female (57 [51.8%]) and male (53 [48.2%]) participants were enrolled. The median duration of treatment with alglucosidase alfa prior to enrollment in the Safety Sub-Registry was 5.28 (range 0.1 to 16.7) years based on recorded date of first treatment. All 110 participants have received alglucosidase alfa during observation in the Safety Sub-Registry, for a minimum of 0.4 years to a maximum of 5.0 years (mean±SD: 3.48±0.99 years), with the majority of participants (105 [95.5%]) having been observed for at least 1 year (≥ 366 days) including 87 participants (79.1%) with observation for more than 3 years (> 1096 days). The most frequent dose was ≥ 17.5 and < 22.5 mg/kg body weight every 2 weeks in 94 (85.5%) participants.

  Thirty participants (27.3%) experienced a total of 589 AEs during or up to 2 hours post infusion. Twenty-four participants (21.8%) experienced mild AEs and 13 participants (11.8%) experienced moderate AEs by maximal intensity. Four participants (3.6%) reported a total of 4 severe AEs. These included supraventricular tachycardia in 1 participant who recovered, cardiac arrest in a second participant who recovered with sequelae, cardiopulmonary failure in a third participant which was fatal, and cardiac arrest in a fourth participant which was fatal. None of these AEs were related to treatment. Eight participants (7.3%) had a total of 11 AEs assessed as serious: 2 participants with cardiac arrest, 1 participant with cardiopulmonary failure, 1 participant with supraventricular tachycardia (2 times) and oxygen saturation decreased, 1 participant with influenza, 1 participant with type I diabetes mellitus, 1 participant with non-cardiac chest pain, and 1 participant with fall and fractured sacrum. The majority of AEs in most participants with AEs were resolved at study end.

  Adverse drug reactions were reported in 23 (20.9%) out of 110 participants, the most frequent being urticaria (7 participants, 6.4%) and headache, pyrexia, and fatigue (4 participants each, 3.6%). The majority of ADRs were mild and resolved. An analysis of ADRs by age at Pompe disease symptom onset indicated a higher frequency of participants experiencing ADRs with age less than or equal to 1 year of age at Pompe disease symptom onset (8 out of 15 [53.3%]) than those with age at symptom onset greater than 1 year of age or with missing age for symptom onset (15 out of 95 [15.8%]).

  Infusion-associated reactions were reported in 23 participants (20.9%), the most frequent being urticaria (7 participants, 6.4%) and headache, fatigue, and pyrexia (4 participants each, 3.6%). Sixteen participants (14.5%) experienced only mild IARs and 7 participants (6.4%) experienced moderate IARs by maximal intensity; no IARs were assessed as severe. One participant experienced an IAR of non-cardiac chest pain which was assessed as serious. In most participants with IARs, the events occurred during or up to 2 hours post infusion (21 participants, 19.1% of total) and decreased thereafter. Delayed IARs were

only reported in 3 participants (2.7%), the most frequent being fatigue (2 participants, 1.8%). All of these delayed IARs occurred from 24 to ≤48 hours post infusion.

Twenty-two participants (20.0%) experienced AEs that coded to PTs included in the anaphylaxis SMQ, of which, 7 participants (6.4%) experienced events that were assessed by the Investigator as not related to treatment and 15 participants (13.6%) experienced events assessed as related. In these 15 participants, the AEs reported as related were urticaria (7 participants), dyspnea (3 participants), flushing (2 participants), rash (2 participants), erythema (2 participants), pruritus (2 participants), chest discomfort (2 participants). hypotension (1 participant), cough (1 participant), and angioedema (1 participant). The anaphylaxis SMQ AEs were of mild or moderate intensity, with the exception of severe cardiac arrest in 2 participants. The outcomes were resolved in most events, with the exception of cardiac arrest that was fatal in 1 participant and recovered with sequelae in another and dyspnea in 1 participant that was not resolved.

Four deaths occurred during the study, one from cardiopulmonary failure due to fluid buildup, one from cardiac arrest, one due to a febrile event at home, and one from oropharyngeal cancer. Three were not related to study drug as determined by the Investigator and the febrile event had unknown relatedness to study drug.

Fourteen participants (12.7%) experienced AEs that coded to PTs included in the SMQ for hypersensitivity, of which, 4 participants (3.6%) experienced events that were assessed by the Investigator as not related to treatment and 10 participants (9.1%) were experienced events assessed as related. In these 10 participants, the AEs reported as related were urticaria (7 participants), flushing (2 participants), rash (2 participants), erythema (2 participants), pruritus (2 participants), angioedema (1 participant), infusion site urticaria (1 participant), and injection site rash (1 participant). None of the hypersensitivity SMQ AEs were serious; all were of mild or moderate intensity. The outcomes were all resolved.

One participant (0.9%) experienced an AE (oral mucosal blistering) identified as a potential immune mediated reaction. The AE was assessed by the Investigator as related to treatment, non-serious, and of mild intensity. This was a single clinical event that occurred during or up to 2 hours after infusion and the outcome was resolved. No action was taken with respect to the dose of alglucosidase alfa and no medication was given for management of the event.

Discussion

Four of the 110 participants (3.6%) reported severe AEs and none of these were related to treatment. Eight participants (7.3%) reported SAEs, of which 1 event of non-cardiac chest pain was reported as related to alglucosidase alfa. Four deaths occurred during the study, none of which were reported as ADRs.

Adverse drug reactions were reported in 23 (20.9%) out of 110 participants. All were of mild to moderate intensity, and most were known to be associated with alglucosidase alfa. Participants with age at symptom onset less than or equal to 1 year were more likely to experience ADRs

compared to those with age at symptom onset greater than 1 year of age or missing (8 out of 15 [53.3%] versus 15 out of 95 [15.8%]).

Twenty-two (20.0%), 14 (12.7%), and 1 (0.9%) of the participants experienced AEs that coded to PTs included in the SMQs for anaphylaxis, hypersensitivity, and immune-mediated reactions, respectively. The sponsor's medical review found none of the AEs of anaphylaxis identified through the MedDRA SMQ to be clinically confirmed anaphylaxis, and none of the hypersensitivity AEs nor the potential immune-mediated reaction were severe.

Based on the final analysis of the 4-year Safety Sub-Registry study, there is no new safety information that may impact the safety profile of alglucosidase alfa.

Marketing Authorization Holder(s)

Genzyme Europe B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

Study Personnel

The Coordinating Investigator's and Company responsible medical officer's signed approvals of the report are provided in Annex 2.

This report was prepared by:

- [redacted], Medical Writer
- [redacted] Pharmacovigilance Global Safety Officer
- [redacted], Statistician
- [redacted], Global Study Manager
- [redacted] Study Medical Manager

The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

Names and affiliations of Principal Investigators

[redacted]

National coordinators

Not applicable.